

## CLINICAL STUDY PROTOCOL

**Protocol Number:** CA-ALT-801-02-09

**Protocol Title:** Phase Ib/II Study of ALT-801 with Cisplatin in Patients with Metastatic Melanoma

**Date of Protocol:**  
Version # 01 September 18, 2009

**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.

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Principal Investigator's Signature

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Date

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Principal Investigator's Name (Print)

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## SYNOPSIS

**Sponsor:** Altor Bioscience Corporation

**Protocol#:** CA-ALT-801-02-09

**Study Drug Name:** Not applicable

### Study Treatment

**Active Ingredients:** ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein and cisplatin

**Study Type:** Interventional

**Study Phase:** Ib/II

**Protocol Title:** Phase Ib/II Study of ALT-801 with Cisplatin in Patients with Metastatic Melanoma

**Objectives:** The objectives of this study are to evaluate the safety, determine the Maximum-Tolerated Dose (MTD), and characterize the pharmacokinetic profile of ALT-801 given with cisplatin in patients who are chemotherapy naïve and have metastatic melanoma that is considered surgically incurable. We will also assess the anti-tumor responses of ALT-801 with cisplatin in this trial.

**Study Design:** This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-801 combined with cisplatin in patients who are chemotherapy naïve and have metastatic melanoma that is considered surgically incurable, who are serologically HLA-A2 positive and whose tumors present HLA-A2.1/p53 aa264-272 complexes. The study includes a dose escalation phase to determine the MTD and a two-stage expansion phase at the MTD. The dose escalation in this study is conducted using a traditional (3+3) dose escalation design. The two-stage expansion phase will be conducted at the MTD using a modified Simon two-stage design (1, 2). All enrolled patients will receive two courses of the treatment regimen. 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.

**Treatments:** Each treatment course consists of a 4-week regimen: one week of combined therapy with the study drug and cisplatin, a 9-day rest period, one week of monotherapy with the study drug ALT-801, and one week of recovery period. In the first treatment cycle, each enrolled patient will receive one dose of cisplatin at 70 mg/m<sup>2</sup> on day 1 and one dose of the study drug on day 3 and 5. In the second treatment cycle following a 9-day rest period, the enrolled patient will receive one dose of the study drug on day 1, 3, and 5. In total, patients will receive 5 doses of the study drug ALT-801 and 1 dose of cisplatin for a complete course of a 4-week treatment regimen.

One Course of The ALT-801-Cisplatin Regimen Treatment Schema is as follows:

|           | Week 1 (Cycle 1) |   |   |   |   | Week 2         | Week 3 (Cycle 2) |   |   |   |   | Week 4             |
|-----------|------------------|---|---|---|---|----------------|------------------|---|---|---|---|--------------------|
| Day       | 1                | 2 | 3 | 4 | 5 | Rest<br>Period | 1                | 2 | 3 | 4 | 5 | Recovery<br>Period |
| ALT-801   |                  |   | X |   | X |                | X                |   | X |   | X |                    |
| Cisplatin | X                |   |   |   |   |                |                  |   |   |   |   |                    |

The second course of study drug treatment starts at the 5<sup>th</sup> week after the initiation of the first course of treatment.

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 study drug and cisplatin will be administered by intravenous infusion into a central vein under the supervision of a qualified physician experienced in the use of anti-cancer agents including Proleukin<sup>®</sup> and cisplatin.

During the escalation phase of the study, the dose levels of the study drug and cisplatin are as follows:

| Cohort | ALT-801 Dose (mg/kg) | Cisplatin (mg/m <sup>2</sup> ) |
|--------|----------------------|--------------------------------|
| 1      | 0.04                 | 70                             |
| 2      | 0.06                 | 70                             |
| 3      | 0.08                 | 70                             |

#### Dose Escalation:

In this phase of the study, three patients will be enrolled per dose level. All patients will be monitored for any Dose Limiting Toxicity (DLT) for 7 weeks from the initiation of the first course of treatment. If one patient in a cohort experiences DLT, the enrollment of that dose level and each subsequent higher dose level will be expanded to include up to six patients. If 2 of 6 patients of a cohort experience DLT, subsequent enrollment at that dose level will be temporarily suspended and an assessment will be made whether the MTD has been reached. The dose escalation scheme will continue until the MTD is reached.

If more than two of six patients experience any DLT at the lowest dose level of the dose escalation, patient enrollment will be temporarily suspended. The sponsor, the Data Safety Monitoring Board and the principal investigators will meet to determine how to adjust downward the dose level of cisplatin and/or the study drug and how to proceed with the study.

A DLT is defined as any toxicity that results in study treatment discontinuation. Study treatment discontinuation due to patient's disease progression or patient's decision to withdraw from the study treatment without occurrence of any study treatment discontinuation event is not a DLT. The MTD is the dose level that is one level below the dose level at which two patients experience DLT, and at which fewer than 2 of 6 patients

experiences DLT. If patient enrollment at the highest dose level is completed and less than 2 of 6 patients experiences DLT, this dose level is designated as the MTD.

**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 (ORR = 5%; CBR = 20%) and an efficacy level of interest (ORR = 20%; CBR = 40%) will be selected. The sample size was driven by the parameter that had the larger sample size for each stage. An  $\alpha$  error rate of 5% and  $\beta$  error rate of 20% yielded a common set sample size of 13 patients for stage 1 and 30 patients for stage 2 (2). A total of 13 patients, including the number of patients already enrolled during the escalation phase, will be enrolled and evaluated in the first stage of the expansion phase at the MTD. An additional 30 assessable patients will then be enrolled and evaluated at the same dose level of the first stage if one or more ORs or four or more CBs are confirmed. Upon completion of the second stage, an observation of at least six ORs or 13 CBs would be sufficient to reject the null hypothesis of a lack of an effect of ALT-801 with cisplatin on OR and/or CB in favor of the alternative hypothesis that ALT-801 with cisplatin has a favorable effect on OR and/or CB.

**Stopping Rule:** If, at any time during the expansion phase of the study, 33% or more of the patients experience DLT, enrollment in this expansion cohort will be temporarily suspended. The sponsor, the Data Safety Monitoring Board and the principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

**Evaluations:** Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug, and to evaluate the study drug induced cell-mediated immune response. The anti-tumor response will be evaluated for up to 12 weeks from the initiation of the first course of treatment. All patients who receive at least one dose of the study drug will be included in the anti-tumor response evaluation. Survival of all enrolled patients will be assessed at 6 and 12 months from the start of study treatment. 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 have metastatic melanoma that is considered surgically incurable, are chemotherapy naïve, who are serologically HLA-A2 positive and whose tumors present HLA-A2.1/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. Patients who have had prior systemic treatment with cytotoxic chemotherapy agents will be excluded.

**Sample Size:** There are three cohorts in this study. A total of up to 18 patients will be accrued to the initial dose escalation phase of the study. An additional 7 and 30 patients will be enrolled at the MTD in stage 1 and stage 2 of the expansion phase, respectively.

**Primary  
Endpoints:**

For Stage I and II:

- (1) To evaluate the safety of the ALT-801-Cisplatin regimen.
- (2) To assess the objective response (OR) which includes CR and PR.
- (3) To assess the clinical benefit (CB) of the ALT-801-Cisplatin regimen which includes CR, PR and SD.

For Stage I only:

- (4) To determine the MTD of the ALT-801-Cisplatin regimen.

**Secondary  
Endpoints:**

- (1) To assess the six-month and one-year survival rates.
- (2) To evaluate the immunogenicity and pharmacokinetic profile of ALT-801.

**Pharmacokinetic  
Analysis & Cell-  
Mediated Immune  
Responses:**

Blood samples for pharmacokinetic analysis of ALT-801 will be taken on the first dose of ALT-801 of each course of study treatment. On each sampling day, venous blood will be obtained at Time 0 (before the start of infusion), at 30 min (completion of drug infusion), and 1 hr, 3 hr, and 6 hr from Time 0 for the assessment of ALT-801 serum concentration. Non-compartmental and compartmental analyses will be conducted. Serum levels of  $\text{INF}\gamma$  and  $\text{TNF}\alpha$  will also be evaluated using the same blood samples and at the same schedule as PK analysis. Serum levels of Vascular Endothelial Growth Factor (VEGF) and Fibronectin will be assessed once at pre-treatment for the entire study. The cell-mediated immune responses will be evaluated once each treatment cycle in the pre-dosing blood samples of the first ALT-801 infusion.

**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 the assays for anti-ALT-801 and IL-2 neutralizing antibodies, will be collected at pre-dosing on the first ALT-801 infusion day and 8 weeks after the start of the first course of treatment.

**Anti-tumor  
Response  
Evaluation:**

The initial anti-tumor response will be evaluated 8 weeks after the start of the first course of treatment. Patients who have at least stable disease from the two-course treatment will be further evaluated for anti-tumor responses to the study treatment at 12 weeks after the start of the first course of treatment. Objective Response will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (3). All measurements should be taken and recorded in metric notation using a ruler or calipers, or electronically. All baseline evaluations

should be performed as closely as possible to the start of treatment and never more than 28 days before the start of 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-up. 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.

**Survival**

**Assessment:**

Survival of all enrolled patients at 6 and 12 months from the start of study treatment will be evaluated.

**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 3.0 (CTCAEv3.0), 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 and/or email within 24 hours of 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 via phone, fax and/or email within 24 hours of its learning of the event 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. The study centers should report the other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related AEs that are both serious and unexpected will be reported to the FDA in an expedited manner in accordance with 21 CFR §312.32.

**Statistical Plan:**

All AEs will be tabulated and examined for each cohort. All safety and pharmacokinetic data will be evaluated for each cohort. 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 <sup>5</sup> | TREATMENT PERIOD<br>For Course 1 & 2 |                 |   |                                                    |      |   |   | FOLLOW-UP PERIOD                                                       |   |    |   |    |   |   |
|------------------------------------------------------------------------------------|------------|---------------------|--------------------------------------|-----------------|---|----------------------------------------------------|------|---|---|------------------------------------------------------------------------|---|----|---|----|---|---|
| MONTH                                                                              |            |                     |                                      |                 |   |                                                    |      |   |   | 4                                                                      |   |    | 6 | 12 |   |   |
| WEEK (Course 2 in parenthesis)                                                     |            |                     | 1 (5)                                |                 |   | 2(6)                                               | 3(7) |   |   | 4                                                                      | 8 | 12 |   |    |   |   |
| DAY                                                                                |            |                     | 1                                    | 3               | 5 | R<br>E<br>S<br>T<br><br>P<br>E<br>R<br>I<br>O<br>D | 1    | 3 | 5 | R<br>E<br>C<br>O<br>V<br>E<br>R<br>Y<br><br>P<br>E<br>R<br>I<br>O<br>D |   |    |   |    |   |   |
| Informed consent PART I <sup>1</sup>                                               | X          |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |   |
| Informed consent PART II                                                           |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |   |
| HLA A2 Typing <sup>2, 4</sup>                                                      | X          |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |   |
| HLA-A2.1/p53 aa264-272 tumor typing <sup>3, 4</sup>                                | X          |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |   |
| Medical history <sup>15</sup>                                                      |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |   |
| Serum pregnancy test <sup>6</sup>                                                  |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |   |
| Complete physical exam                                                             |            | X                   | X                                    |                 |   |                                                    |      | X |   |                                                                        |   |    | X | X  |   |   |
| Vital signs, weight <sup>7</sup>                                                   |            | X                   | X                                    | X               | X |                                                    |      | X | X |                                                                        | X |    | X | X  |   |   |
| Concurrent medication                                                              |            | X                   | X                                    | X               | X |                                                    |      | X | X |                                                                        | X |    | X | X  |   |   |
| Blood tests: CBC with Differential, Blood Chemistry & Coagulation                  |            | X                   | X                                    | X               | X |                                                    |      | X | X |                                                                        | X |    | X | X  |   |   |
| Urinalysis                                                                         |            | X                   | X                                    | X               | X |                                                    |      | X | X |                                                                        | X |    | X | X  |   |   |
| Cardiac functions <sup>8</sup>                                                     |            | X                   | X                                    | X               | X |                                                    |      | X | X |                                                                        | X |    |   |    |   |   |
| Pulmonary functions                                                                |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |   |
| Adverse event assessment <sup>9</sup>                                              |            | X                   | X                                    | X               | X |                                                    |      | X | X |                                                                        | X |    | X | X  |   |   |
| Tumor assessment <sup>10</sup>                                                     |            |                     | X <sup>14</sup>                      |                 |   |                                                    |      |   |   |                                                                        |   |    | X | X  |   |   |
| Survival Assessment                                                                |            |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    | X | X |
| PK <sup>11</sup> , INF $\gamma$ <sup>11, 15</sup> , TNF $\alpha$ <sup>11, 15</sup> |            |                     |                                      | X               |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |   |
| VEGF <sup>12</sup> , Fibronectin <sup>12</sup>                                     |            |                     | X                                    |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |   |
| Cell-mediated immune responses <sup>13</sup>                                       |            |                     | X                                    |                 |   |                                                    |      | X |   |                                                                        |   |    |   |    |   |   |
| Immunogenicity tests                                                               |            |                     |                                      | X <sup>15</sup> |   |                                                    |      |   |   |                                                                        |   |    | X |    |   |   |
| Cisplatin therapy                                                                  |            |                     | X                                    |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |   |
| Study drug administration                                                          |            |                     |                                      | X               | X |                                                    | X    | X | X |                                                                        |   |    |   |    |   |   |

<sup>1</sup>Authorization of the Part I Informed Consent is required before obtaining patients' blood and tumor samples for HLA-A2 blood typing and HLA-A2.1/p53 aa264-272 tumor typing. <sup>2</sup> Only patients with positive test result on HLA A2 blood typing will continue on the HLA-A2.1/p53 aa264-272 tumor typing. <sup>3</sup>Only patients with positive results on HLA A2 blood typing and HLA-A2.1/p53 aa264-272 tumor typing will continue on the further screening procedures and have the possibility of being enrolled in the study. <sup>4</sup>Any previous HLA A2 blood typing result, from serological or DNA-based typing, and HLA-A2.1/p53 aa264-272 tumor typing result can be used for screening. <sup>5</sup>Baseline 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. <sup>6</sup>Pregnancy test is for women with childbearing potential only. <sup>7</sup>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 the discharge, and body weight before the study treatment infusion on study treatment infusion day. <sup>8</sup>Patients are closely monitored for hypotension, arrhythmia, angina and myocardial infarction. At screening, patients who are  $\geq 50$  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. <sup>9</sup>Patients who have an on-going study drug-related serious adverse event 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. <sup>10</sup>Tumor response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. <sup>11</sup>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. INF $\gamma$ , TNF $\alpha$  assays are performed using the same samples and at the same schedule as PK. <sup>12</sup>VEGF and Fibronectin assays are performed only once at pre-treatment for the entire study. <sup>13</sup>Collect blood samples before dosing. Residual samples may be used by Sponsor for research studies of other biomarkers. <sup>14</sup>Not performed for the 2<sup>nd</sup> course of study treatment. <sup>15</sup>Using the PK blood sample.

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

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Principal Investigator's Signature

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Date

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Principal Investigator's Name (Print)

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## SYNOPSIS

**Sponsor:** Altor Bioscience Corporation

**Protocol#:** CA-ALT-801-02-09

**Study Drug Name:** Not applicable

### Study Treatment

**Active Ingredients:** ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein and cisplatin

**Study Type:** Interventional

**Study Phase:** Ib/II

**Protocol Title:** Phase Ib/II Study of ALT-801 with Cisplatin in Patients with Metastatic Melanoma

**Objectives:** The objectives of this study are to evaluate the safety, determine the Maximum-Tolerated Dose (MTD), and characterize the pharmacokinetic profile of ALT-801 given with cisplatin in patients who are chemotherapy naïve and have metastatic melanoma that is considered surgically incurable. We will also assess the anti-tumor responses of ALT-801 with cisplatin in this trial.

**Study Design:** This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-801 combined with cisplatin in patients who are chemotherapy naïve and have metastatic melanoma that is considered surgically incurable, who are serologically HLA-A2 positive and whose tumors present HLA-A2.1/p53 aa264-272 complexes. The study includes a dose escalation phase to determine the MTD and a two-stage expansion phase at the MTD. The dose escalation in this study is conducted using a traditional (3+3) dose escalation design. The two-stage expansion phase will be conducted at the MTD using a modified Simon two-stage design (1, 2). All enrolled patients will receive two courses of the treatment regimen. 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.

**Treatments:** Each treatment course consists of a 4-week regimen: one week of combined therapy with the study drug and cisplatin, a 9-day rest period, one week of monotherapy with the study drug ALT-801, and one week of recovery period. In the first treatment cycle, each enrolled patient will receive one dose of cisplatin at 70 mg/m<sup>2</sup> on day 1 and one dose of the study drug on day 3 and 5. In the second treatment cycle following a 9-day rest period, the enrolled patient will receive one dose of the study drug on day 1, 3, and 5. In total, patients will receive 5 doses of the study drug ALT-801 and 1 dose of cisplatin for a complete course of a 4-week treatment regimen.

One Course of The ALT-801-Cisplatin Regimen Treatment Schema is as follows:

|           | Week 1 (Cycle 1) |   |   |   |   | Week 2         | Week 3 (Cycle 2) |   |   |   |   | Week 4             |
|-----------|------------------|---|---|---|---|----------------|------------------|---|---|---|---|--------------------|
| Day       | 1                | 2 | 3 | 4 | 5 | Rest<br>Period | 1                | 2 | 3 | 4 | 5 | Recovery<br>Period |
| ALT-801   |                  |   | X |   | X |                | X                |   | X |   | X |                    |
| Cisplatin | X                |   |   |   |   |                |                  |   |   |   |   |                    |

The second course of study drug treatment starts at the 5<sup>th</sup> week after the initiation of the first course of treatment.

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 study drug and cisplatin will be administered by intravenous infusion into a central vein under the supervision of a qualified physician experienced in the use of anti-cancer agents including Proleukin<sup>®</sup> and cisplatin.

During the escalation phase of the study, the dose levels of the study drug and cisplatin are as follows:

| Cohort | ALT-801 Dose (mg/kg) | Cisplatin (mg/m <sup>2</sup> ) |
|--------|----------------------|--------------------------------|
| 1      | 0.04                 | 70                             |
| 2      | 0.06                 | 70                             |
| 3      | 0.08                 | 70                             |

**Dose Escalation:**

In this phase of the study, three patients will be enrolled per dose level. All patients will be monitored for any Dose Limiting Toxicity (DLT) for 7 weeks from the initiation of the first course of treatment. If one patient in a cohort experiences DLT, the enrollment of that dose level and each subsequent higher dose level will be expanded to include up to six patients. If 2 of 6 patients of a cohort experience DLT, subsequent enrollment at that dose level will be temporarily suspended and an assessment will be made whether the MTD has been reached. The dose escalation scheme will continue until the MTD is reached.

If more than two of six patients experience any DLT at the lowest dose level of the dose escalation, patient enrollment will be temporarily suspended. The sponsor, the Data Safety Monitoring Board and the principal investigators will meet to determine how to adjust downward the dose level of cisplatin and/or the study drug and how to proceed with the study.

A DLT is defined as any toxicity that results in study treatment discontinuation. Study treatment discontinuation due to patient's disease progression or patient's decision to withdraw from the study treatment without occurrence of any study treatment discontinuation event is not a DLT. The MTD is the dose level that is one level below the dose level at which two patients experience DLT, and at which fewer than 2 of 6 patients experiences DLT. If patient enrollment at the highest dose level is completed and less than 2 of 6 patients experiences DLT, this dose level is designated as the MTD.

- 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 (ORR = 5%; CBR = 20%) and an efficacy level of interest (ORR = 20%; CBR = 40%) will be selected. The sample size was driven by the parameter that had the larger sample size for each stage. An  $\alpha$  error rate of 5% and  $\beta$  error rate of 20% yielded a common set sample size of 13 patients for stage 1 and 30 patients for stage 2 (2). A total of 13 patients, including the number of patients already enrolled during the escalation phase, will be enrolled and evaluated in the first stage of the expansion phase at the MTD. An additional 30 assessable patients will then be enrolled and evaluated at the same dose level of the first stage if one or more ORs or four or more CBs are confirmed. Upon completion of the second stage, an observation of at least six ORs or 13 CBs would be sufficient to reject the null hypothesis of a lack of an effect of ALT-801 with cisplatin on OR and/or CB in favor of the alternative hypothesis that ALT-801 with cisplatin has a favorable effect on OR and/or CB.
- Stopping Rule:** If, at any time during the expansion phase of the study, 33% or more of the patients experience DLT, enrollment in this expansion cohort will be temporarily suspended. The sponsor, the Data Safety Monitoring Board and the principal investigators will meet to discuss how to proceed with future patient enrollment in the study.
- Evaluations:** Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug, and to evaluate the study drug induced cell-mediated immune response. The anti-tumor response will be evaluated for up to 12 weeks from the initiation of the first course of treatment. All patients who receive at least one dose of the study drug will be included in the anti-tumor response evaluation. Survival of all enrolled patients will be assessed at 6 and 12 months from the start of study treatment. 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 have metastatic melanoma that is considered surgically incurable, are chemotherapy naïve, who are serologically HLA-A2 positive and whose tumors present HLA-A2.1/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. Patients who have had prior systemic treatment with cytotoxic chemotherapy agents will be excluded.
- Sample Size:** There are three cohorts in this study. A total of up to 18 patients will be accrued to the initial dose escalation phase of the study. An additional 7 and 30 patients will be enrolled at the MTD in stage 1 and stage 2 of the expansion phase, respectively.

**Primary**

**Endpoints:**

For Stage I and II:

- (1) To evaluate the safety of the ALT-801-Cisplatin regimen.
- (2) To assess the objective response (OR) which includes CR and PR.
- (3) To assess the clinical benefit (CB) of the ALT-801-Cisplatin regimen which includes CR, PR and SD.

For Stage I only:

- (4) To determine the MTD of the ALT-801-Cisplatin regimen.

**Secondary**

**Endpoints:**

- (1) To assess the six-month and one-year survival rates.
- (2) To evaluate the immunogenicity and pharmacokinetic profile of ALT-801.

**Pharmacokinetic  
Analysis & Cell-  
Mediated Immune  
Responses:**

Blood samples for pharmacokinetic analysis of ALT-801 will be taken on the first dose of ALT-801 of each course of study treatment. On each sampling day, venous blood will be obtained at Time 0 (before the start of infusion), at 30 min (15 min after completion of drug infusion), and 1 hr, 3 hr, and 6 hr from Time 0 for the assessment of ALT-801 serum concentration. Non-compartmental and compartmental analyses will be conducted. Serum levels of INF $\gamma$  and TNF $\alpha$  will also be evaluated using the same blood samples and at the same schedule as PK analysis. Serum levels of Vascular Endothelial Growth Factor (VEGF) and Fibronectin will be assessed once at pre-treatment for the entire study. The cell-mediated immune responses will be evaluated once each treatment cycle in the pre-dosing blood samples of the first ALT-801 infusion.

**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 the assays for anti-ALT-801 and IL-2 neutralizing antibodies, will be collected at pre-dosing on the first ALT-801 infusion day and 8 weeks after the start of the first course of treatment.

**Anti-tumor  
Response**

**Evaluation:**

The initial anti-tumor response will be evaluated 8 weeks after the start of the first course of treatment. Patients who have at least stable disease from the two-course treatment will be further evaluated for anti-tumor responses to the study treatment at 12 weeks after the start of the first course of treatment. Objective Response will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (3). All measurements should be taken and recorded in metric notation using a ruler or calipers, or electronically. All baseline evaluations should be performed as closely as possible to the start of treatment and never more than 28 days before the start of 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-up. Imaging-

## 8. STUDY CALENDAR, CLINICAL PROCEDURES & TESTS

### 8.1 Study Calendar

| TESTS & PROCEDURES                                                                             | Pre Screen | Screen <sup>5</sup> | TREATMENT PERIOD<br>For Course 1 & 2 |                 |   |                                                    |      |   |   | FOLLOW-UP PERIOD                                                       |   |    |    |   |   |
|------------------------------------------------------------------------------------------------|------------|---------------------|--------------------------------------|-----------------|---|----------------------------------------------------|------|---|---|------------------------------------------------------------------------|---|----|----|---|---|
| MONTH                                                                                          |            |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   | 6  | 12 |   |   |
| WEEK (Course 2 in parenthesis)                                                                 |            |                     | 1 (5)                                |                 |   | 2(6)                                               | 3(7) |   |   | 4                                                                      | 8 | 12 |    |   |   |
| DAY                                                                                            |            |                     | 1                                    | 3               | 5 | R<br>E<br>S<br>T<br><br>P<br>E<br>R<br>I<br>O<br>D | 1    | 3 | 5 | R<br>E<br>C<br>O<br>V<br>E<br>R<br>Y<br><br>P<br>E<br>R<br>I<br>O<br>D |   |    |    |   |   |
| Informed consent PART I <sup>1</sup>                                                           | X          |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |    |   |   |
| Informed consent PART II                                                                       |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |    |   |   |
| HLA A2 Typing <sup>2, 4, 17</sup>                                                              | X          |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |    |   |   |
| HLA-A2.1/p53 aa264-272 tumor typing <sup>3, 4, 17</sup>                                        | X          |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |    |   |   |
| Medical history <sup>15</sup>                                                                  |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |    |   |   |
| Serum pregnancy test <sup>6</sup>                                                              |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |    |   |   |
| Complete physical exam                                                                         |            | X                   | X                                    |                 |   |                                                    | X    |   |   |                                                                        |   | X  | X  |   |   |
| Vital signs, weight <sup>7</sup>                                                               |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        |   | X  | X  |   |   |
| Concurrent medication <sup>16</sup>                                                            |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        |   | X  | X  |   |   |
| Blood tests: CBC with Differential, Blood Chemistry & Coagulation                              |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        |   | X  | X  |   |   |
| Urinalysis                                                                                     |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        |   | X  | X  |   |   |
| Cardiac functions <sup>8</sup>                                                                 |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        |   |    |    |   |   |
| Pulmonary functions <sup>17</sup>                                                              |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |    |   |   |
| Adverse event assessment <sup>9</sup>                                                          |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        |   | X  | X  |   |   |
| Tumor assessment <sup>10, 16</sup>                                                             |            | X <sup>14</sup>     |                                      |                 |   |                                                    |      |   |   |                                                                        |   | X  | X  |   |   |
| Survival Assessment <sup>16</sup>                                                              |            |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |    | X | X |
| PK <sup>11, 17</sup> , INF $\gamma$ <sup>11, 15, 17</sup> , TNF $\alpha$ <sup>11, 15, 17</sup> |            |                     |                                      | X               |   |                                                    |      |   |   |                                                                        |   |    |    |   |   |
| VEGF <sup>12, 17</sup> , Fibronectin <sup>12, 17</sup>                                         |            |                     | X                                    |                 |   |                                                    |      |   |   |                                                                        |   |    |    |   |   |
| Cell-mediated immune responses <sup>15, 17</sup>                                               |            |                     | X                                    |                 |   |                                                    | X    |   |   |                                                                        |   |    |    |   |   |
| Immunogenicity tests                                                                           |            |                     |                                      | X <sup>15</sup> |   |                                                    |      |   |   |                                                                        |   | X  |    |   |   |
| Cisplatin therapy                                                                              |            |                     | X                                    |                 |   |                                                    |      |   |   |                                                                        |   |    |    |   |   |
| Study drug administration                                                                      |            |                     |                                      | X               | X | X                                                  | X    | X |   |                                                                        |   |    |    |   |   |

<sup>1</sup>Authorization of the Part I Informed Consent is required before obtaining patients' blood and tumor samples for HLA-A2 blood typing and HLA-A2.1/p53 aa264-272 tumor typing. <sup>2</sup>Only patients with positive test result on HLA A2 blood typing will continue on the HLA-A2.1/p53 aa264-272 tumor typing. <sup>3</sup>Only patients with positive results on HLA A2 blood typing and HLA-A2.1/p53 aa264-272 tumor typing will continue on the further screening procedures and have the possibility of being enrolled in the study. <sup>4</sup>Any previous HLA A2 blood typing result, from serological or DNA-based typing, and HLA-A2.1/p53 aa264-272 tumor typing result can be used for screening. <sup>5</sup>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. <sup>6</sup>Pregnancy test is for women with childbearing potential only. <sup>7</sup>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 the discharge, and body weight before the study treatment infusion on study treatment infusion day. <sup>8</sup>Patients are closely monitored for hypotension, arrhythmia, angina and myocardial infarction. At screening, patients who are  $\geq 50$  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. The stress test is not required for repeated treatment; EKG will be performed at the start of each treatment cycle. <sup>9</sup>Patients who have an on-going study drug-related serious adverse event 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. <sup>10</sup>Tumor response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. <sup>11</sup>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. INF $\gamma$ , TNF $\alpha$  assays are performed using the same samples and at the same schedule as PK. <sup>12</sup>VEGF and Fibronectin assays are performed only once at pre-treatment for the entire study. <sup>13</sup>Collect blood samples before dosing. Residual samples may be used by Sponsor for research studies of other biomarkers. <sup>14</sup>Not required for repeated treatment unless last scans are performed >28 days. <sup>15</sup>Using the PK blood sample. <sup>16</sup>Information about tumor assessment & other therapies received after completion of study treatment will be collected if available; <sup>17</sup>Not required for repeated treatment.

## CLINICAL STUDY PROTOCOL

**Protocol Number:** CA-ALT-801-02-09

**Protocol Title:** Phase Ib/II Study of ALT-801 with Cisplatin in  
Patients with Metastatic Melanoma

**Date of Protocol:**

Version # 01 September 18, 2009

Version # 02 August 18, 2010

Version # 03 February 10, 2011

**Sponsor Contact:**



Hing C. Wong, Ph.D.

Altor Bioscience Corporation.

Miramar, Florida 33025

Telephone: 954-443-8600

Safety Data Fax: 954-443-8602

## INVESTIGATOR SIGNATURE PAGE

**Protocol Number:** CA-ALT-801-02-09

**Protocol Title:** Phase Ib/II Study of ALT-801-with Cisplatin in Patients with Metastatic Melanoma

**Date of Protocol:**

|              |                    |
|--------------|--------------------|
| Version # 01 | September 18, 2009 |
| Version # 02 | August 18, 2010    |
| Version # 03 | February 10, 2011  |

**Sponsor Contact:**



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

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

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

---

Principal Investigator's Signature

---

Date

---

Principal Investigator's Name (Print)

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## SYNOPSIS

**Sponsor:** Altor Bioscience Corporation

**Protocol#:** CA-ALT-801-02-09

**Study Drug Name:** Not applicable

### Study Treatment

**Active Ingredients:** ALT-801 (c264scTCR-IL2), recombinant humanized, soluble single-chain TCR-cytokine fusion protein and cisplatin

**Study Type:** Interventional

**Study Phase:** Ib/II

**Protocol Title:** Phase Ib/II Study of ALT-801 with Cisplatin in Patients with Metastatic Melanoma

**Objectives:** The objectives of this study are to evaluate the safety, determine the Maximum-Tolerated Dose (MTD), and characterize the pharmacokinetic profile of ALT-801 given with cisplatin in patients who are chemotherapy naïve and have metastatic melanoma that is considered surgically incurable. We will also assess the anti-tumor responses of ALT-801 with cisplatin in this trial.

**Study Design:** This is a Phase Ib/II, open-label, multi-center, competitive enrollment and dose-escalation study of ALT-801 combined with cisplatin in patients who are chemotherapy naïve and have metastatic melanoma that is considered surgically incurable, who are serologically HLA-A2 positive and whose tumors present HLA-A2.1/p53 aa264-272 complexes. The study includes a dose escalation phase to determine the MTD and a two-stage expansion phase at the MTD. The dose escalation in this study is conducted using a traditional (3+3) dose escalation design. The two-stage expansion phase will be conducted at the MTD using a modified Simon two-stage design (1, 2). All enrolled patients will receive two courses of the treatment regimen. 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.

**Treatments:** Each treatment course consists of a 4-week regimen: one week of combined therapy with the study drug and cisplatin, a 9-day rest period, one week of monotherapy with the study drug ALT-801, and one week of recovery period. In the first treatment cycle, each enrolled patient will receive one dose of cisplatin at 70 mg/m<sup>2</sup> on day 1 and one dose of the study drug on day 3 and 5. In the second treatment cycle following a 9-day rest period, the enrolled patient will receive one dose of the study drug on day 1, 3, and 5. In total, patients will receive 5 doses of the study drug ALT-801 and 1 dose of cisplatin for a complete course of a 4-week treatment regimen.

One Course of The ALT-801-Cisplatin Regimen Treatment Schema is as follows:

|           | Week 1 (Cycle 1) |   |   |   |   | Week 2         | Week 3 (Cycle 2) |   |   |   |   | Week 4             |
|-----------|------------------|---|---|---|---|----------------|------------------|---|---|---|---|--------------------|
| Day       | 1                | 2 | 3 | 4 | 5 | Rest<br>Period | 1                | 2 | 3 | 4 | 5 | Recovery<br>Period |
| ALT-801   |                  |   | X |   | X |                | X                |   | X |   | X |                    |
| Cisplatin | X                |   |   |   |   |                |                  |   |   |   |   |                    |

The second course of study drug treatment starts at the 5<sup>th</sup> week after the initiation of the first course of treatment.

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 study drug and cisplatin will be administered by intravenous infusion into a central vein under the supervision of a qualified physician experienced in the use of anti-cancer agents including Proleukin<sup>®</sup> and cisplatin.

During the escalation phase of the study, the dose levels of the study drug and cisplatin are as follows:

| Cohort | ALT-801 Dose (mg/kg) | Cisplatin (mg/m <sup>2</sup> ) |
|--------|----------------------|--------------------------------|
| 1      | 0.04                 | 70                             |
| 2      | 0.06                 | 70                             |
| 3      | 0.08                 | 70                             |
| 4      | 0.10                 | 70                             |
| 5      | 0.12                 | 70                             |

**Dose Escalation:**

In this phase of the study, three patients will be enrolled per dose level. All patients will be monitored for any Dose Limiting Toxicity (DLT) for 7 weeks from the initiation of the first course of treatment. If one patient in a cohort experiences DLT, the enrollment of that dose level and each subsequent higher dose level will be expanded to include up to six patients. If 2 of 6 patients of a cohort experience DLT, subsequent enrollment at that dose level will be temporarily suspended and an assessment will be made whether the MTD has been reached. The dose escalation scheme will continue until the MTD is reached.

If more than two of six patients experience any DLT at the lowest dose level of the dose escalation, patient enrollment will be temporarily suspended. The sponsor, the Data Safety Monitoring Board and the principal investigators will meet to determine how to adjust downward the dose level of cisplatin and/or the study drug and how to proceed with the study.

A DLT is defined as any toxicity that results in study treatment discontinuation. Study treatment discontinuation due to patient's disease progression or patient's decision to withdraw from the study treatment without occurrence of any study treatment discontinuation event is not a DLT. The MTD is the dose level that is one level below the dose level at which two patients experience DLT, and at which fewer than 2 of 6 patients experiences DLT. If patient enrollment at the highest dose level is

completed and less than 2 of 6 patients experiences DLT, this dose level is designated as the MTD.

**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 (ORR = 5%; CBR = 20%) and an efficacy level of interest (ORR = 20%; CBR = 40%) will be selected. The sample size was driven by the parameter that had the larger sample size for each stage. An  $\alpha$  error rate of 5% and  $\beta$  error rate of 20% yielded a common set sample size of 13 patients for stage 1 and 30 patients for stage 2 (2). A total of 13 patients, including the number of patients already enrolled during the escalation phase, will be enrolled and evaluated in the first stage of the expansion phase at the MTD. An additional 30 assessable patients will then be enrolled and evaluated at the same dose level of the first stage if one or more ORs or four or more CBs are confirmed. Upon completion of the second stage, an observation of at least six ORs or 13 CBs would be sufficient to reject the null hypothesis of a lack of an effect of ALT-801 with cisplatin on OR and/or CB in favor of the alternative hypothesis that ALT-801 with cisplatin has a favorable effect on OR and/or CB.

**Stopping Rule:** If, at any time during the expansion phase of the study, 33% or more of the patients experience DLT, enrollment in this expansion cohort will be temporarily suspended. The sponsor, the Data Safety Monitoring Board and the principal investigators will meet to discuss how to proceed with future patient enrollment in the study.

**Evaluations:** Patients will be evaluated for clinical toxicities during the treatment. Patients' blood samples will be collected to assess the pharmacokinetic profile and immunogenicity of the study drug, and to evaluate the study drug induced cell-mediated immune response. The anti-tumor response will be evaluated for up to 12 weeks from the initiation of the first course of treatment. All patients who receive at least one dose of the study drug will be included in the anti-tumor response evaluation. Survival of all enrolled patients will be assessed at 6 and 12 months from the start of study treatment. 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 have metastatic melanoma that is considered surgically incurable, are chemotherapy naïve, who are serologically HLA-A2 positive and whose tumors present HLA-A2.1/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. Patients who have had prior systemic treatment with cytotoxic chemotherapy agents will be excluded.

**Sample Size:** There are five cohorts in this study. A total of up to 30 patients will be accrued to the initial dose escalation phase of the study. An additional 7-10 and 30 patients will be enrolled at the MTD in stage 1 and stage 2 of the expansion phase, respectively.

**Primary  
Endpoints:**

For Stage I and II:

- (1) To evaluate the safety of the ALT-801-Cisplatin regimen.
- (2) To assess the objective response (OR) which includes CR and PR.
- (3) To assess the clinical benefit (CB) of the ALT-801-Cisplatin regimen which includes CR, PR and SD.

For Stage I only:

- (4) To determine the MTD of the ALT-801-Cisplatin regimen.

**Secondary  
Endpoints:**

- (1) To assess the six-month and one-year survival rates.
- (2) To evaluate the immunogenicity and pharmacokinetic profile of ALT-801.

**Pharmacokinetic  
Analysis & Cell-  
Mediated Immune  
Responses:**

Blood samples for pharmacokinetic analysis of ALT-801 will be taken on the first dose of ALT-801 of each course of study treatment. On each sampling day, venous blood will be obtained at Time 0 (before the start of infusion), at 30 min (15 min after completion of drug infusion), and 1 hr, 3 hr, and 6 hr from Time 0 for the assessment of ALT-801 serum concentration. Non-compartmental and compartmental analyses will be conducted. Serum levels of IFN $\gamma$  and TNF $\alpha$  will also be evaluated using the same blood samples and at the same schedule as PK analysis. Serum levels of Vascular Endothelial Growth Factor (VEGF) and Fibronectin will be assessed once at pre-treatment for the entire study. The cell-mediated immune responses will be evaluated once each treatment cycle in the pre-dosing blood samples of the first ALT-801 infusion.

**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 the assays for anti-ALT-801 and IL-2 neutralizing antibodies, will be collected at pre-dosing on the first ALT-801 infusion day and 8 weeks after the start of the first course of treatment.

**Anti-tumor  
Response  
Evaluation:**

The initial anti-tumor response will be evaluated 8 weeks after the start of the first course of treatment. Patients who have at least stable disease from the two-course treatment will be further evaluated for anti-tumor responses

to the study treatment at 12 weeks after the start of the first course of treatment. Objective Response will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (3). All measurements should be taken and recorded in metric notation using a ruler or calipers, or electronically. All baseline evaluations should be performed as closely as possible to the start of treatment and never more than 28 days before the start of 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-up. 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.

**Survival****Assessment:**

Survival of all enrolled patients at 6 and 12 months from the start of study treatment will be evaluated.

**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 3.0 (CTCAEv3.0), 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 and/or email within 24 hours of 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 via phone, fax and/or email within 24 hours of its learning of the event 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. The study centers should report the other adverse events to the sponsor following the guidelines defined in the study protocol. All study drug related AEs that are both serious and unexpected will be reported to the FDA in an expedited manner in accordance with 21 CFR §312.32.

**Repeated treatment:** A patient who: (1) has achieved at least stable disease in the RECIST criteria-based tumor assessment, (2) has consented to receive two additional courses of treatment and (3) did not experience any serious adverse events with the study treatment regimen during the previous two courses of treatment, is eligible to receive two additional courses consisting of two cycles per course.

**Statistical Plan:**

All AEs will be tabulated and examined for each cohort. All safety and pharmacokinetic data will be evaluated for each cohort. 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 <sup>5</sup> | TREATMENT PERIOD<br>For Course 1 & 2 |                 |   |                                                    |      |   |   | FOLLOW-UP PERIOD                                                       |   |    |   |    |   |
|------------------------------------------------------------------------------|------------|---------------------|--------------------------------------|-----------------|---|----------------------------------------------------|------|---|---|------------------------------------------------------------------------|---|----|---|----|---|
| MONTH                                                                        |            |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    | 6 | 12 |   |
| WEEK (Course 2 in parenthesis)                                               |            |                     | 1 (5)                                |                 |   | 2(6)                                               | 3(7) |   |   | 4                                                                      | 8 | 12 |   |    |   |
| DAY                                                                          |            |                     | 1                                    | 3               | 5 | R<br>E<br>S<br>T<br><br>P<br>E<br>R<br>I<br>O<br>D | 1    | 3 | 5 | R<br>E<br>C<br>O<br>V<br>E<br>R<br>Y<br><br>P<br>E<br>R<br>I<br>O<br>D |   |    |   |    |   |
| Informed consent PART I <sup>1</sup>                                         | X          |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |
| Informed consent PART II                                                     |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |
| HLA A2 Typing <sup>2, 4, 17</sup>                                            | X          |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |
| HLA-A2.1/p53 aa264-272 tumor typing <sup>3, 4, 17</sup>                      | X          |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |
| Medical history <sup>15</sup>                                                |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |
| Serum pregnancy test <sup>6</sup>                                            |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |
| Complete physical exam                                                       |            | X                   | X                                    |                 |   |                                                    | X    |   |   |                                                                        |   | X  | X |    |   |
| Vital signs, weight <sup>7</sup>                                             |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        | X | X  | X |    |   |
| Concurrent medication <sup>16</sup>                                          |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        | X | X  | X |    |   |
| Blood tests: CBC with Differential, Blood Chemistry & Coagulation            |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        | X | X  | X |    |   |
| Urinalysis                                                                   |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        | X | X  | X |    |   |
| Cardiac functions <sup>8</sup>                                               |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        | X |    |   |    |   |
| Pulmonary functions <sup>17</sup>                                            |            | X                   |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |
| Adverse event assessment <sup>9</sup>                                        |            | X                   | X                                    | X               | X |                                                    | X    | X | X |                                                                        | X | X  | X |    |   |
| Tumor assessment <sup>10, 16</sup>                                           |            | X <sup>14</sup>     |                                      |                 |   |                                                    |      |   |   |                                                                        |   | X  | X |    |   |
| Survival Assessment <sup>16</sup>                                            |            |                     |                                      |                 |   |                                                    |      |   |   |                                                                        |   |    |   | X  | X |
| PK <sup>11, 17</sup> , IFN <sup>11, 15, 17</sup> , TNF <sup>11, 15, 17</sup> |            |                     |                                      | X               |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |
| VEGF <sup>12, 17</sup> , Fibronectin <sup>12, 17</sup>                       |            |                     | X                                    |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |
| Cell-mediated immune responses <sup>13, 17</sup>                             |            |                     | X                                    |                 |   |                                                    | X    |   |   |                                                                        |   |    |   |    |   |
| Immunogenicity tests                                                         |            |                     |                                      | X <sup>15</sup> |   |                                                    |      |   |   |                                                                        |   | X  |   |    |   |
| Cisplatin therapy                                                            |            |                     | X                                    |                 |   |                                                    |      |   |   |                                                                        |   |    |   |    |   |
| Study drug administration                                                    |            |                     |                                      | X               | X | X                                                  | X    | X | X |                                                                        |   |    |   |    |   |

<sup>1</sup> Authorization of the Part I Informed Consent is required before obtaining patients' blood and tumor samples for HLA-A2 blood typing and HLA-A2.1/p53 aa264-272 tumor typing. <sup>2</sup> Only patients with positive test result on HLA A2 blood typing will continue on the HLA-A2.1/p53 aa264-272 tumor typing. <sup>3</sup> Only patients with positive results on HLA A2 blood typing and HLA-A2.1/p53 aa264-272 tumor typing will continue on the further screening procedures and have the possibility of being enrolled in the study. <sup>4</sup> Any previous HLA A2 blood typing result, from serological or DNA-based typing, and HLA-A2.1/p53 aa264-272 tumor typing result can be used for screening. <sup>5</sup> 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. <sup>6</sup> Pregnancy test is for women with childbearing potential only. <sup>7</sup> 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 the discharge, and body weight before the study treatment infusion on study treatment infusion day. <sup>8</sup> Patients are closely monitored for hypotension, arrhythmia, angina and myocardial infarction. At screening, patients who are  $\geq 50$  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. The stress test is not required for repeated treatment; EKG will be performed at the start of each treatment cycle. <sup>9</sup> Patients who have an on-going study drug-related serious adverse event 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. <sup>10</sup> Tumor response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. <sup>11</sup> 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. IFN $\gamma$ , TNF $\alpha$  assays are performed using the same samples and at the same schedule as PK. <sup>12</sup> VEGF and Fibronectin assays are performed only once at pre-treatment for the entire study. <sup>13</sup> Collect blood samples before dosing. Residual samples may be used by Sponsor for research studies of other biomarkers. <sup>14</sup> Not required for repeated treatment unless last scans are performed >28 days. <sup>15</sup> Using the PK blood sample. <sup>16</sup> Information about tumor assessment & other therapies received after completion of study treatment will be collected if available; <sup>17</sup> Not required for repeated treatment.