**NCI Protocol #:** CITN06-ALT-803

**Local Protocol #:** CA-ALT-803-01-13

**TITLE:** A Phase 1/2 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma

(Advanced Melanoma – ICD-10053571)

**Sponsor:**

Altor BioScience CORPORATION
Hing C. Wong, Ph.D.
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**Coordinating Center:** Cancer Immunotherapy Trials Network, Fred Hutchinson Cancer Research Center

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## INVESTIGATOR SIGNATURE PAGE

**Protocol Number:** **CA-ALT-803-01-13**

**Protocol Title:** A Phase 1/2 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma

**Date of Protocol:**
Version # 01 April 8, 2013

**Sponsor Contact:**

Altor BioScience CORPORATION
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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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**Study Coordinator: N/A**

**Responsible Research Nurse: N/A**

**Responsible Data Manager: N/A**

**NCI-Supplied Agent(s): N/A**

**Other Agent(s):** ALT-803: a "recombinant human superagonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D:IL-15RαSu/IgG1 Fc complex) NSC#: TBD

| Investigational Agent | IND# | IND Sponsor |
|---|---|---|
| ALT-803 | TBD | Altor Bioscience Corporation |

**Protocol Type / Version # / Version Date:** Original/Version 1/April 8, 2013

**SCHEMA**

| Regimen Description | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-Medications: Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| ALT-803 | *1 dose of antipyretic medication within 30 min of ALT-803 administration<br><br>*1 dose of antipyretic medication 4 h after ALT-803 administration | 0.003 mg/kg<br>or<br>0.006 mg/kg<br>or<br>0.01 mg/kg<br>or<br>0.02 mg/kg<br>or<br>0.03 mg/kg | IV | D1, W1<br>D1, W2<br>D1, W3<br>D1, W4 | 42 days<br>(4 weeks on, 2 weeks off)<br>With up to 4 cycles in the absence of unacceptable toxicity and disease progression |

*Non-steroidal anti-inflammatory medication such as acetaminophen, ibuprofen, Naproxen or aspirin may be given per physician discretion. Not to exceed standard maximum thresholds:

Acetaminophen: not to exceed 3000 mg (3 g) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours
Aspirin: not to exceed 3800 mg in 24 hours

| Dose Escalation Schedule | |
|---|---|
| **Dose Level** | **Dose of ALT-803** |
| **Level -1** | 0.001 mg/kg (only if the first level is too toxic) |
| Level 1 | 0.003 mg/kg |
| Level 2 | 0.006 mg/kg |
| Level 3 | 0.01 mg/kg |
| Level 4 | 0.02 mg/kg |
| Level 5 | 0.03 mg/kg |

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 to 30 days before start of protocol therapy, as indicated in the study calendar, except for pregnancy testing, which must be performed within 48 hours prior to initial ALT-803 administration. Scans and x-rays must be performed within 30 days before the start of therapy. In the event that the patient's condition is changing, laboratory evaluations should be repeated within 24 hours before initiating the next cycle of therapy. Please refer to the study calendar below for specific timing of required evaluations.

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | **Cycle 2 (Weeks)** | | | | | | **F/U 14 days post last injection** | **6 Month F/U Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Within 30 d | Within 14 d | W1 D1 | W2 D8 | W3 D15 | W4 D22 | W5 D29 | W6 D36 | W1 D1 | W2 D8 | W3 D15 | W4 D22 | W5 D29 | W6 D36 | | |
| **ALT-803*(A)** | | | X | X | X | X | | | X | X | X | X | | | | |
| Informed consent | X | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | |
| Concomitant meds | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical exam | | X | X | X | X | X | X | | X | X | X | X | X | | X | X |
| Vital signs | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | |
| Weight | X | X | X | | X | | X | X | X | X | | X | | X | X | X |
| Performance status | | X | X | | | | | | X | | | | | | X | X |
| CBC w/diff, plts | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| PT/PTT | | X | | | | | | | | | | | | | | |
| Serum chemistry[a] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Antinuclear antibody (ANA) | X | | | | | | | | X | | | | | | | X |
| Electrocardiogram (ECG)[b] | | | X[b] X[b] | | | | | X[b] | X[b] X[b] | | | | | X[b] | | |
| ECHO (as indicated) | X | | | | | | | | | | | | | | | |
| Adverse event evaluation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tumor measurements[c] | X | Tumor measurements are repeated every 8 ± 1 week and 16 ± 2 weeks | | | | | | | | | | | | | | X |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CT, MRI, or PET of chest, abdomen, pelvis[d] | X | Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | | | |
| CT or MRI Brain[d] [as indicated for symptoms only] | X | If negative at baseline, to be repeated only with symptoms | | | | | | | | | | | | | | X |
| Radiologic evaluation by RECIST 1.1 | X | Radiologic measurements should be performed every 8 ± 1 week and 16 ± 2 weeks | | | | | | | | | | | | | | X |
| B-HCG[e] | | | X | | | | | | | | | | | | | |
| EBV serostatus | X | | | | | | | | | | | | | | | |
| CMV serostatus | X | | | | | | | | | | | | | | | |
| Thyroid studies: TSH, T4 | X | | | | | | | | | | | | | | | X |
| PK | | | X | | | | | | X | | | | | | | |
| WB Immunophenotyping[g] | | | X | X | X | X | X | | X | | X | | X | | | |
| IFN-γ ELISPOT[g] | | | X | | | | X | | X | | | | X | | | |
| NK-cell function[g] | | | X | | | | X | | X | | | | X | | | |
| Plasma cytokines[g] | | | X | | | | X | | X | | | | X | | | |
| Serum Ab to ALT-803[g] | | | X | | | | | | X | | | | | | X | |
| PBMC | | | X | | | | X | | X | | | | X | | | X |
| Serum | | | X | | | | X | | X | | | | X | | | |

Abbreviations: Ab, antibodies; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; PPT, partial thromboplastin time; PT, prothrombin time

*(A), Agent

[a] Blood chemistries include: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide ($CO_2$), albumin, total bilirubin, phosphorus, alkaline phosphatase, aspartate transaminae (AST), and alanine transaminase (ALT)

[b] ECGs are to be done before ALT-803 injections on Day 1 and 6 hours after the first ALT-803 injection (Day1) of all treatment cycles. In addition an ECG is to be done at the end of treatment, *i.e.,* end of cycle 1, or after subsequent cycles have been completed.

[c] baseline tumor assessment scans should be done 1 to 30 days before beginning treatment.

[d] CT, MRI, or PET is acceptable for imaging assessment purposes

[e] Pregnancy test may be done up to 48 hours before ALT-803 administration

[f] See pharmacokinetic flow sheet for specific draw times

[g] Blood for WB Immunophenotyping, IFN-γ ELISPOT, NK-cell function, plasma cytokines, and serum Ab to ALT-803 must be drawn **before** the patient receives ALT-803 injections on Days 1, 8, 15 and 22 of each treatment cycle.

**NCI Protocol #:** CITN06-ALT-803

**Local Protocol #:** CA-ALT-803-01-13

**TITLE:** A Phase 1/2 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma

(Advanced Melanoma – ICD-10053571)

**Sponsor:**

Altor BioScience CORPORATION
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***Principal Investigator:**
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## INVESTIGATOR SIGNATURE PAGE

**Protocol Number:** **CA-ALT-803-01-13**

**Protocol Title:** A Phase 1/2 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma

**Date of Protocol:**
Version # 01 April 8, 2013
Version # 02 May 6, 2013

**Sponsor Contact:**

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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)

**Statistician:**
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**Study Coordinator: N/A**

**Responsible Research Nurse: N/A**

**Responsible Data Manager: N/A**

**NCI-Supplied Agent(s): N/A**

**Other Agent(s):** ALT-803: a "recombinant human superagonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D:IL-15RαSu/IgG1 Fc complex) NSC#: TBD

| Investigational Agent | IND# | IND Sponsor |
|---|---|---|
| ALT-803 | 118280 | Altor Bioscience Corporation |

**Protocol Type / Version # / Version Date:** Version 2/May 6, 2013

**SCHEMA**

| Regimen Description | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-Medications: Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| ALT-803 | *1 dose of antipyretic medication within 30 min of ALT-803 administration<br><br>*1 dose of antipyretic medication 4 h after ALT-803 administration | 0.003 mg/kg<br>or<br>0.006 mg/kg<br>or<br>0.01 mg/kg<br>or<br>0.02 mg/kg<br>or<br>0.03 mg/kg | IV | D1, W1<br>D1, W2<br>D1, W3<br>D1, W4 | 42 days<br>(4 weeks on, 2 weeks off)<br>With up to 4 cycles in the absence of unacceptable toxicity and disease progression |

*Non-steroidal anti-inflammatory medication including agents such as acetaminophen, ibuprofen, or Naproxen may be given per physician discretion. Not to exceed standard maximum thresholds, for example:

Acetaminophen: not to exceed 3000 mg (3 g) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours

| Dose Escalation Schedule | |
|---|---|
| **Dose Level** | **Dose of ALT-803** |
| **Level -1** | 0.001 mg/kg (only if the first level is too toxic) |
| Level 1 | 0.003 mg/kg |
| Level 2 | 0.006 mg/kg |
| Level 3 | 0.01 mg/kg |
| Level 4 | 0.02 mg/kg |
| Level 5 | 0.03 mg/kg |

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 to 30 days before start of protocol therapy, as indicated in the study calendar, except for pregnancy testing, which must be performed within 48 hours prior to initial ALT-803 administration. Scans and x-rays must be performed within 30 days before the start of therapy. In the event that the patient's condition is changing, laboratory evaluations should be repeated within 24 hours before initiating the next cycle of therapy. Please refer to the study calendar below for specific timing of required evaluations.

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | **Cycle 2 (Weeks)** | | | | | | **F/U 14 days post last injection** | **6 Month F/U Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Within 30 d | Within 14 d | W1 D1 | W2 D8 | W3 D15 | W4 D22 | W5 D29 | W6 D36 | W1 D1 | W2 D8 | W3 D15 | W4 D22 | W5 D29 | W6 D36 | | |
| **ALT-803*(A)** | | | X | X | X | X | | | X | X | X | X | | | | |
| Informed consent | X | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | |
| Concomitant meds | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical exam[#] | | X | X | X | X | X | X | | X | X | X | X | X | | X | X |
| Vital signs with oxygen saturation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | |
| Weight | X | X | X | | X | | X | X | X | X | | X | | X | X | X |
| Performance status | | X | X | | | | | | X | | | | | | X | X |
| CBC w/diff, plts | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| PT/PTT | | X | | | | | | | | | | | | | | |
| Serum chemistry[a] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Antinuclear antibody (ANA) | X | | | | | | | | X | | | | | | | X |
| Electrocardiogram (ECG)[b] | | | X[b] X[b] | | | | | X[b] | X[b] X[b] | | | | | X[b] | | |
| ECHO (as indicated) | X | | | | | | | | | | | | | | | |
| Pulmonary function test (spirometry) | X | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adverse event evaluation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tumor measurements[c] | X | Tumor measurements are repeated every 8 ± 1 week and 16 ± 2 weeks | | | | | | | | | | | | | | X |
| CT, MRI, or PET of chest, abdomen, pelvis[d] | X | Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | | | |
| CT or MRI Brain[d] [as indicated for symptoms only] | X | If negative at baseline, to be repeated only with symptoms | | | | | | | | | | | | | | X |
| Radiologic evaluation by RECIST 1.1 | X | Radiologic measurements should be performed every 8 ± 1 week and 16 ± 2 weeks | | | | | | | | | | | | | | X |
| B-HCG[e] | | | X | | | | | | | | | | | | | |
| EBV serostatus | X | | | | | | | | | | | | | | | |
| CMV serostatus | X | | | | | | | | | | | | | | | |
| Thyroid studies: TSH, T4 | X | | | | | | | | | | | | | | | X |
| PK | | | X | | | | | | X | | | | | | | |
| WB Immunophenotyping[g] | | | X | X | X | X | X | | X | | X | | X | | | |
| IFN-γ ELISPOT[g] | | | X | | | | X | | X | | | | X | | | |
| NK-cell function[g] | | | X | | | | X | | X | | | | X | | | |
| Plasma cytokines[g] | | | X | | | | X | | X | | | | X | | | |
| Serum Ab to ALT-803[g] | | | X | | | | | | X | | | | | | X | |
| PBMC | | | X | | | | X | | X | | | | X | | | X |
| Serum | | | X | | | | X | | X | | | | X | | | |

Abbreviations: Ab, antibodies; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; PPT, partial thromboplastin time; PT, prothrombin time

*(A), Agent

[#] Physical exam must always include neurological assessment. In addition, all patients will have formal ophthalmologic testing prior to starting therapy and repeated if clinically indicated.

[a] Blood chemistries include: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide ($CO_2$), albumin, total bilirubin, phosphorus, alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT)

[b] ECGs are to be done before ALT-803 injections on Day 1 and 4, 12 and 24 hours post-dose. ECGs are to be repeated before and at 4 hours (the end of the outpatient observation period) following each subsequent dose.

[c] Baseline tumor assessment scans should be done 1 to 30 days before beginning treatment.

[d] CT, MRI, or PET is acceptable for imaging assessment purposes

[e] Pregnancy test may be done up to 48 hours before ALT-803 administration

[f] See pharmacokinetic flow sheet for specific draw times

[g] Blood for WB Immunophenotyping, IFN-γ ELISPOT, NK-cell function, plasma cytokines, and serum Ab to ALT-803 must be drawn **before** the patient receives ALT-803 injections on Days 1, 8, 15 and 22 of each treatment cycle.

**NCI Protocol #:** CITN06-ALT-803

**Local Protocol #:** CA-ALT-803-01-13

**TITLE:** A Phase 1/2 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma

(Advanced Melanoma – ICD-10053571)

**Sponsor:**

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**Coordinating Center:** Cancer Immunotherapy Trials Network, Fred Hutchinson Cancer Research Center

***Principal Investigator:**
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## INVESTIGATOR SIGNATURE PAGE

**Protocol Number:** **CA-ALT-803-01-13**

**Protocol Title:** A Phase 1/2 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma

**Date of Protocol:**

| | |
|---|---|
| Version # 01 | April 8, 2013 |
| Version # 02 | May 6, 2013 |
| Version # 03 | July 26, 2013 |

**Sponsor Contact:**

Altor BioScience CORPORATION
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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) _____

**Statistician:**
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Fax: (206) 667-4378
zoe@fhcrc.org

**Study Coordinator: N/A**

**Responsible Research Nurse: N/A**

**Responsible Data Manager: N/A**

**NCI-Supplied Agent(s): N/A**

**Other Agent(s):** ALT-803: a "recombinant human superagonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D:IL-15RαSu/IgG1 Fc complex) NSC#: TBD

| Investigational Agent | IND# | IND Sponsor |
|---|---|---|
| ALT-803 | 118280 | Altor Bioscience Corporation |

**Protocol Type / Version # / Version Date:** Version 3/July 26, 2013

**SCHEMA**

| Regimen Description | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-Medications: Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| ALT-803 | *1 dose of antipyretic medication within 30 min of ALT-803 administration<br><br>*1 dose of antipyretic medication 4 h after ALT-803 administration | 0.001 mg/kg<br>or<br>0.003 mg/kg<br>or<br>0.006 mg/kg<br>or<br>0.01 mg/kg<br>or<br>0.02 mg/kg<br>or<br>0.03 mg/kg | IV | D1, W1<br>D1, W2<br>D1, W3<br>D1, W4 | 42 days<br>(4 weeks on, 2 weeks off)<br>With up to 4 cycles in the absence of unacceptable toxicity and disease progression |

*Non-steroidal anti-inflammatory medication including agents such as acetaminophen, ibuprofen, or Naproxen may be given per physician discretion. Not to exceed standard maximum thresholds, for example:

Acetaminophen: not to exceed 3000 mg (3 g) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours

| Dose Escalation Schedule | |
|---|---|
| **Dose Level** | **Dose of ALT-803** |
| Level -1 | 0.0005 mg/kg (only if the first level is too toxic) |
| Level 1 | 0.001 mg/kg |
| Level 2 | 0.003 mg/kg |
| Level 3 | 0.006 mg/kg |
| Level 4 | 0.01 mg/kg |
| Level 5 | 0.02 mg/kg |
| Level 6 | 0.03 mg/kg |

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 to 30 days before start of protocol therapy, as indicated in the study calendar, except for pregnancy testing, which must be performed within 48 hours prior to initial ALT-803 administration. Scans and x-rays must be performed within 30 days before the start of therapy. In the event that the patient's condition is changing, laboratory evaluations should be repeated within 24 hours before initiating the next cycle of therapy. Please refer to the study calendar below for specific timing of required evaluations.

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | **Cycle 2 (Weeks)** | | | | | | **F/U 14 days post last injection** | **6 Month F/U Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Within 30 d | Within 14 d | W1 D1 | W2 D8 | W3 D15 | W4 D22 | W5 D29 | W6 D36 | W1 D1 | W2 D8 | W3 D15 | W4 D22 | W5 D29 | W6 D36 | | |
| **ALT-803*(A)** | | | X | X | X | X | | | X | X | X | X | | | | |
| Informed consent | X | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | |
| Concomitant meds | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical exam[#] | | X | X | X | X | X | X | | X | X | X | X | X | | X | X |
| Vital signs with oxygen saturation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | |
| Weight | X | X | X | | X | | X | X | X | X | | X | | X | X | X |
| Performance status | | X | X | | | | | | X | | | | | | X | X |
| CBC w/diff, plts | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| PT/PTT | | X | | | | | | | | | | | | | | |
| Serum chemistry[a] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Antinuclear antibody (ANA) | X | | | | | | | | X | | | | | | | X |
| Electrocardiogram (ECG)[b] | | | X[b] X[b] | | | | | X[b] | X[b] X[b] | | | | | X[b] | | |
| ECHO (as indicated) | X | | | | | | | | | | | | | | | |
| Pulmonary function test (spirometry) | X | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Adverse event evaluation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tumor measurements[c] | X | Tumor measurements are repeated every 8 ± 1 week and 16 ± 2 weeks | | | | | | | | | | | | | | X |
| CT, MRI, or PET of chest, abdomen, pelvis[d] | X | Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | | | |
| CT or MRI Brain[d] [as indicated for symptoms only] | X | If negative at baseline, to be repeated only with symptoms | | | | | | | | | | | | | | X |
| Radiologic evaluation by RECIST 1.1 | X | Radiologic measurements should be performed every 8 ± 1 week and 16 ± 2 weeks | | | | | | | | | | | | | | X |
| B-HCG[e] | | | X | | | | | | | | | | | | | |
| EBV serostatus | X | | | | | | | | | | | | | | | |
| CMV serostatus | X | | | | | | | | | | | | | | | |
| Thyroid studies: TSH, T4 | X | | | | | | | | | | | | | | | X |
| PK | | | X | | | | | | X | | | | | | | |
| WB Immunophenotyping[g] | | | X | X | X | X | X | | X | | X | | X | | | |
| IFN-γ ELISPOT[g] | | | X | | | | X | | X | | | | X | | | |
| NK-cell function[g] | | | X | | | | X | | X | | | | X | | | |
| Plasma cytokines[g] | | | X | | | | X | | X | | | | X | | | |
| Serum Ab to ALT-803[g] | | | X | | | | | | X | | | | | | X | |
| PBMC | | | X | | | | X | | X | | | | X | | | X |
| Serum | | | X | | | | X | | X | | | | X | | | |

Abbreviations: Ab, antibodies; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; PPT, partial thromboplastin time; PT, prothrombin time

*(A), Agent

[#] Physical exam must always include neurological assessment. In addition, all patients will have formal ophthalmologic testing prior to starting therapy and repeated if clinically indicated.

[a] Blood chemistries include: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide ($CO_2$), albumin, total bilirubin, phosphorus, alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT)

[b] ECGs are to be done before ALT-803 injections on Day 1 and 4, 12 and 24 hours post-dose. ECGs are to be repeated before and at 4 hours (the end of the outpatient observation period) following each subsequent dose.

[c] Baseline tumor assessment scans should be done 1 to 30 days before beginning treatment.

[d] CT, MRI, or PET is acceptable for imaging assessment purposes

[e] Pregnancy test may be done up to 48 hours before ALT-803 administration

[f] See pharmacokinetic flow sheet for specific draw times

[g] Blood for WB Immunophenotyping, IFN-γ ELISPOT, NK-cell function, plasma cytokines, and serum Ab to ALT-803 must be drawn **before** the patient receives ALT-803 injections on Days 1, 8, 15 and 22 of each treatment cycle.

**NCI Protocol #:** CITN-06-ALT-803

**Local Protocol #:** CA-ALT-803-01-13

**TITLE:** A ***Phase 1*** Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma

(Advanced Melanoma – ICD-10053571)

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

**Coordinating Center:** Cancer Immunotherapy Trials Network, Fred Hutchinson Cancer Research Center

***Principal Investigator:** Kim Margolin, MD
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***The University of Washington and USCF will participate to the dose-escalation phase of the trial. Dartmouth and the NCI will be added in the expansion phase of the trial.***

## INVESTIGATOR SIGNATURE PAGE

**Protocol Number:** **CA-ALT-803-01-13**

**Protocol Title:** A ***Phase 1*** Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma

**Date of Protocol:**

| | |
|---|---|
| Version # 01 | April 8, 2013 |
| Version # 02 | May 6, 2013 |
| Version # 03 | July 26, 2013 |
| ***Version # 04*** | ***December 02, 2013*** |

**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) _____

**Statistician:**
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**Study Coordinator: N/A**

**Responsible Research Nurse: N/A**

**Responsible Data Manager: N/A**

**NCI-Supplied Agent(s): N/A**

**Other Agent(s):** ALT-803: a "recombinant human superagonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D: IL-15RαSu/IgG1 Fc complex) NSC#: TBD

| **Investigational Agent** | **IND#** | **IND Sponsor** |
|---|---|---|
| ALT-803 | 118280 | Altor Bioscience Corporation |

**Protocol Type / Version # / Version Date:** ***Amendment/Version 1.0/November 22, 2013***

***CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION***

| ***To submit site registration documents:*** | ***For patient enrollments:*** | ***Submit study data*** |
|---|---|---|
| ***CTSU Regulatory Office***<br>***1818 Market Street, Suite 1100***<br>***Philadelphia, PA 19103***<br>***Phone – 1-866-651-CTSU***<br>***Fax – 215-569-0206***<br>***Email:***<br>***CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)*** | ***Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.***<br><br>***Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.*** | ***Data collection for this study will be done via Medidata Rave (Axio Research).***<br><br>***Please see the data submission section of the protocol for further instructions.*** |
| ***The current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org.*** | | |
| ***For patient eligibility or treatment-related questions:***<br>***Contact the CITN Coordinating Center at citn@fhcrc.org or 206-667-6606*** | | |
| ***For questions unrelated to patient eligibility, treatment, or clinical data submission contact the CTSU Help Desk by phone or e-mail:***<br>***CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.*** | | |
| ***The CTSU Web site is located at https://www.ctsu.org*** | | |

**SCHEMA**

| **Regimen Description** | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-Medications: Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| ALT-803 | *1 dose of antipyretic medication within 30 min of ALT-803 administration<br><br>*1 dose of antipyretic medication 4 h after ALT-803 administration | ***0.3 µg/kg*** or ***0.5 µg/kg*** or ***1 µg/kg*** or ***3 µg/kg*** or ***6 µg/kg*** | IV | D1, W1<br>D1, W2<br>D1, W3<br>D1, W4 | 42 days<br>(4 weeks on, 2 weeks off)<br>With up to 4 cycles in the absence of unacceptable toxicity and disease progression** |

*Non-steroidal anti-inflammatory medication including agents such as acetaminophen, ibuprofen, or Naproxen may be given per physician discretion. Not to exceed standard maximum thresholds:

Acetaminophen: not to exceed 3000 mg (3 g) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours

***** Additional cycles beyond the 4th cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.***

| **Dose Escalation Schedule** | |
|---|---|
| **Dose Level** | **Dose of ALT-803** |
| **Level -1** | ***0.1 µg/kg*** (only if the first level is too toxic) |
| Level 1 | ***0.3 µg/kg*** |
| Level 2 | ***0.5 µg/kg*** |
| Level 3 | ***1 µg/kg*** |
| Level 4 | ***3 µg/kg*** |
| Level 5 | ***6 µg/kg*** |

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 to 30 days before start of protocol therapy, as indicated in the study calendar, except for pregnancy testing, which must be performed within 48 hours prior to initial ALT-803 administration. Scans and x-rays must be performed within 30 days before the start of therapy. In the event that the patient's condition is changing, laboratory evaluations should be repeated within 24 hours before initiating the next cycle of therapy. Please refer to the study calendar below for specific timing of required evaluations.

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | **Cycle 2 (Weeks)** | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | **14 d post last *inf.*** | **6 Mo** | ***1 year***[i] |
| | Within 30 d | Within 14 d | W1 D1±***1*** | W2 D8±***1*** | W3 D15±***1*** | W4 D22±***1*** | W5 D29±***1*** | W6 D36±***1*** | W1 D1±***1*** | W2 D8±***1*** | W3 D15±***1*** | W4 D22±***1*** | W5 D29±***1*** | W6 D36±***1*** | | | |
| **ALT-803*(A)** | | | X | X | X | X | | | X | X | X | X | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | |
| Concomitant meds | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical exam[h] | | X | X | X | X | X | X | | X | X | X | X | X | | X | X | X |
| Vital signs with oxygen saturation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | | |
| Weight | X | X | X | | X | | X | X | X | X | | X | | X | X | X | X |
| Performance status | | X | X | | | | | | X | | | | | | X | X | X |
| CBC w/diff, plts | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X | X |
| PT/PTT | | X | | | | | | | | | | | | | | | |
| Serum chemistry[a] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Antinuclear antibody (ANA) | X | | | | | | | | X | | | | | | | X | X |
| Electrocardiogram (ECG)[b] | | | X | X | X | X | | | X | X | X | X | | | X | X | X |
| ECHO (as indicated) | X | | | | | | | | | | | | | | | | |
| Adverse event evaluation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tumor measurements[c] | X | Tumor measurements are repeated every ***6*** ± ***1*** week and ***12*** ± ***2*** weeks | | | | | | | | | | | | | | X | |
| CT, MRI, or PET of chest, | X | Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | | | | |

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | **Cycle 2 (Weeks)** | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | **14 d post last *inf.*** | **6 Mo** | ***1 year*[j]** |
| abdomen, pelvis[d] | | | | | | | | | | | | | | | | | |
| CT or MRI Brain[d] [as indicated for symptoms only] | X | If negative at baseline, to be repeated only with symptoms | | | | | | | | | | | | | | X | |
| Radiologic evaluation by RECIST 1.1 | X | Radiologic measurements should be performed every ***6 ± 1*** week and ***12 ± 2*** weeks | | | | | | | | | | | | | | X | |
| B-HCG[e] | | | X | | | | | | | | | | | | | | |
| Thyroid studies: TSH, T4 | X | | | | | | | | | | | | | | | X | X |
| PK[f] | | | X | | | | | | | | | | | | | | |
| WB Immunophenotyping[g] | | | X | X | X | X | X | | X | | X | | X | | | | |
| IFN-γ ELISPOT[g] | | | X | | | | X | | X | | | | X | | | | |
| NK-cell function[g] | | | X | | | | X | | X | | | | X | | | | |
| Plasma cytokines[g] | | | X | | | | X | | X | | | | X | | | | |
| Serum Ab to ALT-803[g] | | | X | | | | | | X | | | | | | X | | |
| ***Other laboratories*[j]** | | | X | | | | | | | | | | | | | | |
| Serum | | | | | | | X | | X | | | | X | | | | |

Abbreviations: Ab, antibodies; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; ***PTT***, partial thromboplastin time; PT, prothrombin time

*(A), Agent

[a] Blood chemistries include: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide ($CO_2$), albumin, total bilirubin, phosphorus, alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT)

[b] ECGs are to be done before ALT-803 ***infusions*** on Day 1 and 4, 12 and 24 hours ***after the first ALT-803 infusion (Cycle 1, Week 1, Day1). As clinically indicated, ECGs are to be obtained to evaluate for cardiac toxicity during subsequent doses and cycles of therapy and follow-up visits.***

[c] Baseline tumor assessment scans should be done 1 to 30 days before beginning treatment.

[d] CT, MRI, or PET is acceptable for imaging assessment purposes

[e] Pregnancy test may be done up to 48 hours before ALT-803 administration

[f] See pharmacokinetic flow sheet for specific draw times

[g] Blood for WB Immunophenotyping, IFN-γ ELISPOT, NK-cell function, plasma cytokines, and serum Ab to ALT-803 must be drawn **before** the patient receives ALT-803 ***infusions*** on Days 1, 8, 15, and 22 of each treatment cycle.

[h] Physical exam must always include neurological assessment. In addition, all patients will have formal ophthalmologic testing prior to starting therapy and repeated if clinically indicated.

[i] ***Additional cycles beyond the 4th cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.***

[j] ***Other labs include: Lactate dehydrogenase, magnesium, phosphate, creatinine kinase and troponin I; must be drawn before and at 12 and 24 hours after the first ALT-803 dose***.

**NCI Protocol #:** CITN-06-ALT-803

**Local Protocol #:** CA-ALT-803-01-13

**TITLE:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma

(Advanced Melanoma – ICD-10053571)

**Sponsor:**

Altor BioScience CORPORATION
Hing C. Wong, Ph.D.
Altor Bioscience Corporation.
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Telephone: 954-443-8600
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**Coordinating Center:** Cancer Immunotherapy Trials Network, Fred Hutchinson Cancer Research Center

***Principal Investigator:**

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***The SCCA, UCSF, Dartmouth, University of Minnesota, Rutgers University and Stanford University will participate to the dose-escalation phase of the trial. NCI will be added in the expansion phase of the trial.***

## INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Protocol Number:** | **CA-ALT-803-01-13** |
| **Protocol Title:** | A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma |
| **Date of Protocol:** | |
| Version # 01 | April 8, 2013 |
| Version # 02 | May 6, 2013 |
| Version # 03 | July 26, 2013 |
| Version # 04 | December 02, 2013 |
| ***Version # 05*** | ***October 08, 2014*** |

**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) _____

**Statistician:**
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**Study Coordinator: N/A**

**Responsible Research Nurse: N/A**

**Responsible Data Manager: N/A**

**NCI-Supplied Agent(s): N/A**

**Other Agent(s):** ALT-803: a "recombinant human superagonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D: IL-15RαSu/IgG1 Fc complex) NSC#: TBD

| **Investigational Agent** | **IND#** | **IND Sponsor** |
|---|---|---|
| ALT-803 | 118280 | Altor Bioscience Corporation |

**Protocol Type / Version # / Version Date:** Amendment /***Version 3.0 /August 27, 2014***

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data** |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br>Phone – 1-866-651-CTSU<br>Fax – 215-569-0206<br>Email:<br>CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only) | Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.<br><br>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com. | Data collection for this study will be done via Medidata Rave (Axio Research).<br><br>Please see the data submission section of the protocol for further instructions. |
| The current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. | | |
| **For patient eligibility or treatment-related questions:**<br>Contact the CITN Coordinating Center at citn@fhcrc.org or 206-667-6606 | | |
| **For questions unrelated to patient eligibility, treatment, or clinical data submission** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU Web site is located at https://www.ctsu.org** | | |

**SCHEMA**

| Regimen Description | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-Medications: Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| ALT-803 | *1 dose of antipyretic medication within 30 min of ALT-803 administration<br><br>*1 dose of antipyretic medication 4 h after ALT-803 administration | 0.3 μg/kg or 0.5 μg/kg or 1 μg/kg or 3 μg/kg or 6 μg/kg | IV | D1, W1<br>D1, W2<br>D1, W3<br>D1, W4 | 42 days (4 weeks on, 2 weeks off)<br>With up to 4 cycles in the absence of unacceptable toxicity and disease progression** |

*Non-steroidal anti-inflammatory medication including agents such as acetaminophen, ibuprofen, or Naproxen may be given per physician discretion. Not to exceed standard maximum thresholds:

Acetaminophen: not to exceed 3000 mg (3 g) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours

** Additional cycles beyond the 4$^{th}$ cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

| Dose Escalation Schedule | |
|---|---|
| **Dose Level** | **Dose of ALT-803** |
| **Level -1** | 0.1 μg/kg (only if the first level is too toxic) |
| Level 1 | 0.3 μg/kg |
| Level 2 | 0.5 μg/kg |
| Level 3 | 1 μg/kg |
| Level 4 | 3 μg/kg |
| Level 5 | 6 μg/kg |

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 to 30 days before start of protocol therapy, as indicated in the study calendar, except for pregnancy testing, which must be performed within 48 hours prior to initial ALT-803 administration. Scans and x-rays must be performed within 30 days before the start of therapy. In the event that the patient's condition is changing, laboratory evaluations should be repeated within 24 hours before initiating the next cycle of therapy. Please refer to the study calendar below for specific timing of required evaluations.

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | **Cycle 2 (Weeks)** | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | **14 d post last inf.** | **6 Mo** | **1 year[i]** |
| | Within 30 d | Within 14 d | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | | | |
| **ALT-803*(A)** | | | X | X | X | X | | | X | X | X | X | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | |
| Concomitant meds | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical exam[h] | | X | X | X | X | X | X | | X | X | X | X | X | | X | X | X |
| Vital signs with oxygen saturation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | | |
| Weight | X | X | X | | X | | X | X | X | X | | X | | X | X | X | X |
| Performance status | | X | X | | | | | | X | | | | | | X | X | X |
| CBC w/diff, plts | | X | ***X***[k] | X | X | X | X | ***X*** | X | X | X | X | X | X | X | X | X |
| PT/PTT | | X | | | | | | | | | | | | | | | |
| Serum chemistry[a] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Antinuclear antibody (ANA) | X | | | | | | | | X | | | | | | | X | X |
| Electrocardiogram (ECG)[b] | | | X | X | X | X | | | X | X | X | X | | | X | X | X |
| ECHO (as indicated) | X | | | | | | | | | | | | | | | | |
| Adverse event evaluation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tumor measurements[c] | X | Tumor measurements are repeated every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | X | |
| CT, MRI, or PET of chest, abdomen, pelvis[d] | X | Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | | | | |
| CT or MRI Brain[d] [as indicated for sympt only] | X | If negative at baseline, to be repeated only with symptoms | | | | | | | | | | | | | | X | |

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | **Cycle 2 (Weeks)** | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | **14 d post last inf.** | **6 Mo** | **1 year[i]** |
| | Within 30 d | Within 14 d | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | | | |
| Radiologic evaluation by RECIST 1.1 | X | Radiologic measurements should be performed every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | X | |
| B-HCG[e] | | | X | | | | | | | | | | | | | | |
| Thyroid studies: TSH, T4 | X | | | | | | | | | | | | | | | X | X |
| PK[f] | | | X | | | | | | | | | | | | | | |
| WB Immunophenotyping[g] | | | X | X | X | X | X | | X | | X | | X | | | | |
| IFN-γ ELISPOT[g] | | | X | | | | X | | X | | | | X | | | | |
| NK-cell function[g] | | | X | | | | X | | X | | | | X | | | | |
| Plasma cytokines[g] | | | X | | | | X | | X | | | | X | | | | |
| ***Kyn/Trp ratio[g]*** | | | ***X*** | | | | ***X*** | | ***X*** | | | | ***X*** | | | | |
| Serum Ab to ALT-803[g] | | | X | | | | | | X | | | | | | X | | |
| Other laboratories[j] | | | X | | | | | | | | | | | | | | |
| Serum | | | | | | | X | | X | | | | X | | | | |

Abbreviations: Ab, antibodies; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; PTT, partial thromboplastin time; PT, prothrombin time

*(A): Agent

[a] Blood chemistries include: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide ($CO_2$), albumin, total bilirubin, phosphorus, alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT)

[b] ECGs are to be done before ALT-803 infusions on Day 1 and 4, 12 and 24 hours after the first ALT-803 infusion (Cycle 1, Week 1, Day1). As clinically indicated, ECGs are to be obtained to evaluate for cardiac toxicity during subsequent doses and cycles of therapy and follow-up visits.

[c] Baseline tumor assessment scans should be done 1 to 30 days before beginning treatment.

[d] CT, MRI, or PET is acceptable for imaging assessment purposes

[e] Pregnancy test may be done up to 48 hours before ALT-803 administration

[f] See pharmacokinetic flow sheet for specific draw times

[g] Blood for WB Immunophenotyping, IFN-γ ELISPOT, NK-cell function, plasma cytokines, ***Kyn/Trp ratio*** and serum Ab to ALT-803 must be drawn **before** the patient receives ALT-803 infusions on Days 1, 8, 15, and 22 of each treatment cycle.

[h] Physical exam must always include neurological assessment. In addition, ***a funduscopic exam, conducted by the investigator with a hand-held ophthalmoscope, must be done prior to starting therapy (Cycle 1, Day 1, Week 1)*** and repeated if clinically indicated ***(See Section 6.0 for additional details).***

[i] Additional cycles beyond the 4th cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

[j] Other labs include: Lactate dehydrogenase, magnesium, phosphate, CK and troponin ***I or T***; must be drawn **before** and at 12 and 24 hours after the first ALT-803 dose.

[k] ***CBC w/diff, plts (Cycle 1, Week 1, Day 1); must be drawn before and at 12 and 24 hours after the first ALT-803 dose.***

**NCI Protocol #:** CITN-06-ALT-803

**Local Protocol #:** CA-ALT-803-01-13

**TITLE:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced ***Solid Tumors: Melanoma, Renal Cell, Non-Small Cell Lung and Squamous Cell Head and Neck Cancer***

**Sponsor:**

Altor BioScience CORPORATION
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**Coordinating Center:** Cancer Immunotherapy Trials Network, Fred Hutchinson Cancer Research Center

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The SCCA, ***Cleveland Clinic Foundation***, UCSF, Dartmouth, University of Minnesota, Rutgers University and Stanford University will participate to the dose-escalation phase of the trial. NCI will be added in the expansion phase of the trial.

## INVESTIGATOR SIGNATURE PAGE

**Protocol Number:** **CA-ALT-803-01-13**

**Protocol Title:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced ***Solid Tumors:*** Melanoma, ***Renal Cell, Non-Small Cell Lung and Squamous Cell Head and Neck Cancer***

**Date of Protocol:**

| | |
|---|---|
| Version # 01 | April 8, 2013 |
| Version # 02 | May 6, 2013 |
| Version # 03 | July 26, 2013 |
| Version # 04 | December 02, 2013 |
| Version # 05 | October 08, 2014 |
| ***Version # 06*** | ***November 20, 2014*** |

**Sponsor Contact:**

Altor BioScience CORPORATION

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

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

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

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Print)

**Statistician:**
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(206) 667-7077
Fax: (206) 667-4378
zoe@fhcrc.org

**Study Coordinator: N/A**

**Responsible Research Nurse: N/A**

**Responsible Data Manager: N/A**

**NCI-Supplied Agent(s): N/A**

**Other Agent(s):** ALT-803: a "recombinant human superagonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D: IL-15RαSu/IgG1 Fc complex) NSC#: TBD

| **Investigational Agent** | **IND#** | **IND Sponsor** |
|---|---|---|
| ALT-803 | 118280 | Altor Bioscience Corporation |

**Protocol Type / Version # / Version Date:** Amendment /***Version 4.0 /October 30, 2014***

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data** |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br>Phone – 1-866-651-CTSU<br>Fax – 215-569-0206<br>Email:<br>CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only) | Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.<br><br>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com. | Data collection for this study will be done via Medidata Rave (Axio Research).<br><br>Please see the data submission section of the protocol for further instructions. |
| The current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. | | |
| **For patient eligibility or treatment-related questions:**<br>Contact the CITN Coordinating Center at citn@fhcrc.org or 206-667-6606 | | |
| **For questions unrelated to patient eligibility, treatment, or clinical data submission** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU Web site is located at https://www.ctsu.org** | | |

**SCHEMA**

| Regimen Description | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-Medications: Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| ALT-803 | *1 dose of antipyretic medication within 30 min of ALT-803 administration<br><br>*1 dose of antipyretic medication 4 h after ALT-803 administration | 0.3 μg/kg or 0.5 μg/kg or 1 μg/kg or 3 μg/kg or 6 μg/kg | IV | D1, W1<br>D1, W2<br>D1, W3<br>D1, W4 | 42 days (4 weeks on, 2 weeks off)<br>With up to 4 cycles in the absence of unacceptable toxicity and disease progression** |

*Non-steroidal anti-inflammatory medication including agents such as acetaminophen, ibuprofen, or Naproxen may be given per physician discretion. Not to exceed standard maximum thresholds:

Acetaminophen: not to exceed 3000 mg (3 g) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours

** Additional cycles beyond the 4$^{th}$ cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

| Dose Escalation Schedule | |
|---|---|
| **Dose Level** | **Dose of ALT-803** |
| **Level -1** | 0.1 μg/kg (only if the first level is too toxic) |
| Level 1 | 0.3 μg/kg |
| Level 2 | 0.5 μg/kg |
| Level 3 | 1 μg/kg |
| Level 4 | 3 μg/kg |
| Level 5 | 6 μg/kg |

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 to 30 days before start of protocol therapy, as indicated in the study calendar, except for pregnancy testing, which must be performed within 48 hours prior to initial ALT-803 administration. Scans and x-rays must be performed within 30 days before the start of therapy. In the event that the patient's condition is changing, laboratory evaluations should be repeated within 24 hours before initiating the next cycle of therapy. Please refer to the study calendar below for specific timing of required evaluations.

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | **Cycle 2 (Weeks)** | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | **14 d post last inf.** | **6 Mo** | **1 year[i]** |
| | Within 30 d | Within 14 d | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | | | |
| **ALT-803*(A)** | | | X | X | X | X | | | X | X | X | X | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | |
| Concomitant meds | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical exam[h] | | X | X | X | X | X | X | | X | X | X | X | X | | X | X | X |
| Vital signs with oxygen saturation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | | |
| Weight | X | X | X | | X | | X | X | X | X | | X | | X | X | X | X |
| Performance status | | X | X | | | | | | X | | | | | | X | X | X |
| CBC w/diff, plts | | X | ***X***[k] | X | X | X | X | ***X*** | X | X | X | X | X | X | X | X | X |
| PT/PTT | | X | | | | | | | | | | | | | | | |
| Serum chemistry[a] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Antinuclear antibody (ANA) | X | | | | | | | | X | | | | | | | X | X |
| Electrocardiogram (ECG)[b] | | | X | X | X | X | | | X | X | X | X | | | X | X | X |
| ECHO (as indicated) | X | | | | | | | | | | | | | | | | |
| Adverse event evaluation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tumor measurements[c] | X | Tumor measurements are repeated every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | X | |
| CT, MRI, or PET of chest, abdomen, pelvis[d] | X | Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | | | | |
| CT or MRI Brain[d] [as indicated for sympt only] | X | If negative at baseline, to be repeated only with symptoms | | | | | | | | | | | | | | X | |

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | **Cycle 2 (Weeks)** | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | **14 d post last inf.** | **6 Mo** | **1 year[i]** |
| | Within 30 d | Within 14 d | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | | | |
| Radiologic evaluation by RECIST 1.1 | X | Radiologic measurements should be performed every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | X | |
| B-HCG[e] | | | X | | | | | | | | | | | | | | |
| Thyroid studies: TSH, T4 | X | | | | | | | | | | | | | | | X | X |
| PK[f] | | | X | | | | | | | | | | | | | | |
| WB Immunophenotyping[g] | | | X | X | X | X | X | | X | | X | | X | | | | |
| IFN-γ ELISPOT[g] | | | X | | | | X | | X | | | | X | | | | |
| NK-cell function[g] | | | X | | | | X | | X | | | | X | | | | |
| Plasma cytokines[g] | | | X | | | | X | | X | | | | X | | | | |
| ***Kyn/Trp ratio[g]*** | | | ***X*** | | | | ***X*** | | ***X*** | | | | ***X*** | | | | |
| Serum Ab to ALT-803[g] | | | X | | | | | | X | | | | | | X | | |
| Other laboratories[j] | | | X | | | | | | | | | | | | | | |
| Serum | | | | | | | X | | X | | | | X | | | | |

Abbreviations: Ab, antibodies; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; PTT, partial thromboplastin time; PT, prothrombin time

*(A): Agent

[a] Blood chemistries include: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide ($CO_2$), albumin, total bilirubin, phosphorus, alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT)

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[f] See pharmacokinetic flow sheet for specific draw times

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[h] Physical exam must always include neurological assessment. In addition, a funduscopic exam, conducted by the investigator with a hand-held ophthalmoscope, must be done prior to starting therapy (Cycle 1, Day 1, Week 1) and repeated if clinically indicated (See Section 6.0 for additional details).

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**NCI Protocol #:** CITN-06-ALT-803

**Local Protocol #:** CA-ALT-803-01-13

**TITLE:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Solid Tumors: Melanoma, Renal Cell, Non-Small Cell Lung and Squamous Cell Head and Neck Cancer

**Sponsor:**

Altor BioScience CORPORATION
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Miramar, Florida 33025
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**Coordinating Center:** Cancer Immunotherapy Trials Network, Fred Hutchinson Cancer Research Center

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The SCCA, Cleveland Clinic Foundation, UCSF, Dartmouth, University of Minnesota, Rutgers University and Stanford University will participate to the dose-escalation phase of the trial. NCI will be added in the expansion phase of the trial.

## INVESTIGATOR SIGNATURE PAGE

**Protocol Number:** **CA-ALT-803-01-13**

**Protocol Title:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Solid Tumors: Melanoma, Renal Cell, Non-Small Cell Lung and Squamous Cell Head and Neck Cancer

**Date of Protocol:**

| | |
|---|---|
| Version # 01 | April 8, 2013 |
| Version # 02 | May 6, 2013 |
| Version # 03 | July 26, 2013 |
| Version # 04 | December 02, 2013 |
| Version # 05 | October 08, 2014 |
| Version # 06 | November 20, 2014 |
| ***Version # 07*** | ***January 26, 2015*** |

**Sponsor Contact:**

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

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

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Print)

**Statistician:**
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(206) 667-7077
Fax: (206) 667-4378
zoe@fhcrc.org

**Study Coordinator: N/A**

**Responsible Research Nurse: N/A**

**Responsible Data Manager: N/A**

**NCI-Supplied Agent(s): N/A**

**Other Agent(s):** ALT-803: a "recombinant human superagonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D: IL-15RαSu/IgG1 Fc complex) NSC#: TBD

| **Investigational Agent** | **IND#** | **IND Sponsor** |
|---|---|---|
| ALT-803 | 118280 | Altor Bioscience Corporation |

**Protocol Type / Version # / Version Date:** Amendment /***Version 5.0 /January 21, 2015***

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data** |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br>Phone – 1-866-651-CTSU<br>Fax – 215-569-0206<br>Email:<br>CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only) | Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.<br><br>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com. | Data collection for this study will be done via Medidata Rave (Axio Research).<br><br>Please see the data submission section of the protocol for further instructions. |
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**SCHEMA**

| Regimen Description | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-Medications: Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| ALT-803 | *1 dose of antipyretic medication within 30 min of ALT-803 administration<br><br>*1 dose of antipyretic medication 4 h after ALT-803 administration | 0.3 μg/kg or 0.5 μg/kg or 1 μg/kg or 3 μg/kg or 6 μg/kg | IV | D1, W1<br>D1, W2<br>D1, W3<br>D1, W4 | 42 days (4 weeks on, 2 weeks off)<br>With up to 4 cycles in the absence of unacceptable toxicity and disease progression** |

*Non-steroidal anti-inflammatory medication including agents such as acetaminophen, ibuprofen, or Naproxen may be given per physician discretion. Not to exceed standard maximum thresholds:

Acetaminophen: not to exceed 3000 mg (3 g) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours

** Additional cycles beyond the 4$^{th}$ cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

| Dose Escalation Schedule | |
|---|---|
| **Dose Level** | **Dose of ALT-803** |
| **Level -1** | 0.1 μg/kg (only if the first level is too toxic) |
| Level 1 | 0.3 μg/kg |
| Level 2 | 0.5 μg/kg |
| Level 3 | 1 μg/kg |
| Level 4 | 3 μg/kg |
| Level 5 | 6 μg/kg |

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 to 30 days before start of protocol therapy, as indicated in the study calendar, except for pregnancy testing, which must be performed within 48 hours prior to initial ALT-803 administration. Scans and x-rays must be performed within 30 days before the start of therapy. In the event that the patient's condition is changing, laboratory evaluations should be repeated within 24 hours before initiating the next cycle of therapy. Please refer to the study calendar below for specific timing of required evaluations.

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | **Cycle 2 (Weeks)** | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | **14 d post last inf.** | **6 Mo** | **1 year[i]** |
| | Within 30 d | Within 14 d | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | | | |
| **ALT-803*(A)** | | | X | X | X | X | | | X | X | X | X | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | |
| Concomitant meds | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical exam[h] | | X | X | X | X | X | X | | X | X | X | X | X | | X | X | X |
| Vital signs with oxygen saturation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | | |
| Weight | X | X | X | | X | | X | X | X | X | | X | | X | X | X | X |
| Performance status | | X | X | | | | | | X | | | | | | X | X | X |
| CBC w/diff, plts | | X | ***X***[k] | X | X | X | X | ***X*** | X | X | X | X | X | X | X | X | X |
| PT/PTT | | X | | | | | | | | | | | | | | | |
| Serum chemistry[a] | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Antinuclear antibody (ANA) | X | | | | | | | | X | | | | | | | X | X |
| Electrocardiogram (ECG)[b] | | | X | X | X | X | | | X | X | X | X | | | X | X | X |
| ECHO (as indicated) | X | | | | | | | | | | | | | | | | |
| Adverse event evaluation | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tumor measurements[c] | X | Tumor measurements are repeated every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | X | |
| CT, MRI, or PET of chest, abdomen, pelvis[d] | X | Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | | | | |
| CT or MRI Brain[d] [as indicated for sympt only] | X | If negative at baseline, to be repeated only with symptoms | | | | | | | | | | | | | | X | |

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | **Cycle 2 (Weeks)** | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | **14 d post last inf.** | **6 Mo** | **1 year[i]** |
| | Within 30 d | Within 14 d | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | W1 D1±1 | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | | | |
| Radiologic evaluation by RECIST 1.1 | X | Radiologic measurements should be performed every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | X | |
| B-HCG[e] | | | X | | | | | | | | | | | | | | |
| Thyroid studies: TSH, T4 | X | | | | | | | | | | | | | | | X | X |
| PK[f] | | | X | | | | | | | | | | | | | | |
| WB Immunophenotyping[g] | | | X | X | X | X | X | | X | | X | | X | | | | |
| IFN-γ ELISPOT[g] | | | X | | | | X | | X | | | | X | | | | |
| NK-cell function[g] | | | X | | | | X | | X | | | | X | | | | |
| Plasma cytokines[g] | | | X | | | | X | | X | | | | X | | | | |
| ***Kyn/Trp ratio[g]*** | | | ***X*** | | | | ***X*** | | ***X*** | | | | ***X*** | | | | |
| Serum Ab to ALT-803[g] | | | X | | | | | | X | | | | | | X | | |
| Other laboratories[j] | | | X | | | | | | | | | | | | | | |
| Serum | | | | | | | X | | X | | | | X | | | | |

Abbreviations: Ab, antibodies; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; PTT, partial thromboplastin time; PT, prothrombin time

*(A): Agent

[a] Blood chemistries include: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide ($CO_2$), albumin, total bilirubin, phosphorus, alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT)

[b] ECGs are to be done before ALT-803 infusions on Day 1 and 4, 12 and 24 hours after the first ALT-803 infusion (Cycle 1, Week 1, Day1). As clinically indicated, ECGs are to be obtained to evaluate for cardiac toxicity during subsequent doses and cycles of therapy and follow-up visits.

[c] Baseline tumor assessment scans should be done 1 to 30 days before beginning treatment.

[d] CT, MRI, or PET is acceptable for imaging assessment purposes

[e] Pregnancy test may be done up to 48 hours before ALT-803 administration

[f] See pharmacokinetic flow sheet for specific draw times

[g] Blood for WB Immunophenotyping, IFN-γ ELISPOT, NK-cell function, plasma cytokines, Kyn/Trp ratio and serum Ab to ALT-803 must be drawn **before** the patient receives ALT-803 infusions on Days 1, 8, 15, and 22 of each treatment cycle.

[h] Physical exam must always include neurological assessment. In addition, a funduscopic exam, conducted by the investigator with a hand-held ophthalmoscope, must be done prior to starting therapy (Cycle 1, Day 1, Week 1) and repeated if clinically indicated (See Section 6.0 for additional details).

[i] Additional cycles beyond the 4th cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

[j] Other labs include: Lactate dehydrogenase, magnesium, phosphate, CK and troponin I or T; must be drawn **before** and at 12 and 24 hours after the first ALT-803 dose.

[k] CBC w/diff, plts (Cycle 1, Week 1, Day 1); must be drawn **before** and at **12** and **24** hours after the first ALT-803 dose.

**NCI Protocol #:** CITN-06-ALT-803

**Local Protocol #:** CA-ALT-803-01-13

**TITLE:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Solid Tumors: Melanoma, Renal Cell, Non-Small Cell Lung and Squamous Cell Head and Neck Cancer

**Sponsor:** Altor BioScience

Hing C. Wong, Ph.D.
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Miramar, Florida 33025
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**Coordinating Center:** Cancer Immunotherapy Trials Network, Fred Hutchinson Cancer Research Center

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***The SCCA, Cleveland Clinic Foundation, UCSF, University of Minnesota and Rutgers University will participate to the dose-escalation phase of the trial. NCI will be added in the expansion phase of the trial.***

## INVESTIGATOR SIGNATURE PAGE

**Protocol Number:** **CA-ALT-803-01-13**

**Protocol Title:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Solid Tumors: Melanoma, Renal Cell, Non-Small Cell Lung and Squamous Cell Head and Neck Cancer

**Date of Protocol:**

| | |
|---|---|
| Version # 01 | April 8, 2013 |
| Version # 02 | May 6, 2013 |
| Version # 03 | July 26, 2013 |
| Version # 04 | December 02, 2013 |
| Version # 05 | October 08, 2014 |
| Version # 06 | November 20, 2014 |
| Version # 07 | January 26, 2015 |
| ***Version #08*** | ***June 11, 2015*** |

**Sponsor Contact:**

Altor BioScience CORPORATION

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Safety Data Fax: 954-443-8602

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

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

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Print)

**Statistician:**
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**Study Coordinator: N/A**

**Responsible Research Nurse: N/A**

**Responsible Data Manager: N/A**

**NCI-Supplied Agent(s): N/A**

**Other Agent(s):** ALT-803: a "recombinant human superagonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D: IL-15RαSu/IgG1 Fc complex) NSC#: TBD

| **Investigational Agent** | **IND#** | **IND Sponsor** |
|---|---|---|
| ALT-803 | 118280 | Altor Bioscience Corporation |

**Protocol Type / Version # / Version Date:** Amendment /***Version 6.0 /June 3, 2015***

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data** |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br>Phone – 1-866-651-CTSU<br>Fax – 215-569-0206<br>Email:<br>CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only) | Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.<br><br>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com. | Data collection for this study will be done via Medidata Rave (Axio Research).<br><br>Please see the data submission section of the protocol for further instructions. |
| The current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. | | |
| **For patient eligibility or treatment-related questions:**<br>Contact the CITN Coordinating Center at citn@fhcrc.org or 206-667-6606 | | |
| **For questions unrelated to patient eligibility, treatment, or clinical data submission** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU Web site is located at https://www.ctsu.org** | | |

**SCHEMA**

| Regimen Description | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-Medications: Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| ALT-803 | *1 dose of antipyretic medication within 30 min of ALT-803 administration<br><br>*1 dose of antipyretic medication 4 h after ALT-803 administration | 0.3 μg/kg or 0.5 μg/kg or 1 μg/kg or 3 μg/kg or 6 μg/kg | IV | D1, W1<br>D1, W2<br>D1, W3<br>D1, W4 | 42 days (4 weeks on, 2 weeks off)<br>With up to 4 cycles in the absence of unacceptable toxicity and disease progression** |

*Non-steroidal anti-inflammatory medication including agents such as acetaminophen, ibuprofen, or Naproxen may be given per physician discretion. Not to exceed standard maximum thresholds:

Acetaminophen: not to exceed 3000 mg (3 g) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours

** Additional cycles beyond the 4$^{th}$ cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

| Dose Escalation Schedule | |
|---|---|
| **Dose Level** | **Dose of ALT-803** |
| **Level -1** | 0.1 μg/kg (only if the first level is too toxic) |
| Level 1 | 0.3 μg/kg |
| Level 2 | 0.5 μg/kg |
| Level 3 | 1 μg/kg |
| Level 4 | 3 μg/kg |
| Level 5 | 6 μg/kg |

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 to 30 days before start of protocol therapy, as indicated in the study calendar, except for pregnancy testing, which must be performed within 48 hours prior to initial ALT-803 administration. Scans and x-rays must be performed within 30 days before the start of therapy. In the event that the patient's condition is changing, laboratory evaluations should be repeated within 24 hours before initiating the next cycle of therapy. Please refer to the study calendar below for specific timing of required evaluations.

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | | **Cycle 2 (Weeks)** | | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | **14 days post last infusion** | **6 Mo** | **1 year[i]** |
| | Within 30 days | Within 14 days | Week 1 D1±1 | ***D4±1*** | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | Week 1 D1±1 | ***D4±1*** | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | | | |
| **ALT-803*(A)** | | | X | | X | X | X | | | X | | X | X | X | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | |
| Concomitant meds | X | | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Physical exam[h] | | X | X | | X | X | X | X | | X | | X | X | X | X | | X | X | X |
| Vital signs with oxygen saturation | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | | | | |
| Weight | X | X | X | | | X | | X | X | X | | X | | X | | X | X | X | X |
| Performance status | | X | X | | | | | | | X | | | | | | | X | X | X |
| CBC w/diff, plts | | X | X[k] | ***X*** | X | X | X | X | X | X | ***X*** | X | X | X | X | X | X | X | X |
| PT/PTT | | X | | | | | | | | | | | | | | | | | |
| Serum chemistry[a] | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Antinuclear antibody (ANA) | X | | | | | | | | | X | | | | | | | | X | X |
| Electrocardiogram (ECG)[b] | | | X | | X | X | X | | | X | | X | X | X | | | X | X | X |
| ECHO (as indicated) | X | | | | | | | | | | | | | | | | | | |
| Adverse event evaluation | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Tumor measurements[c] | X | Tumor measurements are repeated every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | | | X | |
| CT, MRI, or PET of chest, abdomen, pelvis[d] | X | Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | | | | | | |
| CT or MRI Brain[d] [as indicated for sympt only] | X | If negative at baseline, to be repeated only with symptoms | | | | | | | | | | | | | | | | X | |
| Radiologic evaluation by RECIST 1.1 | X | Radiologic measurements should be performed every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | | | X | |

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | | **Cycle 2 (Weeks)** | | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 | | W2 | W3 | W4 | W5 | W6 | Week 1 | | W2 | W3 | W4 | W5 | W6 | **14 days post last infusion** | **6 Mo** | **1 year[i]** |
| | Within 30 days | Within 14 days | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | | | |
| B-HCG[e] | | | X | | | | | | | | | | | | | | | | |
| Thyroid studies: TSH, T4 | X | | | | | | | | | | | | | | | | | X | X |
| PK[f] | | | X | | | | | | | | | | | | | | | | |
| WB Immunophenotyping[g] | | | X | ***X*** | X | X | ***X*** | X | | X | ***X*** | | | | X | | | | |
| IFN-γ ELISPOT[g] | | | X | | | | | ***X*** | | X | | | | | | | | | |
| NK-cell function[g] | | | X | ***X*** | ***X*** | | | ***X*** | | X | ***X*** | | | | | | | | |
| Plasma cytokines[g] | | | X | | | | | X | | X | | | | | X | | | | |
| Kyn/Trp ratio[g] | | | X | | | | | X | | X | | | | | X | | | | |
| Serum Ab to ALT-803[g] | | | X | | | | | | | X | | | | | | | X | | |
| Other laboratories[j] | | | X | | | | | | | | | | | | | | | | |
| Serum Storage (optional) | | | ***X*** | | | | | X | | | | | | | | | | | |

Abbreviations: Ab, antibodies; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; PTT, partial thromboplastin time; PT, prothrombin time

*(A): Agent

[a] Blood chemistries include: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide ($CO_2$), albumin, total bilirubin, phosphorus, alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT)

[b] ECGs are to be done before ALT-803 infusions on Day 1 and 4, 12 and 24 hours after the first ALT-803 infusion (Cycle 1, Week 1, Day1). As clinically indicated, ECGs are to be obtained to evaluate for cardiac toxicity during subsequent doses and cycles of therapy and follow-up visits.

[c] Baseline tumor assessment scans should be done 1 to 30 days before beginning treatment.

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[e] Pregnancy test may be done up to 48 hours before ALT-803 administration

[f] See pharmacokinetic flow sheet for specific draw times

[g] Blood for WB Immunophenotyping, IFN-γ ELISPOT, NK-cell function, plasma cytokines, Kyn/Trp ratio and serum Ab to ALT-803 must be drawn **before** the patient receives ALT-803 infusions on Days 1, 8, 15, and 22 of each treatment cycle.

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[j] Other labs include: Lactate dehydrogenase, magnesium, phosphate, CK and troponin I or T; must be drawn **before** and at 12 and 24 hours after the first ALT-803 dose.

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**NCI Protocol #:** CITN-06-ALT-803

**Local Protocol #:** CA-ALT-803-01-13

**TITLE:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Solid Tumors: Melanoma, Renal Cell, Non-Small Cell Lung and Squamous Cell Head and Neck Cancer

**Sponsor:**

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**Coordinating Center:** Cancer Immunotherapy Trials Network, Fred Hutchinson Cancer Research Center

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The SCCA, Cleveland Clinic Foundation, UCSF, University of Minnesota and Rutgers University will participate to the dose-escalation phase of the trial. NCI will be added in the expansion phase of the trial.

## INVESTIGATOR SIGNATURE PAGE

**Protocol Number:** **CA-ALT-803-01-13**

**Protocol Title:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Solid Tumors: Melanoma, Renal Cell, Non-Small Cell Lung and Squamous Cell Head and Neck Cancer

**Date of Protocol:**

| | |
|---|---|
| Version # 01 | April 8, 2013 |
| Version # 02 | May 6, 2013 |
| Version # 03 | July 26, 2013 |
| Version # 04 | December 02, 2013 |
| Version # 05 | October 08, 2014 |
| Version # 06 | November 20, 2014 |
| Version # 07 | January 26, 2015 |
| Version # 08 | June 11, 2015 |
| ***Version # 09*** | ***August 5, 2015*** |

**Sponsor Contact:**

Altor BioScience CORPORATION

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Safety Data Fax: 954-443-8602

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

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

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Name (Print)

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(206) 667-7077
Fax: (206) 667-4378
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**Study Coordinator: N/A**

**Responsible Research Nurse: N/A**

**Responsible Data Manager: N/A**

**NCI-Supplied Agent(s): N/A**

**Other Agent(s):** ALT-803: a "recombinant human superagonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D: IL-15RαSu/IgG1 Fc complex) NSC#: TBD

| **Investigational Agent** | **IND#** | **IND Sponsor** |
|---|---|---|
| ALT-803 | 118280 | Altor Bioscience Corporation |

**Protocol Type / Version # / Version Date:** Amendment /***Version 7.0 /July 28, 2015***

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data** |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br>Phone – 1-866-651-CTSU<br>Fax – 215-569-0206<br>Email:<br>CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only) | Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.<br><br>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com. | Data collection for this study will be done via Medidata Rave (Axio Research).<br><br>Please see the data submission section of the protocol for further instructions. |
| The current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. | | |
| **For patient eligibility or treatment-related questions:**<br>Contact the CITN Coordinating Center at citn@fhcrc.org or 206-667-6606 | | |
| **For questions unrelated to patient eligibility, treatment, or clinical data submission** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU Web site is located at https://www.ctsu.org** | | |

**SCHEMA**

| **Regimen Description** | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-Medications: Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| ALT-803 | *1 dose of antipyretic medication within 30 min of ALT-803 administration<br><br>*1 dose of antipyretic medication 4 h after ALT-803 administration | 0.3 µg/kg or 0.5 µg/kg or 1 µg/kg or 3 µg/kg or 6 µg/kg<br><br>***6 µg/kg***<br>***10 µg/kg***<br>***15 µg/kg***<br>***20 µg/kg*** | IV<br><br>***SQ*** | D1, W1<br>D1, W2<br>D1, W3<br>D1, W4 | 42 days<br>(4 weeks on, 2 weeks off)<br>With up to 4 cycles in the absence of unacceptable toxicity and disease progression** |

*Non-steroidal anti-inflammatory medication including agents such as acetaminophen, ibuprofen, or Naproxen may be given per physician discretion. Not to exceed standard maximum thresholds:

Acetaminophen: not to exceed 3000 mg (3 g) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours

** Additional cycles beyond the 4th cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

| **Dose Escalation Schedule** | | |
|---|---|---|
| **Dose Level** | **Dose of ALT-803** | ***Route of Administration*** |
| **Level -1** | 0.1 µg/kg (only if the first level is too toxic) | ***IV*** |
| Level 1 | 0.3 µg/kg | ***IV*** |
| Level 2 | 0.5 µg/kg | ***IV*** |
| Level 3 | 1 µg/kg | ***IV*** |
| Level 4 | 3 µg/kg | ***IV*** |
| Level 5 | 6 µg/kg | ***IV*** |
| ***Level 5a[1]*** | ***6 µg/kg*** | ***SQ*** |
| ***Level 6*** | ***10 µg/kg*** | ***SQ*** |
| ***Level 7*** | ***15 µg/kg*** | ***SQ*** |
| ***Level 8[2]*** | ***20 µg/kg*** | ***SQ*** |

***[1]With protocol version #9, ALT-803 dosing is changed from IV to SQ, and dose level 5 is repeated to confirm safety with the new route of administration.***

***[2]The dose of ALT-803 will be increased in increments of 5 µg/kg if a minimum of three patients have been treated at dose level 8 (20 µg/kg), and the Maximum Tolerated Dose (MTD) and Optimum Biological Dose (OBD) have not been identified. Enrollment will continue until the MTD/OBD is identified.***

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 to 30 days before start of protocol therapy, as indicated in the study calendar, except for pregnancy testing, which must be performed within 48 hours prior to initial ALT-803 administration. Scans and x-rays must be performed within 30 days before the start of therapy. In the event that the patient's condition is changing, laboratory evaluations should be repeated within 24 hours before initiating the next cycle of therapy. Please refer to the study calendar below for specific timing of required evaluations.

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | | **Cycle 2 (Weeks)** | | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | **14 days post last *dose*** | **6 Mo** | **1 year[i]** |
| | Within 30 days | Within 14 days | Week 1 D1±1 | ***D4±1*** | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | Week 1 D1±1 | ***D4±1*** | W2 D8±1 | W3 D15±1 | W4 D22±1 | W5 D29±1 | W6 D36±1 | | | |
| **ALT-803*(A)** | | | X | | X | X | X | | | X | | X | X | X | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | |
| Concomitant meds | X | | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Physical exam[h] | | X | X | | X | X | X | X | | X | | X | X | X | X | | X | X | X |
| Vital signs with oxygen saturation | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | | | | |
| Weight | X | X | X | | | X | | X | X | X | | X | | X | | X | X | X | X |
| Performance status | | X | X | | | | | | | X | | | | | | | X | X | X |
| CBC w/diff, plts | | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PT/PTT | | X | | | | | | | | | | | | | | | | | |
| Serum chemistry[a] | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Antinuclear antibody (ANA) | X | | | | | | | | | X | | | | | | | | X | X |
| Electrocardiogram (ECG)[b] | | | X | | X | X | X | | | X | | X | X | X | | | X | X | X |
| ECHO (as indicated) | X | | | | | | | | | | | | | | | | | | |
| Adverse event evaluation | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Tumor measurements[c] | X | Tumor measurements are repeated every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | | | X | |
| CT, MRI, or PET of chest, abdomen, pelvis[d] | X | Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | | | | | | |
| CT or MRI Brain[d] [as indicated for sympt only] | X | If negative at baseline, to be repeated only with symptoms | | | | | | | | | | | | | | | | X | |
| Radiologic evaluation by RECIST 1.1 | X | Radiologic measurements should be performed every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | | | X | |

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | | **Cycle 2 (Weeks)** | | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 | | W2 | W3 | W4 | W5 | W6 | Week 1 | | W2 | W3 | W4 | W5 | W6 | **14 days post last *dose*** | **6 Mo** | **1 year[i]** |
| | Within 30 days | Within 14 days | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | | | |
| ***Injection Site Evaluation*** | | | | ***X*** | ***X*** | ***X*** | ***X*** | | | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** | | | ***X*** | | |
| B-HCG[e] | | | X | | | | | | | | | | | | | | | | |
| Thyroid studies: TSH, T4 | X | | | | | | | | | | | | | | | | | X | X |
| PK[f] | | | X | | | | | | | | | | | | | | | | |
| WB Immunophenotyping[g] | | | X | ***X*** | X | X | ***X*** | X | | X | ***X*** | | | | X | | | | |
| IFN-γ ELISPOT[g] | | | X | | | | | ***X*** | | X | | | | | | | | | |
| NK-cell function[g] | | | X | ***X*** | ***X*** | | | ***X*** | | X | ***X*** | | | | | | | | |
| Plasma cytokines[g] | | | X | | | | | X | | X | | | | | X | | | | |
| Kyn/Trp ratio[g] | | | X | | | | | X | | X | | | | | X | | | | |
| Serum Ab to ALT-803[g] | | | X | | | | | | | X | | | | | | | X | | |
| Other laboratories[j] | | | X | | | | | | | | | | | | | | | | |
| Serum Storage (optional) | | | ***X*** | | | | | X | | | | | | | | | | | |

Abbreviations: Ab, antibodies; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; PTT, partial thromboplastin time; PT, prothrombin time

*(A): Agent

[a] Blood chemistries include: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide ($CO_2$), albumin, total bilirubin, phosphorus, alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT)

[b] ECGs are to be done before ALT-803 ***administration*** on Day 1 and 4, 12 and 24 hours after the first ALT-803 ***dose*** (Cycle 1, Week 1, Day1). As clinically indicated, ECGs are to be obtained to evaluate for cardiac toxicity during subsequent doses and cycles of therapy and follow-up visits.

[c] Baseline tumor assessment scans should be done 1 to 30 days before beginning treatment.

[d] CT, MRI, or PET is acceptable for imaging assessment purposes

[e] Pregnancy test may be done up to 48 hours before ALT-803 administration

[f] See pharmacokinetic flow sheet for specific draw times

[g] Blood for WB Immunophenotyping, IFN-γ ELISPOT, NK-cell function, plasma cytokines, Kyn/Trp ratio and serum Ab to ALT-803 must be drawn **before** the patient receives ***the dose of*** ALT-803 on Days 1, 8, 15, and 22 of each treatment cycle.

[h] Physical exam must always include neurological assessment. In addition, a funduscopic exam, conducted by the investigator with a hand-held ophthalmoscope, must be done prior to starting therapy (Cycle 1, Day 1, Week 1) and repeated if clinically indicated (See Section 6.0 for additional details).

[i] Additional cycles beyond the 4th cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

[j] Other labs include: Lactate dehydrogenase, magnesium, phosphate, CK and troponin I or T; must be drawn **before** and at 12 and 24 hours after the first ALT-803 dose.

[k] CBC w/diff, plts (Cycle 1, Week 1, Day 1); must be drawn **before** and at **12** and **24** hours after the first ALT-803 dose.

**NCI Protocol #:** CITN-06-ALT-803

**Local Protocol #:** CA-ALT-803-01-13

**TITLE:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Solid Tumors: Melanoma, Renal Cell, Non-Small Cell Lung and Squamous Cell Head and Neck Cancer

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

**Coordinating Center:** Cancer Immunotherapy Trials Network, Fred Hutchinson Cancer Research Center

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The SCCA, Cleveland Clinic Foundation, UCSF, University of Minnesota and Rutgers University will participate to the dose-escalation phase of the trial. NCI will be added in the expansion phase of the trial.

## INVESTIGATOR SIGNATURE PAGE

| | |
|---|---|
| **Protocol Number:** | **CA-ALT-803-01-13** |
| **Protocol Title:** | A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Solid Tumors: Melanoma, Renal Cell, Non-Small Cell Lung and Squamous Cell Head and Neck Cancer |
| **Date of Protocol:** | |
| Version # 01 | April 8, 2013 |
| Version # 02 | May 6, 2013 |
| Version # 03 | July 26, 2013 |
| Version # 04 | December 02, 2013 |
| Version # 05 | October 08, 2014 |
| Version # 06 | November 20, 2014 |
| Version # 07 | January 26, 2015 |
| Version # 08 | June 11, 2015 |
| Version # 09 | August 5, 2015 |
| ***Version # 10*** | ***April 13, 2016*** |
| **Sponsor Contact:** | Altor BioScience CORPORATION<br>Hing C. Wong, Ph.D.<br>Altor Bioscience Corporation.<br>Miramar, Florida 33025<br>Telephone: 954-443-8600<br>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)

**Statistician:**
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**Study Coordinator: N/A**

**Responsible Research Nurse: N/A**

**Responsible Data Manager: N/A**

**NCI-Supplied Agent(s): N/A**

**Other Agent(s):** ALT-803: a "recombinant human superagonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D: IL-15RαSu/IgG1 Fc complex) NSC#: TBD

| **Investigational Agent** | **IND#** | **IND Sponsor** |
|---|---|---|
| ALT-803 | 118280 | Altor Bioscience Corporation |

**Protocol Type / Version # / Version Date:** Amendment /***Version 8.0 /March 31, 2016***

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data** |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br>Phone – 1-866-651-CTSU<br>Fax – 215-569-0206<br>Email:<br>CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only) | Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.<br><br>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com. | Data collection for this study will be done via Medidata Rave (Axio Research).<br><br>Please see the data submission section of the protocol for further instructions. |
| The current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. | | |
| **For patient eligibility or treatment-related questions:**<br>Contact the CITN Coordinating Center at citn@fhcrc.org or 206-667-6606 | | |
| **For questions unrelated to patient eligibility, treatment, or clinical data submission** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU Web site is located at https://www.ctsu.org** | | |

**SCHEMA**

| Regimen Description | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-Medications: Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| ALT-803 | *1 dose of antipyretic medication within 30 min of ALT-803 administration<br><br>*1 dose of antipyretic medication 4 h after ALT-803 administration | 0.3 µg/kg or 0.5 µg/kg or 1 µg/kg or 3 µg/kg or 6 µg/kg | IV | D1, W1<br>D1, W2<br>D1, W3<br>D1, W4 | 42 days (4 weeks on, 2 weeks off)<br>With up to 4 cycles in the absence of unacceptable toxicity and disease progression** |
| | | 6 µg/kg 10 µg/kg 15 µg/kg 20 µg/kg | SQ | | |

*Non-steroidal anti-inflammatory medication including agents such as acetaminophen, ibuprofen, or Naproxen may be given per physician discretion. Not to exceed standard maximum thresholds:

Acetaminophen: not to exceed 3000 mg (3 g) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours

** Additional cycles beyond the 4$^{th}$ cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

| Dose Escalation Schedule | | |
|---|---|---|
| **Dose Level** | **Dose of ALT-803** | **Route of Administration** |
| **Level -1** | 0.1 µg/kg (only if the first level is too toxic) | IV |
| Level 1 | 0.3 µg/kg | IV |
| Level 2 | 0.5 µg/kg | IV |
| Level 3 | 1 µg/kg | IV |
| Level 4 | 3 µg/kg | IV |
| Level 5 | 6 µg/kg | IV |
| Level 5a[1] | 6 µg/kg | SQ |
| Level 6 | 10 µg/kg | SQ |
| Level 7 | 15 µg/kg | SQ |
| Level 8[2] | 20 µg/kg | SQ |

[1]With protocol version #9, ALT-803 dosing is changed from IV to SQ, and dose level 5 is repeated to confirm safety with the new route of administration.

[2]The dose of ALT-803 will be increased in increments of 5 µg/kg if a minimum of three patients have been treated at dose level 8 (20 µg/kg), and the Maximum Tolerated Dose (MTD) and Optimum Biological Dose (OBD) have not been identified. Enrollment will continue until the MTD/OBD is identified.

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 to 30 days before start of protocol therapy, as indicated in the study calendar, except for pregnancy testing, which must be performed within 48 hours prior to initial ALT-803 administration. Scans and x-rays must be performed within 30 days before the start of therapy. In the event that the patient's condition is changing, laboratory evaluations should be repeated within 24 hours before initiating the next cycle of therapy. Please refer to the study calendar below for specific timing of required evaluations.

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | | **Cycle 2 (Weeks)** | | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 | | W2 | W3 | W4 | W5 | W6 | Week 1 | | W2 | W3 | W4 | W5 | W6 | **14 days post last *dose*** | **6 Mo** | **1 year[i]** |
| | Within 30 days | Within 14 days | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | | | |
| **ALT-803*(A)** | | | X | | X | X | X | | | X | | X | X | X | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | |
| Concomitant meds | X | | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Physical exam[h] | | X | X | | X | X | X | X | | X | | X | X | X | X | | X | X | X |
| Vital signs with oxygen saturation | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | | | | |
| Weight | X | X | X | | | X | | X | X | X | | X | | X | | X | X | X | X |
| Performance status | | X | X | | | | | | | X | | | | | | | X | X | X |
| CBC w/diff, plts | | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PT/PTT | | X | | | | | | | | | | | | | | | | | |
| Serum chemistry[a] | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Antinuclear antibody (ANA) | X | | | | | | | | | X | | | | | | | | X | X |
| Electrocardiogram (ECG)[b] | | | X | | X | X | X | | | X | | X | X | X | | | X | X | X |
| ECHO (as indicated) | X | | | | | | | | | | | | | | | | | | |
| Adverse event evaluation | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Tumor measurements[c] | X | Tumor measurements are repeated every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | | | X | |
| CT, MRI, or PET of chest, abdomen, pelvis[d] | X | Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | | | | | | |
| CT or MRI Brain[d] [as indicated for sympt only] | X | If negative at baseline, to be repeated only with symptoms | | | | | | | | | | | | | | | | X | |
| Radiologic evaluation by RECIST 1.1 | X | Radiologic measurements should be performed every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | | | X | |

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | | **Cycle 2 (Weeks)** | | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 | | W2 | W3 | W4 | W5 | W6 | Week 1 | | W2 | W3 | W4 | W5 | W6 | **14 days post last *dose*** | **6 Mo** | **1 year[i]** |
| | Within 30 days | Within 14 days | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | | | |
| ***Injection Site Evaluation*** | | | | ***X*** | ***X*** | ***X*** | ***X*** | | | ***X*** | ***X*** | ***X*** | ***X*** | ***X*** | | | ***X*** | | |
| B-HCG[e] | | | X | | | | | | | | | | | | | | | | |
| Thyroid studies: TSH, T4 | X | | | | | | | | | | | | | | | | | X | X |
| PK[f] | | | X | | | | | | | | | | | | | | | | |
| WB Immunophenotyping[g] | | | X | ***X*** | X | X | ***X*** | X | | X | ***X*** | | | | X | | | | |
| IFN-γ ELISPOT[g] | | | X | | | | | ***X*** | | X | | | | | | | | | |
| NK-cell function[g] | | | X | ***X*** | ***X*** | | | ***X*** | | X | ***X*** | | | | | | | | |
| Plasma cytokines[g] | | | X | | | | | X | | X | | | | | X | | | | |
| Kyn/Trp ratio[g] | | | X | | | | | X | | X | | | | | X | | | | |
| Serum Ab to ALT-803[g] | | | X | | | | | | | X | | | | | | | X | | |
| Other laboratories[j] | | | X | | | | | | | | | | | | | | | | |
| Serum Storage (optional) | | | ***X*** | | | | | X | | | | | | | | | | | |

Abbreviations: Ab, antibodies; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; PTT, partial thromboplastin time; PT, prothrombin time

*(A): Agent

[a] Blood chemistries include: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide ($CO_2$), albumin, total bilirubin, phosphorus, alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT)

[b] ECGs are to be done before ALT-803 ***administration*** on Day 1 and 4, 12 and 24 hours after the first ALT-803 ***dose*** (Cycle 1, Week 1, Day1). As clinically indicated, ECGs are to be obtained to evaluate for cardiac toxicity during subsequent doses and cycles of therapy and follow-up visits.

[c] Baseline tumor assessment scans should be done 1 to 30 days before beginning treatment.

[d] CT, MRI, or PET is acceptable for imaging assessment purposes

[e] Pregnancy test may be done up to 48 hours before ALT-803 administration

[f] See pharmacokinetic flow sheet for specific draw times

[g] Blood for WB Immunophenotyping, IFN-γ ELISPOT, NK-cell function, plasma cytokines, Kyn/Trp ratio and serum Ab to ALT-803 must be drawn **before** the patient receives ***the dose of*** ALT-803 on Days 1, 8, 15, and 22 of each treatment cycle.

[h] Physical exam must always include neurological assessment. In addition, a funduscopic exam, conducted by the investigator with a hand-held ophthalmoscope, must be done prior to starting therapy (Cycle 1, Day 1, Week 1) and repeated if clinically indicated (See Section 6.0 for additional details).

[i] Additional cycles beyond the 4th cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

[j] Other labs include: Lactate dehydrogenase, magnesium, phosphate, CK and troponin I or T; must be drawn **before** and at 12 and 24 hours after the first ALT-803 dose.

[k] CBC w/diff, plts (Cycle 1, Week 1, Day 1); must be drawn **before** and at **12** and **24** hours after the first ALT-803 dose.

**NCI Protocol #:** CITN-06-ALT-803

**Local Protocol #:** CA-ALT-803-01-13

**TITLE:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Solid Tumors: Melanoma, Renal Cell, ***Sarcoma, Colon, Non-Hodgkin Lymphoma,*** Non-Small Cell Lung and Squamous Cell Head and Neck Cancer ***and Cutaneous Squamous Cell Cancer***

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The SCCA, Cleveland Clinic Foundation, University of Minnesota and Rutgers University will participate to the dose-escalation phase of the trial. NCI will be added in the expansion phase of the trial.

## INVESTIGATOR SIGNATURE PAGE

**Protocol Number:** **CA-ALT-803-01-13**

**Protocol Title:** A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Solid Tumors: Melanoma, Renal Cell, ***Sarcoma, Colon, Non-Hodgkin Lymphoma,*** Non-Small Cell Lung and Squamous Cell Head and Neck Cancer and ***Cutaneous Squamous Cell Cancer***

**Date of Protocol:**

| | |
|---|---|
| Version # 01 | April 8, 2013 |
| Version # 02 | May 6, 2013 |
| Version # 03 | July 26, 2013 |
| Version # 04 | December 02, 2013 |
| Version # 05 | October 08, 2014 |
| Version # 06 | November 20, 2014 |
| Version # 07 | January 26, 2015 |
| Version # 08 | June 11, 2015 |
| Version # 09 | August 5, 2015 |
| Version # 10 | April 13, 2016 |
| ***Version # 11*** | ***August 9, 2016*** |

**Sponsor Contact:**

Altor BioScience CORPORATION

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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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**Study Coordinator: N/A**

**Responsible Research Nurse: N/A**

**Responsible Data Manager: N/A**

**NCI-Supplied Agent(s): N/A**

**Other Agent(s):** ALT-803: a "recombinant human superagonist interleukin-15 (IL-15) complex" (AKA, IL-15N72D: IL-15RαSu/IgG1 Fc complex) NSC#: TBD

| **Investigational Agent** | **IND#** | **IND Sponsor** |
|---|---|---|
| ALT-803 | 118280 | Altor Bioscience Corporation |

**Protocol Type / Version # / Version Date:** ***Amendment 9 /Version 2.0 /July 13, 2016***

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data** |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street, Suite 1100<br>Philadelphia, PA 19103<br>Phone – 1-866-651-CTSU<br>Fax – 215-569-0206<br>Email:<br>CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only) | Please refer to the patient enrollment section for instructions on using the Oncology Patient Enrollment Network (OPEN) at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.<br><br>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com. | Data collection for this study will be done via Medidata Rave (Axio Research).<br><br>Please see the data submission section of the protocol for further instructions. |
| The current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. | | |
| **For patient eligibility or treatment-related questions:**<br>Contact the CITN Coordinating Center at citn@fhcrc.org or 206-667-6606 | | |
| **For questions unrelated to patient eligibility, treatment, or clinical data submission** contact the CTSU Help Desk by phone or e-mail:<br>CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| **The CTSU Web site is located at https://www.ctsu.org** | | |

**SCHEMA**

| **Regimen Description** | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Pre-Medications: Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| ALT-803 | *1 dose of antipyretic medication within 30 min of ALT-803 administration<br><br>*1 dose of antipyretic medication 4 h after ALT-803 administration | 0.3 µg/kg or<br>0.5 µg/kg or<br>1 µg/kg or<br>3 µg/kg or<br>6 µg/kg | IV | D1, W1<br>D1, W2<br>D1, W3<br>D1, W4 | 42 days<br>(4 weeks on, 2 weeks off)<br>With up to 4 cycles in the absence of unacceptable toxicity and disease progression** |
| | | 6 µg/kg<br>10 µg/kg<br>15 µg/kg<br>20 µg/kg | SQ | | |
| | | ***10 µg/kg + 15 µg/kg SQ***<br>***15 µg/kg + 15 µg/kg SQ***<br>***20 µg/kg + 15 µg/kg SQ*** | ***IT followed by SQ*** | ***D1, W1 (IT)***<br>***D1, W2 (SQ)***<br>***D1, W3 (SQ)***<br>***D1, W4 (SQ)*** | ***42 days (4 weeks on, 2 weeks off)***<br>***With up to 4 cycles in the absence of unacceptable toxicity and disease progression****<br>***Cycle 1 only: pre and post treatment biopsy*** |

*Non-steroidal anti-inflammatory medication including agents such as acetaminophen, ibuprofen, or Naproxen may be given per physician discretion. Not to exceed standard maximum thresholds:

Acetaminophen: not to exceed 3000 mg (3 g) in 24 hours
Ibuprofen: not to exceed 2400 mg in 24 hours
Naproxen: not to exceed 1100 mg in 24 hours

** Additional cycles beyond the 4th cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

| **Dose Escalation Schedule** | | |
|---|---|---|
| ***Cohort 1*** | | |
| **Dose Level** | **Dose of ALT-803** | **Route of Administration** |
| **Level -1** | 0.1 µg/kg (only if the first level is too toxic) | IV |
| Level 1 | 0.3 µg/kg | IV |
| Level 2 | 0.5 µg/kg | IV |
| Level 3 | 1 µg/kg | IV |
| Level 4 | 3 µg/kg | IV |
| Level 5 | 6 µg/kg | IV |
| ***Cohort 2[3]*** | | |

| | | |
|---|---|---|
| Level 5a[1] | 6 µg/kg | SQ |
| Level 6 | 10 µg/kg | SQ |
| Level 7 | 15 µg/kg | SQ |
| Level 8[2] | 20 µg/kg | SQ |
| ***Cohort 3[3,4]*** | | |
| ***Level 1*** | ***10 µg/kg*** | ***IT (Week 1)*** |
| | ***15 µg/kg*** | ***SQ (Week 2, 3, 4)*** |
| ***Level 2*** | ***15 µg/kg*** | ***IT (Week 1)*** |
| | ***15 µg/kg*** | ***SQ (Week 2, 3, 4)*** |
| ***Level 3[2]*** | ***20 µg/kg*** | ***IT (Week 1)*** |
| | ***15 µg/kg*** | ***SQ (Week 2, 3, 4)*** |

[1]With protocol version #9, ALT-803 dosing is changed from IV to SQ, and dose level 5 is repeated to confirm safety with the new route of administration.

[2]The dose of ALT-803 will be increased in increments of 5 µg/kg if a minimum of three patients have been treated at dose level 8 ***in Cohort 2 or dose level 3 in Cohort 3***, and the Maximum Tolerated Dose (MTD) and Optimum Biological Dose (OBD) have not been identified. Enrollment will continue until the MTD/OBD is identified.

***[3]Cohort 2 and Cohort 3 enrollment will occur in parallel. The treatment cohort assignment (Cohort 2 vs Cohort 3) is at the Investigator and patient discretion. Cohort 3 will be receiving both IT injection and SQ injections and must be amenable to undergoing pre and post-treatment biopsy.***

***[4]Cohort 3, dose escalation only for the IT portion; SQ dose remains constant at 15 µg/kg.***

## 10. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 to 30 days before start of protocol therapy, as indicated in the study calendar, except for pregnancy testing, which must be performed within 48 hours prior to initial ALT-803 administration. Scans and x-rays must be performed within 30 days before the start of therapy. In the event that the patient's condition is changing, laboratory evaluations should be repeated within 24 hours before initiating the next cycle of therapy. Please refer to the study calendar below for specific timing of required evaluations.

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | | **Cycle 2 (Weeks)** | | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 | | W2 | W3 | W4 | W5 | W6 | Week 1 | | W2 | W3 | W4 | W5 | W6 | **14 days post last *dose*** | **6 Mo** | **1 year[i]** |
| | Within 30 days | Within 14 days | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | | | |
| **ALT-803** | | | X[l] | | X | X | X | | | X[l] | | X | X | X | | | | | |
| Informed consent | X | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | |
| Concomitant meds | X | | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Physical exam[h] | | X | X | | X | X | X | X | | X | | X | X | X | X | | X | X | X |
| Vital signs with oxygen saturation | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Height | X | | | | | | | | | | | | | | | | | | |
| Weight | X | X | X | | | X | | X | X | X | | X | | X | | X | X | X | X |
| Performance status | | X | X | | | | | | | X | | | | | | | X | X | X |
| CBC w/diff, plts | | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PT/PTT | | X | | | | | | | | | | | | | | | | | |
| Serum chemistry[a] | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Antinuclear antibody (ANA) | X | | | | | | | | | X | | | | | | | | X | X |
| Electrocardiogram (ECG)[b] | | | X | | X | X | X | | | X | | X | X | X | | | X | X | X |
| ECHO (as indicated) | X | | | | | | | | | | | | | | | | | | |
| Adverse event evaluation | | X | X | | X | X | X | X | X | X | | X | X | X | X | X | X | X | X |
| Tumor measurements[c] | X | Tumor measurements are repeated every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | | | X | |
| CT, MRI, or PET of chest, abdomen, pelvis[d] | X | Documentation (radiologic) must be provided for patients removed from study for progressive disease. | | | | | | | | | | | | | | | | | |
| CT or MRI Brain[d] [as indicated for sympt only] | X | If negative at baseline, to be repeated only with symptoms | | | | | | | | | | | | | | | | X | |
| Radiologic evaluation by RECIST 1.1 | X | Radiologic measurements should be performed every 6 ± 1 week and 12 ± 2 weeks | | | | | | | | | | | | | | | | X | |

| | **Pre-study (screening)** | | **Cycle 1 (Weeks)** | | | | | | | **Cycle 2 (Weeks)** | | | | | | | **F/U** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Week 1 | | W2 | W3 | W4 | W5 | W6 | Week 1 | | W2 | W3 | W4 | W5 | W6 | **14 days post last *dose*** | **6 Mo** | **1 year[i]** |
| | Within 30 days | Within 14 days | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | D1±1 | ***D4±1*** | D8±1 | D15±1 | D22±1 | D29±1 | D36±1 | | | |
| Injection Site Evaluation | | | | X | X | X | X | | | X | X | X | X | X | | | X | | |
| B-HCG[e] | | | X | | | | | | | | | | | | | | | | |
| Thyroid studies: TSH, T4 | X | | | | | | | | | | | | | | | | | X | X |
| PK[f] | | | X | | | | | | | | | | | | | | | | |
| WB Immunophenotyping[g] | | | X | ***X*** | X | X | ***X*** | X | | X | ***X*** | | | | X | | | | |
| IFN-γ ELISPOT[g] | | | X | | | | | ***X*** | | X | | | | | | | | | |
| NK-cell function[g] | | | X | ***X*** | ***X*** | | | ***X*** | | X | ***X*** | | | | | | | | |
| Plasma cytokines[g] | | | X | | | | | X | | X | | | | | X | | | | |
| Kyn/Trp ratio[g] | | | X | | | | | X | | X | | | | | X | | | | |
| Serum Ab to ALT-803[g] | | | X | | | | | | | X | | | | | | | X | | |
| Other laboratories[j] | | | X | | | | | | | | | | | | | | | | |
| Serum Storage (optional) | | | X | ***X*** | | | | | | | | | | | | | | | |
| Biopsy[m] | | | ***X*** | | ***X*** | | | | | | | | | | | | | | |

Abbreviations: Ab, antibodies; CBC, complete blood count; CT, computed tomography; MRI, magnetic resonance imaging; NK, natural killer; PET, positron emission tomography; PK, pharmacokinetics; PTT, partial thromboplastin time; PT, prothrombin time

[a] Blood chemistries include: creatinine, glucose, total protein, blood urea nitrogen (BUN), total carbon dioxide ($CO_2$), albumin, total bilirubin, phosphorus, alkaline phosphatase, aspartate transaminase (AST), and alanine transaminase (ALT)

[b] ECGs are to be done before ALT-803 ***administration*** on Day 1 and 4, 12 and 24 hours after the first ALT-803 ***dose*** (Cycle 1, Week 1, Day1). As clinically indicated, ECGs are to be obtained to evaluate for cardiac toxicity during subsequent doses and cycles of therapy and follow-up visits.

[c] Baseline tumor assessment scans should be done 1 to 30 days before beginning treatment.

[d] CT, MRI, or PET is acceptable for imaging assessment purposes

[e] Pregnancy test may be done up to 48 hours before ALT-803 administration

[f] See pharmacokinetic flow sheet for specific draw times

[g] Blood for WB Immunophenotyping, IFN-γ ELISPOT, NK-cell function, plasma cytokines, Kyn/Trp ratio and serum Ab to ALT-803 must be drawn **before** the patient receives ***the dose of*** ALT-803 on Days 1, 8, 15, and 22 of each treatment cycle.

[h] Physical exam must always include neurological assessment. In addition, a funduscopic exam, conducted by the investigator with a hand-held ophthalmoscope, must be done prior to starting therapy (Cycle 1, Day 1, Week 1) and repeated if clinically indicated (See Section 6.0 for additional details).

[i] Additional cycles beyond the 4th cycle may be considered for patients continuing to benefit and tolerating therapy, upon discussion among the sponsor and Principal Investigator.

[j] Other labs include: Lactate dehydrogenase, magnesium, phosphate, CK and troponin I or T; must be drawn **before** and at 12 and 24 hours after the first ALT-803 dose.

[k] CBC w/diff, plts (Cycle 1, Week 1, Day 1); must be drawn **before** and at **12** and **24** hours after the first ALT-803 dose.

[l] ***Cohort 3 only, intratumoral injection (Week 1, Day 1 of each treatment cycle)***

[m] ***Cohort 3 only, biopsy must be done before ALT-803 administration***