Masonic Cancer Center, University of Minnesota
Cancer Experimental Therapeutics Initiative (CETI)

Randomized Study of Single Course of Intraperitoneal (IP) ALT-803 Followed by Subcutaneous (SQ) Maintenance ALT-803 Versus Subcutaneous (SQ) Maintenance ALT-803 Only after 1st Line Chemotherapy for Advanced Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

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Revision History

Revision #	Version Date	Revision Details	Consent Revision
	09/15/2016	Original to CPRC	n/a
	01/06/2017	In response to CPRC minor stips and other interim edits including: • A new IND will be filed with Dr. Geller as the sponsor • Clarify and expand primary objective (triggered in part by CPRC review) • Update and expand genomic, transcriptomic and proteomic correlative testing on archived tumor and fresh blood – add available archived tumor to inclusion criteria • Add cytokine release syndrome (CRS) as a risk of ALT-803 and the planned monitoring/management • Update Section 8 based on updated IB for ALT-803 • Add patient diaries for SQ and IP dosing reactions	n/a
	03/24/2017	in response to FDA's initial review: • Synopsis, *Inclusion Criteria, Appendix I –Patient Eligibility Checklist, Appendix II – FIGO Staging, GOG PS and NYHA Classification* - limit enrollment to FIGO stage III and IV • Synopsis ,*Exclusion Criteria, Appendix I –Patient Eligibility Checklist* - Expand exclusion criteria adding uncontrolled hypertension, history of pulmonary disease or abnormal PFTs, narcolepsy or any neuro condition which may impair consciousness • *Inclusion Criteria, Appendix I –Patient Eligibility Checklist*: Add ANC and ALC requirements for eligibility • *Duration of Study Participation*, *Required Clinical Care Tests and Procedures*: Revise final treatment visit to continue follow-up if ongoing treatment related AEs until resolution/stabilization • *Section 7.2:* Incorporate FDA's recommended following time points for immunogenicity testing: pre cycle 1, 28-30 days after the first exposure of ALT-803, pre cycle 2, pre cycle 3, pre cycle 4, and 30-45 days after the last exposure of ALT-803. Additional revision to the protocol since original FDA submission: • *Synopsis*, *Secondary Objectives*, *Duration of Study Participation*, *Required Clinical Care Tests and Procedures*: Extend follow-up through 2 years from 1st dose (previously 1 year) – update secondary objectives to survival at 1 and 2 years • *Intraperitoneal ALT-803 Administration (Arm 2 only)*: Add pre-medication and monitoring guidelines to IP infusions	yes
1	08/09/2017	• Delete optional pre-screening through-out protocol including Section 7.1 and Section 7.2 • Synopsis – delete reference to all treatment will be given as an outpatient, correct duration of follow-up to 2 years to match rest of protocol • Synopsis and Section 4.1 Inclusion Criteria – clarify a minimum of 3 cycles of IP chemo must be given but patients may continue on IV only for additional cycles and study treatment must begin within 3 weeks (± 1 week) of the final dose of 1st line therapy (previously stated final dose of IP/IV therapy) • Section 4.1.8 Inclusion criteria – delete "available archived tumor" requirement as not a criteria for study treatment • Section 4.27 – reword for clarity exclusion criteria for hypertension • Section 6.1 – subcutaneous ALT-803 language updated to match other ALT-803 protocols requiring provider assessment prior to each dose and situations for skipping ALT-803 dosing. • Sections 6.1 and 6.2 – clarify place of treatment	Yes and delete pre-screening consent

Revision #	Version Date	Revision Details	Consent Revision
		• Sections 6.2.and 6.3 -delete language pertaining to warming of any infusate – fluids for IP washings and drug administration will be given at room temperature • Section 6.7 – update dosing requirements to receive the next treatment course based on changes made to other ALT-803 protocols Minor edits Move S/I contact information back to under revision history Section 2.5 – correct ALT803 to ALT-803 throughout section and replace figure with a better version Section 4.1.7 – delete (<1 mg/day) in regards to steroid use as nonsensical Section 9.1 – update to Cancer Center's new deviation definitions	
2	04/27/2018	• Revise protocol eligibility to permit enrollment within 3 months of last dose of chemotherapy rather than 3 weeks • Revise Sections 4.1 to delete ALC requirement as goal of ALT-803 is to increase ALC and update lab value thresholds to ≥ or ≤ as applicable for consistency • Sections 6.1, 6.2 and 8.6 – clarification ALT-803 dose calculation, monitoring, assessment, minimum dosing to match other ALT-803 protocols • Section 7 – clarify patient must return to clinic for each of the planned visits whether or not they are receiving ALT-803, • Section 7 - add footnote to tables in Section 7.1. and 7.2 that if disease reassessment if required specifically for the protocol, that the costs will be paid for by research (i.e. CT scan needs to be repeated as outside of the study's 30 day window requirement for baseline screening) • Section 8.1 – add vial concentration of ALT-803 2 mg/ml to reflect current lot release (none shipped to UMN yet) • Section 8.6 – cap dose calculation at a max weight of 100 kg, replace D5W with normal saline (NS) for ALT-803 IP administration • Section 8.8 –delete out of date toxicity language from 2016, add pain and cramping as side effect of IP administration and IP fluid collection just prior to ALT-803 • Section 12.4 – revise grade 3 abdominal pain to remove > 3 as no grade 4, 5 abdominal pain in CTCAE and qualify must no respond to pain medication and last more than 72 hours to count as a stopping rule event • Numerous updates to match other ALT-803 protocols and current template • Move S/I contact info to end of table of contents, other minor updates	Yes
3	05/21/2019	Update ALT-803 drug sections based on updated IB – A sufficient number of patients have been treated with ALT-803 (also known as N-803) that the toxicity profile is no longer based on IL-2 Update document with hyperlinks in preparation for electronic submission to FDA • Section 6.4 – delete hypotension management guidelines as hypotension (change in blood pressure) is not included in the updated toxicity profile. • Section 8 – ALT-803 Formulation, Supply and Potential Toxicity – update to reflect updated IB including vial concentration for SC administration and updated toxicity profile.	Yes

Revision #	Version Date	Revision Details	Consent Revision
		• Title page - update list of Co-Is by deleting Drs Cooley, Carson and Downs, Add Dr. Ghebre • Section 4.2.1, Appendix I – exclude women with somatic or germline BRCA 1/2+ as now are eligible for PARP inhibitors as maintenance therapy Minor edits and clarifications • Section 6.1 and Section 6.2 - add diphenhydramine to standard pre-meds • Section 6.1, 6.2 and 7 – replace dosing window language with more flexible dosing language • Section 7.1 – Remove EBV testing, clarify that the anchor for follow-up is based on every 3 months from the last disease reassessment not the end of treatment visit. • Section 7.2 – add back X's for green and red tops as accidentally deleted with last revision, rearrange columns for clarity • Section 8.1 – update ALT-803 formulation • Appendix I – update to new format • Appendix V – Injection Site Reaction Diary add a 2nd page as reactions rarely resolve within 1 week. • Appendix VI IP Reactions Diary - add "Intraperitoneal (IP) Injection" to the header to avoid confusion with the Appendix V Injection Site Reactions Diary	

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Synopsis

Randomized Study of Single Course of Intraperitoneal (IP) ALT-803 Followed by Subcutaneous (SQ) Maintenance ALT-803 Versus Subcutaneous (SQ) Maintenance ALT-803 Only after 1st Line Chemotherapy for Advanced Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

Study Design: This is a single center, randomized phase II study of an IL-15Rα-Fc super-agonist complex (ALT-803, more recently known as N-803) given as maintenance therapy after the completion of 1st line chemotherapy for the treatment of FIGO stage III and IV ovarian, fallopian tube, and primary peritoneal cancer.

In this study all patients receive four 8 week cycles of ALT-803 consisting of 4 weekly doses followed by a 4 week rest (no treatment). As it is not known how intraperitoneal (IP) administration (a route of drug administration frequently used for gynecologic cancers) of ALT-803 compares to subcutaneous (SQ) administration, both routes of administration will be tested. The primary objective of this trial is to select one method of delivery for further testing.

A 1:1 randomization will apply to the 1st treatment course only:
Arm 1: ALT-803 SQ only – patient receives ALT-803 10 mcg/kg SQ weekly x 4 followed by 4 weeks of no treatment before continuing with treatment courses 2, 3, and 4 as described below

Arm 2: ALT-803 IP and SQ – patient receives ALT-803 10 mcg/kg IP weekly x 4 weeks followed by 4 weeks of no treatment before continuing with treatment courses 2, 3, and 4

All patients, regardless of assignment will have weekly IP peritoneal washings through Day 29.

Treatment courses 2, 3, and 4 are identical for all patients – ALT-803 10 mcg/kg SQ weekly x 4 with a 4 week rest (4 weeks on/4 weeks off).

Patients will be followed until disease progression or for a maximum of 2 years from the 1st dose of ALT-803.

Primary Objective: The primary objective of this trial is to select a "winner" for future study with the intent to ensure that if one method is clearly inferior in terms of the primary endpoint of progression free survival (PFS) at 6 months. There is a small probability that the inferior method will be carried forward if the difference between IP and SQ administration is small, selection of the method will be allowed to include other factors (attraction of lymphocytes to the peritoneal cavity, ease of the methodology and safety).

Secondary Objectives:
- To determine one and two year progression free survival (PFS)
- To determine one and two year overall survival (OS)
- To document ALT-803 associated toxicity when administered by IP in this patient population
- To evaluate the safety of ALT-803 when administered by IP on this schedule

Correlative Objectives:
- To evaluate blood and peritoneal washing lymphocyte number, phenotype and function
- To characterize ALT-803 pharmacokinetics and immunogenicity
- To determine genomic and proteomic profile of tumors

Key Inclusion Criteria:
- Diagnosis of FIGO stage III or IV epithelial ovarian, fallopian tube or primary peritoneal carcinoma, has received at least 3 cycles of first line IV/IP cisplatin and paclitaxel chemotherapy and has stable disease or better as defined by measurable/evaluable tumor and/or CA-125 levels
- Able to begin study therapy within 3 months of final dose of first line chemotherapy
- GOG performance status ≤ 2
- Functional IP catheter

Enrollment: 28 patients enrolled over 3 years (8-10 patients per year)

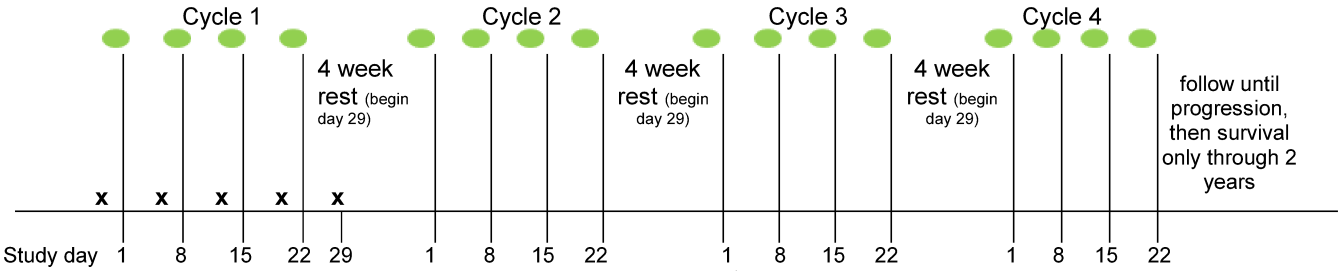
Schema

Randomization to one of the following arms: (14 patients per arm)

● ALT-803 SQ at 10 mcg/kg

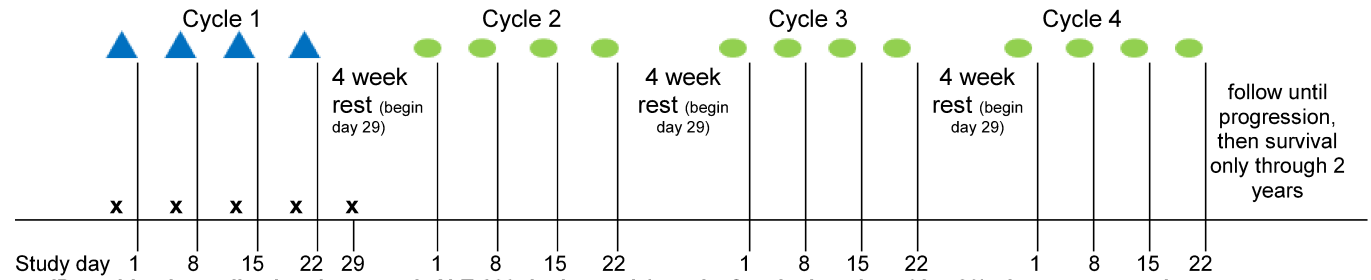
▲ ALT-803 IP at 10 mcg/kg (Arm 2 only)

Arm 1: ALT-803 SQ only: Weekly SQ ALT-803 10 mcg/kg (4 weeks on/4 weeks off) cycles 1 through 4



x – IP washing immediately prior to each ALT-803 dosing and 1 week after the last dose (day 29), then remove catheter

Arm 2: ALT-803 IP and SQ; Weekly IP ALT-803 10 mcg/kg (4 weeks on/4 weeks off) cycle 1 then weekly SQ ALT-803 10 mcg/kg (4 weeks on/4 weeks off) cycles 2 through 4



x – IP washing immediately prior to each ALT-803 dosing and 1 week after the last dose (day 29), then remove catheter

Post-Treatment Disease Reassessment per standard of care for 2 years from 1st dose of ALT-803

Monitoring Guidelines for Safety will employ early stopping rules to monitor excess toxicity:

1) Grade 3-5 organ toxicity (cardiac, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic) not pre-existing within the 1st two months lasting more than 72 hours.
2) Any grade 4 treatment emergent toxicity, grade 3 abdominal pain refractory to pain medication and persisting more than 72 hours or ≥ grade 3 ascites

1 Objectives

1.1 Primary Objective

The primary objective of this trial is to select a "winner" for future study with the intent to ensure that if one method is clearly inferior in terms of the primary endpoint of progression free survival (PFS) by 6 months of subcutaneous administration against intraperitoneal and subcutaneous administration of ALT-803. There is a small probability that the inferior method will be carried forward if the difference between IP and SQ administration is small, selection of the method will be allowed to include other factors (attraction of lymphocytes to the peritoneal cavity, ease of the methodology and safety).

1.2 Secondary Objectives

- To determine one and two year progression free survival (PFS)
- To determine one and two year overall survival (OS)
- To document ALT-803 associated toxicity when administered by IP in this patient population
- To evaluate the safety of ALT-803 when administered by IP on this schedule

1.3 Correlative Objectives

- To evaluate peripheral blood and peritoneal washing lymphocyte number, phenotype and function
- To characterize ALT-803 immunogenicity
- To determine the genomic, transcriptomic, and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic, transcriptomic, and proteomic profiles and efficacy outcomes will be assessed.

2 Background and Significance

2.1 Introduction

Ovarian cancer is the most lethal gynecologic malignancy. The estimated 5-year survival is 46% for all stages of ovarian cancer, and 28% for distant disease. Notably, 62% of women with ovarian cancer present with Stage III or IV disease, for which the rate of recurrence is 60-70% (1). Women who recur cannot be cured with current therapies (2). Our long term research objective is to exploit the innate immune system to treat ovarian cancer and substantially improve survival rates.

2.2 Interleukin-15 (IL-15)

IL-15 induces the activation and proliferation of CD8+ T cells and NK cells with less effect on Tregs. Interleukin-15 (IL-15) is a cytokine and growth factor capable of expanding activated T cells and NK cells. By broad consensus, the NCI Immunotherapy Workshop (2007) ranked IL-15 as the #1 agent with "high potential for immunotherapy" (3). Based on preclinical non-human primate and early phase clinical trial data, IL-15 regimens can unquestionably increase T-cell and NK-cell counts which could augment the efficacy of other immunotherapy modalities.

rhIL-15 increases the number of circulating CD8+ T and NK cells, but has a very short half-life. The NCI Biological Resource Branch has manufactured E. coli-expressed recombinant human IL-15 (rhIL-15). In non-human primates, NCI rhIL-15 was most effective when administered by continuous IV infusion. To a lesser extent, daily SC injection of NCI rhIL-15 was also effective at expanding the number of peripheral blood activated T cells and NK cells. These data strongly imply that low-dose continued presence of IL-15 in serum will be most effective at expanding T cells and NK cells.

2.3 ALT-803

Trans-presentation of IL-15 is the best physiologic signal to expand NK cells. While Jeffrey Miller's group and others have shown that IL-15 is necessary for homeostasis of NK cells,(4, 5) approaches to apply this clinically are complicated. It is believed that after lymphodepleting chemotherapy (as we are currently delivering in our NK cell ovarian cancer trial), endogenous IL-15 in serum binds to IL-15Rα to form a natural complex. This natural complex interacts with IL-2Rβɣ on NK cells and CD8+ T cells through a process called IL-15 trans-presentation(6, 7). Monocytes and dendritic cells express the highest density of IL-15Rα(8). There are three IL-15 products in clinical development (Figure 1). Each has unique structural differences that determine how they interact with NK cells in vivo. Waldmann and colleagues first tested the NCI rhIL-15 as monotherapy for melanoma and renal cell carcinoma. He has established a maximum tolerated dose (MTD) of 0.3 mcg/kg IV for 12 daily doses(9). Ongoing intramural trials at the NCI are testing whether continuous infusion dosing provides optimal in vivo stimulation to lymphocytes. Importantly, for NCI rhIL-15 to be trans-presented, it must be complexed with membrane-bound or soluble IL-15Rβɣ Altor Bioscience Corporation (Altor,

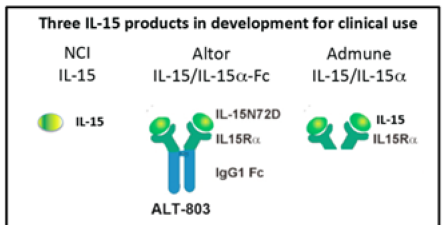


Figure 1. IL-15 products being developed for clinical use.

Miramar, FL) has developed IL-15/IL-15Rα-Fc super-agonist complexes (ALT-803), the design of which includes the addition of a sushi domain to inhibit complement activation, increased avidity of the molecule to IL-2Rβγ on NK cells, and increased half-life and stability by inclusion of the Fc domain(10, 11, 12). We have secured a supply of ALT-803 (Altor IL-15/IL-15Rα-Fc) for testing in the proposed clinical trial.

ALT-803 is a novel IL-15 immunoconjugate designed to have a prolonged serum half-life. The novel IL-15 immunoconjugate, ALT-803 (IL-15N72D:IL-15RαSu/IgG1 Fc complex) (See Figure 1) was developed by our collaborator, Altor BioScience, to overcome some of the biologic, regulatory, and commercial limitations of unmodified E. coli-derived rhIL-15. Under natural circumstances, IL-15 and IL-15 Receptor-alpha (IL-15R) are coordinately expressed by antigen-presenting cells (i.e., monocytes and dendritic cells)(13). During signaling by the IL-15 pathway, IL-15 bound to IL-15R is presented in trans to neighboring NK or CD8+ T cells expressing only the IL-2Rβ (CD122) and the common γ-chain (CD132) receptor components. At the immunologic synapse, IL15 trans-presentation appears to be a dominant mechanism for IL-15 action *in vivo*, providing tight physiologic control over the functions of IL-15 under homeostatic conditions and in response to immune stimuli (14). In addition, ALT-803 contains a novel IL-15 mutant with a single substituted amino acid (rhIL-15N72D) that has a 4-fold increase in biologic activity greater than wild-type IL-15 (IL-15 wt)(15). Normal soluble IL-15R fragments, containing the "sushi" domain (Su) at the N terminus, have been shown to contain most of the structural elements responsible for cytokine binding, and IL-15R binds IL-15 with high affinity (Kd 100 pM). Soluble IL-15R and IL-15 in solution can form stable heterodimeric complexes capable of modulating (ie, either stimulating or blocking) immune responses via the IL-2R complex(16,17,18). Previous studies have shown that the biologic activity of IL-15 could be increased 50-fold by administering preformed complexes of IL-15 and soluble IL-15R, which has a longer half-life than rhIL-15 (16,18). The IL-15:IL-15R complex increases activity at lower concentrations, and the fusion with Ig-G1 Fc increases serum half-life, providing more ideal pharmacokinetics with prolonged cytokine function (19). We hypothesize that ALT-803 will require only weekly administration to achieve similar benefits to that provided by low-dose continuous rhIL15 exposure.

2.4 ALT-803 by Subcutaneous Injection and Intravesical Instillation

In August 2016, Altor prepared a Safety Summary of ALT-803 based on several ongoing early stage trials for various cancer indications (unverified/unaudited

data). At the time 107 patients had received at least 1 dose of ALT-803, of which 35 were by subcutaneous injection and 26 of those patients treated at the University of Minnesota. Dosing ranged from 1 mcg/kg to 20 mcg/kg with the majority treated at 6 mcg/kg (n=16) and 10 mcg/kg (n=12). The Altor clinical update concurred with our experience that subcutaneous dosing was generally well tolerated with an injection site related skin rash as the most notable event, often quite widespread; however none were dose limiting. Typically the rash resolved by 7 days post-injection. Other effects included fever, fatigue, and changes in blood pressure.

In the same Safety Summary, toxicity data was presented on an ongoing Altor-sponsored multi-center trial of intravesical ALT-803 plus BCG in patients with non-invasive bladder cancer (NCT02138734 – University of Minnesota is not a participate). During the phase I dose escalation component, weekly ALT-803 combined with standard BCG was administered in a standard 3+3 design testing dose levels 100, 200, and 300 mcg/instillation. The expansion phase is currently enrolling using ALT-803 mcg/instillation. The most common adverse events (N=9) during dose escalation included hematuria, headache and urinary tract pain.

2.5 Study Rationale

Rationale for Using ALT-803

IL-15, in contrast to IL-2, does not support the expansion of regulatory T cells (Tregs) (20). Thus, IL-15 administration holds promise to specifically boost NK cell alloreactivity without the undesired stimulation of Tregs. ALT-803 is a highly potent recombinant IL-15 super-agonist which has an augmented capacity to expand NK cells compared with IL15 (21,22). We have chosen the 10 mcg/kg subcutaneous dose for this trial based on testing here at the university and Dr. Miller's involvement in national trials through the NCI CITN.

While some studies continue to dose escalate (currently 15 and 20 mcg/kg are under study), 10 mcg/kg is safe in other solid tumor cohorts, especially with subcutaneous dosing. In addition, we have some immunologic data suggesting that 10 mcg/kg induces a stronger proliferative signal in most subjects while the 6 mcg/kg dose seems more variable. Given the safety profile of both doses and the goal of IL-15 in this trial to maintain persistence and possible NK cells in vivo (especially in the peritoneal cavity), we have chosen the 10 mcg/kg subcutaneous dose for studies proposed here.

Rationale for Using IP dosing

Based on our recently published *in vivo* mouse data(23), our current platform for NK cell therapy in ovarian cancer delivers NK cells IP as we have seen significant inhibition of ovarian cancer growth using this delivery. As ovarian cancer is an intraperitoneal disease, rarely metastasizing beyond the abdominal cavity, therapy delivered directly to the tumor site makes intuitive sense. Recent studies done by our collaborators defined the lymphocyte population within the peritoneal fluid (PF) of women with high-grade serous ovarian cancer (Figure 2). They found that women with ovarian cancer had a significantly lower percentage of NK cells in the PF compared to women with benign disease. Importantly, the ovarian cancer patients with lower number of NK cells had significantly lower survival. This data provides the rationale for delivering ALT-803 IP to increase and expand NK cells directly within the peritoneal cavity.

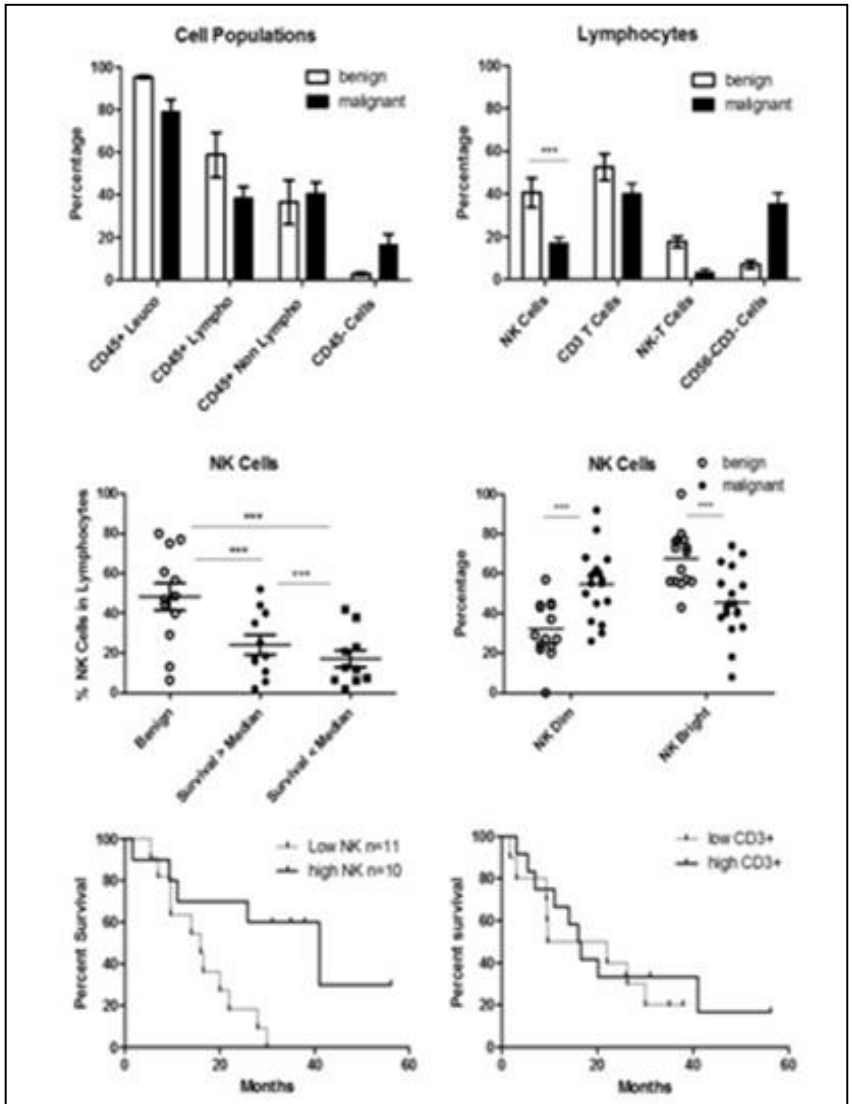


Figure 2 a) main cell populations in the peritoneal fluid (PF) of benign patients vs. high grade serous ovarian ca patients **b)** the percentage of NK cell in PF is significantly higher in benign patients ($p<0.0001$). A higher percentages of PFNK cells is present in patients surviving longer than the median survival rate **c)** the Kaplan Meier curve of the low NK group (< median) vs. patient with high NK cell count in PF ($p<0.01$). CD3 counts

We have recently identified that subcutaneous dosing of ALT-803 is safer than IV. In the switch from IV to SQ ALT-803, we have been able to show better clinical tolerance with less constitutional systems related to a lower ALT-803 peak serum concentration with SQ administration and less early post injection systemic inflammatory cytokines. One interesting and surprising finding serves at the

primary rationale for testing IP injection of ALT-803. Several patients on SQ ALT-803 trials have developed prominent skin rashes, which in some cases involved half the abdomen surface area [with an abdominal SQ injection]. Biopsy of these lesions shows an inflammatory infiltrate comprised of lymphocytes and myeloid cells [macrophage type cells]. The lymphocytes are predominantly T cells with less NK cells. Unexpectedly, the T cell infiltrate in some patients is predominantly of the CD4 subset. This leads to a new hypothesis to be tested here that IP injection of ALT-803 will be safe but will better attract lymphocytes to the site of ovarian cancer, in the abdomen. We propose that ALT-803 has strong chemotactic activity for T and NK cells and will promote an "intratumoral" lymphocyte infiltrate that can be activated locally to overcome tumor induced immune suppression and may lead to better anti-tumor activity.

3 Study Design

This is a single center, randomized phase II study of an IL-15Rα-Fc super-agonist complex (ALT-803) given as maintenance therapy after the completion of 1st line cisplatin and paclitaxel chemotherapy for the treatment of advanced ovarian, fallopian tube, and primary peritoneal cancer.

In this study all patients receive 4 cycles of ALT-803 consisting of 4 weekly doses followed by a 4 week rest (no treatment). As it is not known how intraperitoneal (IP) administration (a route of drug administration frequently used for gynecologic cancers) of ALT-803 compares to subcutaneous (SQ) administration, both routes of administration will be tested. All patients will be required to have a functional IP catheter in place at study enrollment to permit weekly IP washings through Day 29 of the 1st treatment course as attraction of lymphocytes to the peritoneal cavity is a critical factor for the primary endpoint.

Randomization will apply to the 1st treatment course only with the following arms:
Arm 1: ALT-803 10 mcg/kg SQ only – patient receives ALT-803 10 mcg/kg SQ weekly x 4 followed by 4 weeks of no treatment before continuing with treatment courses 2, 3, and 4 as described below
Arm 2: ALT-803 10 mcg/kg IP and SQ – patient receives ALT-803 10 mcg/kg IP weekly x 4 weeks followed by 4 weeks of no treatment before continuing with treatment courses 2, 3, and 4 as described below

Treatment courses 2, 3, and 4 are identical for all patients – ALT-803 10 mcg/kg SQ weekly x 4 with a 4 week rest (4 weeks on/4 weeks off).

Patients will be followed until disease progression, then for survival only for a maximum of 2 years from the 1st dose of ALT-803.

4 Patient Selection

Study entry is open to females 18 years and older regardless of race or ethnic background. While there will be every effort to seek out and include minority patients, enrollment is expected to be similar to other that of other 1st line treatment studies at the University and referring community physicians.

4.1 Inclusion Criteria

4.1.1 Diagnosis of FIGO stage III or grade IV epithelial ovarian, fallopian tube or primary peritoneal carcinoma, has received at least 3 cycles of first line IV/IP cisplatin and paclitaxel chemotherapy and has stable disease or better – refer to Appendix II for FIGO staging system (Note: to be eligible for this study, the patient must receive a minimum of 3 cycles of IP therapy; however, patients may continue on IV only 1st line therapy for additional cycles as long as inclusion criteria 4.1.2 is met)

4.1.2 Able to begin study therapy within 3 months of final dose of first line chemotherapy

4.1.3 Functioning intraperitoneal catheter

4.1.4 ≥ 18 years of age

4.1.5 GOG performance status ≤ 2 (Appendix II)

4.1.6 Adequate organ function within 14 days of enrollment defined as:
Hematology: hemoglobin ≥ 8 g/dl, absolute neutrophil count (ANC) ≥ 1500/ul, platelets ≥ 50 x 10^9/L
Creatinine: ≤ 2.0 mg/dL
Hepatic: SGOT and SGPT ≤ 3 x upper limit of institutional normal (ULN)

4.1.7 Ability to be off prednisone and other immunosuppressive drugs for at least 3 days prior to and while receiving ALT-803

4.1.8 Voluntary written consent prior to the performance of any research related procedures

4.2 Exclusion Criteria

4.2.1 Somatic or germline BRCA1 or BRCA2 mutations

4.2.2 Received any investigational agent within the 14 days before the start of ALT-803

4.2.3 Class II or greater New York Heart Association Functional Classification criteria (Appendix II) or serious cardiac arrhythmias likely to increase the risk of cardiac complications of cytokine therapy (e.g. ventricular tachycardia, frequent ventricular ectopy, or supraventricular tachyarrhythmia requiring chronic therapy)

4.2.4 Marked baseline prolongation of QT/QTc interval (e.g. demonstration of a QTc interval greater than 500 milliseconds)

4.2.5 Uncontrolled bacterial, fungal or viral infections including HIV-1/2 or active hepatitis C/B – chronic asymptomatic viral hepatitis is allowed

4.2.6 Active autoimmune disease requiring systemic immunosuppressive therapy

4.2.7 History of severe asthma and currently on chronic systemic medications (mild asthma requiring inhaled steroids only is eligible)

4.2.8 Uncontrolled hypertension: defined as ≥2 readings over 160 mmHg systolic or 110 mmHg diastolic within month prior to enrollment despite optimal anti-hypertensive medication. Patients with high readings which improve to ≤160/110 after adjustment of medications will be eligible.

4.2.9 History of pulmonary disease or abnormal pulmonary function studies

4.2.10 History of narcolepsy or any neurological condition which may impair consciousness

5 Screening and Study Enrollment

Written consent must be obtained prior to the performance of any research related tests or procedures. Consent is usually obtained before final eligibility is determined.

5.1 Consent and Study Screening in OnCore

Any patient who has been consented is to be entered in OnCore by the Primary Clinical Research Coordinator (PCRC) or designee. If a patient is consented but is not enrolled, the patient's record is updated in OnCore as a screen failure and reason for exclusion recorded.

5.2 Study Enrollment and Treatment Arm Assignment

To be eligible for this study, the patient must sign the treatment consent and meet each inclusion criteria and none of the exclusion criteria listed on the eligibility checklist (found in Appendix I) based on the eligibility assessment documented in the patient's medical record.

The Primary Clinical Research Coordinator (PCRC) or designee will complete the enrollment process in OnCore by assigning the treatment arm and entering the on treatment date.

At the time of enrollment, the patient is randomized to one of the following treatment arms:

Arm 1: ALT-803 SQ only – patient receives ALT-803 10 mcg/kg SQ weekly x 4 followed by 4 weeks of no treatment (rest) before continuing with treatment courses 2, 3, and 4

Arm 2: ALT-803 IP and SQ – patient receives ALT-803 10 mcg/kg IP weekly x 4 weeks followed by 4 weeks (rest) of no treatment before continuing with treatment courses 2, 3, and 4

Treatment courses 2, 3, and 4 are identical for all patients – ALT-803 at 10 mcg/kg SQ weekly x 4 with a 4 week rest (4 weeks on/4 weeks off).

5.3 Patients Who Are Enrolled and Do Not Receive Study Treatment

If a patient is enrolled to the study, and is later found not able to begin ALT-803 within the required timeframe, for whatever reason, the patient will be removed from study and treated at the physician's discretion. The study staff will update OnCore of the patient's non-treatment status (off study). The reason for

removal from study prior to starting study treatment will be clearly indicated in OnCore. The patient will be replaced to complete enrollment.

6 Treatment Plan

In order to provide optimal patient care and to account for individual medical conditions, investigator discretion may be used in the prescribing of all supportive care drug therapy (i.e. acetaminophen, diphenhydramine, antimicrobials, etc.); however the use of systemic steroid medications may result in loss of therapeutic effects of the study drug and should be avoided. Topical steroid cream is permitted.

A 1:1 randomization will be done at the time of enrollment for the 1st treatment course only with the following arms:

Arm 1: ALT-803 10 mcg/kg SQ only – patient receives ALT-803 10 mcg/kg SQ weekly x 4 followed by 4 weeks of no treatment before continuing with treatment courses 2, 3, and 4 per Section 6.1.
Arm 2: ALT-803 10 mcg/kg IP and SQ – patient receives ALT-803 10 mcg/kg IP weekly x 4 weeks followed by 4 weeks of no treatment per Section 6.2 before continuing with treatment courses 2, 3, and 4 as described in Section 6.1.

Note: All patients regardless of treatment assignment will have IP washings weekly through Day 29 of the 1st treatment course per Section 6.3.

6.1 Subcutaneous ALT-803 Administration

The 1st course of ALT-803 is administered on the Phase I unit due to the peritoneal washings required on all patients. Treatment courses 2, 3, and 4 may be administered in the outpatient clinic or the Phase I unit.

ALT-803 10 mcg/kg will be administered subcutaneously once a week on Day 1, 8, 15 and 22 followed by 4 weeks of no treatment (beginning Day 29). This constitutes 1 treatment course. ALT-803 dosing should be weekly (every 7 days) however; in the event of scheduling issues (i.e. holiday, bad weather, etc.), at least 6 days, and no more than 10 days must separate each dose.

A study trained provider must assess the patient prior to administration of each day's ALT-803 injection to ensure no concerns are present. Refer to the Provider's Assessment section below.

ALT-803 dosing will be calculated using a weight obtained within 5 days prior to the first dose. For patients > 100 kilograms weight, the ALT-803 dose will be calculated using a weight capped at 100 kg. The weight will be re-checked at the beginning of each subsequent cycle with the dose re-calculated if ≥ 10% change from the weight used for the previous dose calculation.

All injections are given in the abdominal area. Injection sites should be rotated per institutional guidelines and each injection site separated by at least 1 inch.

Doses of ALT-803 can be administered on an outpatient basis.

Provider's Assessment Prior to Each ALT-803: In order to proceed with a planned ALT-803 injection, a provider must assess the patient prior to administration to rule-out any of the following contraindications for dosing:

- the previous injection site reaction is not showing signs of resolving (improving) based on measurement or intensity
- signs or symptoms of a new infection
- fever > 101°F (38.3 °C)

The ALT-803 dose will not be given if one or more of the above conditions are present.

In addition, ALT-803 may be held on the day of a planned dose for either of the following situations:

- any grade 3 or greater ongoing ALT-803 treatment related toxicity (injection site reaction, neurologic, increased liver function tests)
- if in the opinion of the treating physician, holding ALT-803 would be of benefit to the patient

If after a 1 week rest, the patient meets the provider assessment criteria for treatment; the patient may resume treatment. The intent will be to give all remaining doses of ALT-803 for the treatment course, but the missed dose will not be made up to maintain the 8 week treatment course.

If treatment is not restarted after a 1 week rest, any remaining ALT-803 doses within that course will not be given with the 8 week treatment course maintained. Patients must return for each planned treatment day visit (i.e. Day 8, 15 and 22 of the course) and Day 29 in Course 1 only for assessment and bloodwork even if ALT-803 has been discontinued for that treatment course.

Dose modification: A one-time dose decrease to 6 mcg/kg is allowed for recurrent constitutional symptoms (e.g. fever, fatigue, muscle aches) interfering with activities of daily (ADL) related to ALT-803 dosing despite pre-medication. Patients unable to tolerate the reduced dose will be discontinued from further ALT-803. Re-escalation of the dose is not permitted.

Pre-medications: Administer acetaminophen 650 mg and diphenhydramine 25 mg PO prior to each injection. Use of additional pre-medications is at the discretion of the treating physician on an individual patient basis.

Monitoring: Patients will be observed for a minimum of 2 hours after the 1st SQ dose for immediate adverse events. Vital signs (heart rate, blood pressure, respiration, temperature, and oxygen saturation) will be done prior to each ALT-803 injection and then at 30, 60 and 120 minutes with a ± 20 minute window for each time point.

If the 1st SQ dose is well tolerated, subsequent doses may be administered with a 30 minute post dosing observation period. Vital signs (heart rate, blood pressure, respiration, temperature, and oxygen saturation) will be documented prior to each ALT-803 injection and at 30 minutes (+20 minute window).

Inadequate dosing (Treatment Course 1 only):
If a patient receives only one dose of ALT-803 during treatment course 1, the patient will be taken off treatment and followed per Section 7.1. The patient will be fully evaluable for safety and toxicity, but replaced in the evaluation of efficacy. Patients receiving at least two doses of ALT-803 during treatment course 1 will be evaluable and may continue therapy.

6.2 Intraperitoneal ALT-803 Administration (Arm 2 only)

As this study is the first to use IP delivery of ALT-803, an overnight stay on the Phase I Unit is required for the 1st 2 doses in each of the 1st 3 patients to ensure no unacceptable toxicity occurs post-dosing. Based on the toxicity observed, a recommendation will be made regarding overnight stays for subsequent doses and future patients.

For the 1st treatment course only, ALT-803 is administered intraperitoneally at 10 mcg/kg once a week on Day 1, 8, 15 and 22 followed by 4 weeks of no treatment. ALT-803 dosing should be weekly (every 7 days) however; in the event of scheduling issues (i.e. holiday, bad weather, etc.), at least 6 days, and no more than 10 days must separate each dose.

ALT-803 dosing will be calculated using a weight obtained within 5 days prior to the first dose. For patients > 100 kilograms weight, the ALT-803 dose will be calculated using a weight capped at 100 kg. The weight will be re-checked at the beginning of each subsequent cycle with the dose re-calculated if ≥ 10% change from the weight used for the previous dose calculation.

Treatment course 2, 3, and 4 are administered subcutaneously as detailed in Section 6.1.

ALT-803 is administered IP in approximately 50 cc of room temperature Normal Saline (NS) via peritoneal catheter. After the ALT-803 infusion and the NS flush, the patient will be asked to change position at 15-minute intervals for two hours to ensure adequate intra-abdominal distribution. No attempt will be made to retrieve the infusate.

Provider's Assessment Prior to Each ALT-803: In order to proceed with a planned ALT-803 infusion, a provider must assess the patient prior to administration to rule-out any of the following contraindications for dosing:

- signs or symptoms of a new infection
- fever > 101°F (38.3 °C)
- there are signs or symptoms of disease progression

The ALT-803 dose will not be given if one or more of the above conditions are present.

In addition, ALT-803 may be held on the day of a planned dose for either of the following situations:

- any Grade 3 or greater ongoing ALT-803 treatment related toxicity (neurologic, increased liver function tests)
- if in the opinion of the treating physician, holding ALT-803 would be of benefit to the patient

Pre-medications: Administer acetaminophen 650 mg and diphenhydramine 25 mg PO prior to each injection. Use of additional pre-medications is at the discretion of the treating physician on an individual patient basis.

Monitoring: Patients will be observed for immediate adverse events during the 2 hour IP process. Vital signs (heart rate, blood pressure, respiration, temperature, and oxygen saturation) will be done prior to each ALT-803 IP

dosing and then at 30, 60 and 120 minutes with a ± 20 minute window for each time point.

Dose modification and inadequate dosing as described in Section 6.1 also applies to IP dosing.

In the event the patient "loses" the IP catheter, the treatment modality will be switched to SQ dosing for the remainder of cycle 1. The patient remains in the IP study arm for the purpose of analysis as this study uses the Intent to Treat (ITT) principle per Section 12.2. Blood samples for research will continue to be collected as planned; however, IP fluid collection would not.

6.3 Intraperitoneal Washing (all patients weekly through Day 29 of Treatment Course 1)

The presence of a functioning IP catheter is required for study eligibility. All patients, including those assigned to the SQ treatment arm, will have intraperitoneal washings prior to each ALT-803 administration during treatment course 1 and 1 week after the last dose.

For the peritoneal washing a volume of approximately 250cc of room temperature NS will be infused into the abdomen. After infusion the patient will be asked to change position (right lateral, left lateral, Trendelenburg (feet higher than head by 30 degrees), reverse Trendelenburg) at 5-minute intervals to ensure adequate intra-abdominal distribution. Fifty (50) cc of infusate will then be retrieved through the indwelling catheter.

If a minimum of 50cc of infusate is not retrieved, another 250 cc of NS will be infused and the above process repeated. If insufficient infusate can be retrieved, the process will be terminated.

The collection(s) regardless of volume, will be sent to TTL.

The IP catheter may be removed after the last IP washing 1 week after the last dose of ALT-803 of treatment course 1.

6.4 Managing of Selected Expected Adverse Events

6.4.1 Skin Rash in Association with Subcutaneous ALT-803

Based on current experience, localized skin rashes are common with subcutaneous administration. If a rash occurs and the rash area surrounding the ALT-803 injection site is > 6 cm and symptomatic (painful and/or itchy), it

may be treated (at the discretion of the treating physician) with topical 0.05% clobetasol propionate (i.e. 0.05% Cormax) or 0.1% triamcinolone (i.e., Kenalog) cream. Diphenhydramine may be administered pre- (25-50 mg TID orally) and post-dosing (25-50 mg TID orally x 2 days) of ALT-803 at the discretion of the treating physician. Diphenhydramine should be eliminated if not tolerated.

6.4.2 Cytokine Release Syndrome (CRS) or CRS-Like Symptoms

While CRS is a clearly defined syndrome in T cell therapy, it is not known to occur to the full extent in NK cell therapies. However, we have seen immune activation syndromes that include fever, and rash but without T cell mediated vascular collapse. If symptoms occur, CRP, IL-6 and ferritin levels will be assessed. If medically indicated by the presence of enormously elevated IL-6 levels (> 500), steroids are the first line of treatment.

Patients will be monitored for clinical signs and symptoms of CRS. Refer to Section 9 for the revised CRS grading system that will be used for this study.

6.5 Supportive Care

Supportive care will be provided per institutional guidelines. Guidelines may be updated based on current data/drugs without requiring a protocol amendment or be considered a protocol deviation.

6.6 General Concomitant Medications Guidelines

Administration of additional glucocorticoids is discouraged during the ALT-803 treatment period as the use of systemic steroid medications may result in loss of therapeutic effects of the study drug. Sustained use of steroids or steroid use to treat related toxicity will be an indication to stop ALT-803. Transient use is permitted as needed per standard of care. Topical steroid cream is permitted.

Beta-blockers and other anti-hypertensives may potentiate the hypotension and caution should be used during ALT-803 regimen treatment period. It is recognized, that ALT-803 treatment, like IL-2 and IL-15, may be associated with low blood pressure especially if the patient is not well hydrated.

6.7 Duration of Treatment

ALT-803 post-transplant may continue for up to four 8 week cycles (4 weeks on/4 weeks/off) unless one of the following occurs:

- unacceptable toxicity

- meets the criteria for inadequate dosing during the Course 1 by receiving only 1 dose of ALT-803 (refer to Section 6.1)
- requires new anti-cancer therapy
- consent is withdrawn or patient is not compliant
- the treating investigator feels continuing study treatment is not in the best interest of the patient

6.8 Duration of Study Participation

All patients must be followed for a minimum of 4 weeks after the last dose of ALT-803 for any occurrence of ALT-803 treatment related toxicity. Patients who have an adverse event or serious adverse event must be followed until resolution or stabilization of that event, even if the time to resolution/stabilization greater than 4 weeks after discontinuation of ALT-803.

Evaluable patients will be followed for overall progression free survival and overall survival for 2 years from the 1st dose of ALT-803 unless consent is withdrawn.

7 Clinical Evaluations and Procedures

Scheduled evaluations during the treatment courses may be performed ±2 days from the targeted date unless otherwise specify in the x-chart. ALT-803 dosing should be weekly (every 7 days) however; in the event of scheduling issues (i.e. holiday, bad weather, etc.), at least 6 days, and no more than 10 days must separate each dose.

The End of Treatment visit may be done ±7 days of the targeted date.

Follow-up is by record review through 2 years from the 1st dose of ALT-803. Response assessments are done according to standard of care (usually every 3 months in this patient population). Disease status is recorded in OnCore until disease progression or start of a new therapy, whichever is earlier. Then the patient is followed for survival only until 2 years from the start of ALT-803.

In addition, targeted days may be altered as clinically appropriate.

7.1 Required Clinical Care Tests and Procedures

	Screening (within 30 days of treatment start)[1]	Each Treatment Course = 8 weeks (4 weekly doses followed by 4 weeks no treatment for up to 4 courses)					Course 1 only Day 29	Every 3 months based on SOC assessment schedule	End of treatment visit (4 weeks after the last ALT-803 dose)	SOC Follow-up for response and survival (for 2 years from rx start)
		Dose 1		Dose 2	Dose 3	Dose 4				
		Day 1 (-3 days)	Course 1 Day 5 (- 2 days)	Day 8	Day 15	Day 22				
Consent	X									
Baseline Screening Assessment	X									
Physical Exam	X	X					X		X	
Provider Assessment		X	X	X	X	X				
Medical History	X									
Concomitant medications	X	X								
Vitals and pulse oximetry	X	X		X	X	X	X		X	
Weight	X	X					X			
GOG Performance Status	X	X							X	
Survival Status										X
Toxicity Assessment		X		X	X	X	X		X[3]	
Review of Patient Reactions Diary from previous ALT-803		X					X			
Disease Assessment – Imaging Studies	X[1]							X		X[2]
CA-125	X[1]							X		X[2]
CBC, diff, plt	X	X	X	X	X	X	X		X	
Comprehensive metabolic panel	X	X		X	X	X	X		X	
Basic metabolic panel			X							
EKG	X									
Pulmonary Function Tests[4]	X									

1 - within 14 days for labs required for eligibility per Section 4.1, if SOC imaging studies for screening are not within the 30 day window, imaging must be repeated but will be charged to research, obtaining the consent is exempt from 30 day limit and may be signed at any time

2 –per standard of care (usually every 3 months) using 3 months after the last disease assessment while on study as the starting point – follow response until progression or start of new treatment (by record review) then for survival only

3- any ongoing AE or SAE must be followed until resolution/stabilization per Section 6.8

4 – only required if symptoms or prior impairment

7.2 Research Related Tests and Procedures

	Baseline/ Screening	During Each Treatment Course				Course 1 only		End of Treatment visit (4 weeks after the last ALT-803 dose)
		Day 1 (-3 days)	Day 8	Day 15	Day 22	Day 5 (-2 days)	Day 29	
Toxicity Notation		Refer to Section 9.2 for documentation requirements						
Monitor for Stopping Rule Events		per Section 12.4						X
Disease Assessment – Imaging Studies and CA-125 (only if SOC is outside of the 30 day window)	X[7]							
50 ml of heparinized blood (5 green top tubes)		X	X	X	X	X		X
10 ml of serum (1 red top tube)		X	X	X	X	X		X
IP washing[1] (refer to Section 6.3)		X	X	X	X		X[2]	
Immunogenicity 5 ml of serum (1 red top tube)[5]		X					X	X
Exploratory Molecular Profiling (baseline only) – refer to Section 7.2.3								
1 red top and 1 marble top tube (NantOmics Kit)	X							
FFPE tumor tissue sample[6]	From definitive surgery							

1 Collect prior to ALT-803 dosing, Cycle 1 only – all samples (no matter how small) go to TTL
2 IP catheter may be removed after IP washing
3 Collect research blood samples weekly (i.e. prior to dosing including any weeks where dosing is held)
4 Do not collect any additional research samples once a patient is off treatment for disease progression
5 To TTL per Section 7.2.2
6 If available, a minimum tissue surface area of 25 mm^2, 75 µm thick, with at least 30% malignant tissue
7 Charge to research only if patient's SOC assessments are outside of the 30 day window required for screening

Note: if a patient is not abiding by the required clinical care calendar (Section 7.1), the collection schedule of the toxicity (adverse event) data and research related samples may be altered or discontinued on an individual patient basis, as appropriate. However; in cases where a dose is held, the patient must return for each planned treatment day visit (i.e. Day 8, 15, and 22 of the cycle) and for Cycle 1 only, Day 29, for assessment and bloodwork for that cycle.

It is recognized that with novel therapies as used in this study, the timing of protocol directed research samples may miss important patient specific events. For this

reason, up to 3 extra samples for a total of 180 ml of blood may be drawn at additional relevant time points, as per the PI's opinion, and are not specified above.

7.2.1 Assessment of Immune Activation (TTL)

Blood and IP wash samples to evaluate lymphocyte number, phenotype and function will be collected as detailed above for the Masonic Cancer Center Translational Therapy Lab (TTL) along with serum (red top tubes) for measure of cytokines that can reflect immune activation.

Flow cytometry analysis of a fraction of the PBMC will detect surface markers that define lymphocyte subsets (NK, NKT, B, and T cells, both CD4 and CD8), as well as intracellular markers that define regulatory T cells (Foxp3) and proliferating cells (Ki67). All remaining PBMC will be cryopreserved in 10% DMSO and stored in liquid nitrogen for future testing, if subject agreed to future storage at the time of initial consent.

7.2.2 Immunogenicity (ALTOR)

Immunogenicity assays will be performed at Altor BioScience Corporation.

The blood sample will be processed (centrifuge at 1000-1500 xg for 10 minutes) by TTL and the serum portion will be frozen and shipped to Altor BioScience in batches upon request for evaluation using validated ELISA methods.

In these tests, human anti-ALT-803 antibodies are detected in patient serum samples using a direct sandwich ELISA method with plates coated with ALT-803. After the appropriate wash conditions, biotinylated ALT-803 is used for detection with standard HRP-labeled streptavidin reagents. For analysis of clinical samples, anti-IL-15 antibody serve as reference standard and serum from ALT-803 immunized mice serve as a positive control. The level of anti-ALT-803 antibody in patient samples is determined based on the anti-IL-15 antibody standard curve.

7.2.3 Genomic, Transcriptomic, and Proteomic Analysis (NantOmics)

The objective of this testing is to determine the genomic, transcriptomic, and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic, transcriptomic, and proteomic profiles and efficacy outcomes will be assessed.

Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular

abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations; Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

General Information for Collection of Tumor Tissues and Whole Blood

Tumor tissue and whole blood samples are to be collected according to the instruction cards included in the Tissue Specimen Kit and Blood Specimen Kit. The kits include the materials necessary to collect and ship FFPE tumor tissue samples and whole blood samples.

Consent for these research studies will be embedded in the main treatment consent.

The Primary Clinical Research Coordinator (PCRC) or designee is responsible for completing the Clinical Trial Requisition Form with the following information:

- Clinical Site Information
- Patient Information
- Specimen Information
- Specimen Collection Information

The PCRC or designee will return the completed Clinical Trial Requisition Form via Fax per the instructions provided on the form.

Detailed specimen requirements and procedural instructions for FFPE tumor tissue samples and whole blood samples are provided in the Genomic, Transcriptomic, and Proteomic Sample Collection Manual.

A single FFPE tumor tissue block is required for the extraction of tumor DNA, tumor RNA, and tumor protein. A whole blood sample is required for the extraction of subject normal DNA. Tumor tissue and whole blood will be processed in the NantOmics, LLC CAP accredited/CLIA certified laboratories.

Schedule of Collection for Exploratory Molecular Profiling

Exploratory Molecular Profiling	Baseline
Whole blood (normal comparator against tumor)	
per current kit[a]	✓
Formalin-fixed, paraffin-embedded tumor tissue block[b]	
A minimum tissue surface area of 25 mm^2, 75 µm thick, with at least 30% malignant tissue	✓

[a] Whole blood to be collected at baseline only for genomic sequencing. Tubes are provided in the Blood Specimen Kit (see Genomic, Transcriptomic, and Proteomic Sample Collection Manual).

[b] FFPE tissue blocks to be obtained at baseline when available for genomic sequencing, RNAseq, and proteomic analysis. A single block meeting the minimum requirements for genomics and proteomics is required. FFPE tissue blocks to be collected per local pathology laboratory procedures; detailed specimen and procedural instructions are provided in the Genomic, Transcriptomic, and Proteomic Sample Collection Manual.

The Primary Clinical Research Coordinator or designee will process and ship samples directly to NantOmics. Refer to the Lab Manual for the NantOmics directed procedures (patient enrollment, ordering of supplies, shipping etc.).

8 ALT-803 Formulation, Supply, and Potential Toxicity

ALT-803 (now also known as N-803 as Altor BioScience is a wholly owned subsidiary of NantCell, Inc.), a recombinant human superagonist IL-15 complex, is the working name of the drug under investigation. Its active ingredient is ALT-803 and its pharmacologic class is an anti-cancer and anti-viral immunotherapeutic.

ALT-803 has been referred to as IL-15N72D:IL-15RαSu/IgG1 Fc complex in various preclinical study reports, publications, and other related documents.

8.1 Formulation and Composition

The biological drug product, ALT-803, is formulated in a phosphate buffered saline (PBS) solution. The solution appears as a clear and colorless liquid. The drug substance is produced by a recombinant mammalian cell line and is manufactured using a protein free media. The vialed quantitative composition of ALT-803 is listed in the table below.

Quantitative Composition of ALT-803 (N-803)

Component[a]	Concentration	Amount/Vial
N-803 (ALT-803)	1.0 mg/mL	0.6 mg
N-803 (ALT-803)	2.0 mg/mL	1.2 mg
PBS[b]	QS	0.6 mL[c]

a – N-803 is available in 2 different concentrations. The volume of PBS used is the same for both.
b- PBS Formulation: Sodium Chloride (USP) 8.18 g/L; Sodium Phosphate Dibasic (USP) 2.68 g/L; Potassium Phosphate Monobasic (NF) 1.36 g/L pH 7.4.
c- Fill volume is 0.6 mL, extractable volume is 0.5mL.

8.2 Structural Formula

ALT-803 is a soluble complex consisting of 2 protein subunits of a human IL-15 variant associated with high affinity to a dimeric IL-15R sushi domain/human IgG1

Fc fusion protein. The IL-15 variant is a 114 aa polypeptide comprising the mature human IL-15 cytokine sequence with an Asn to Asp substitution at position 72 of helix C (N72D).6. The human IL-15R sushi domain/human IgG1 Fc fusion protein comprises the sushi domain of the IL-15R subunit (aa 1-65 of the mature human IL-15Rα protein) linked with the human IgG1 CH2-CH3 region containing the Fc domain (232 amino acids). Aside from the N72D substitution, all of the protein sequences are human. Based on the amino acid sequence of the subunits, calculated molecular weight of the complex comprising 2 IL-15N72D polypeptides and a disulfide linked homodimeric IL-15RαSu/IgG1 Fc protein is 92.4 kDa. Each IL-15N72D polypeptide has a calculated molecular weight of approximately 12.8 kDa and the IL-15RαSu/IgG1 Fc fusion protein has a calculated molecular weight of approximately 33.4 kDa. Both the IL-15N72D and IL-15RαSu/IgG1 Fc proteins are glycosylated resulting in an apparent molecular weight of ALT-803 as approximately 114 kDa by size exclusion chromatography. The isoelectric point (pI) determined for ALT-803 range from approximately 5.6 to 6.5. Thus, the fusion protein is negatively charged at pH 7. The calculated molar extinction coefficient at A280 for ALT-803 is 116,540 M-1, or 1.26 OD280 for a 1 mg/mL solution of ALT-801, or one OD280 is equivalent to 0.79 mg/mL solution of ALT-803.

8.3 Storage and Handling

N-803 is supplied in a 2-mL single-dose/single-use vial containing 0.6 mL of N-803 (extractable volume is 0.5 mL) at a concentration of 1 mg/mL or 2 mg/mL. Vials are packaged in cartons and shipped to the clinical site. Study medication must be maintained at a temperature between 2°C and 8°C.

8.4 Study Drug Preparation and Administration

ALT-803 dose calculation will be based on actual body weight; however for patients > 100 kilograms weight, the ALT-803 dose will be calculated using a weight capped at 100 kg. Refer to Section 6.1 and 6.2 for additional details.

The calculated amount of ALT-803 will be drawn into a syringe for subcutaneous injection. The current IDS stock concentration is 1 mg/ml. Doses will be drawn directly into the syringe for injection. If the total subcutaneous dose is greater than 1.5 mL, the dose will be divided into 2-3 subcutaneous injections as needed.

For intraperitoneal administration, the ALT-803 dose is administered IP in 50 cc of room temperature Normal Saline via peritoneal catheter. Refer to Section 6.2 for full details.

8.5 Agent Inventory Records

The investigator, or a responsible party designated by the investigator (e.g. institutional investigational pharmacy), must maintain a record of the inventory and disposition of study product using the Study Agent Drug Accountability Record.

8.6 Toxicity

The most common side effects seen in studies with subcutaneous (under the skin) injections have been, fever, chills, hypoalbuminemia, and injection site reaction, and skin rash, which at times has been widespread. These localized skins reactions are common (occurring in more than 50% of patients).

Very common	Common	Rare
• injection site reactions • fever • hypoalbuminemia • chills	• fatigue • decreased lymphocyte count • limb edema • arthralgia • achiness • vomiting • headache • abdominal pain • back pain	• anemia • edema • anorexia • hematuria • immunogenicity

Anti-N-803 antibodies have been detected in subjects receiving N-803. The impact of anti-N-803 antibody formation on clinical efficacy and safety of N-803 is unknown.

ALT-803 has not been given intraperitoneally, although this route of administration is common for other agents in the treatment of gynecological cancers with the most common complaints of pain and cramping during and after instillation, often severe enough to require pain medication. In a study using intravesical administration of ALT-803, the most common side effects have included hypertension, hematuria, pollakiuria, and fatigue.

Previous editions of the ALT-803 Investigator's Brochure relied heavily on clinical experience with the related cytokine therapeutic Proleukin® Interleukin-2 to anticipate potential risks associated with ALT-803 (N-803) administration. This approach was based on the fact that N-803 and IL-2 are both γ chain cytokines and thus could reasonably be predicted to have similar immunostimulatory properties. However, the substantial accumulated information on N-803 effects in humans presented the most recent IB (version 6 dated April 2019) indicates that many side effects of IL-2 are not observed in patients treated with N-803 at the doses being used clinically. For this reason, side effects observed in subjects treated with IL-2 but not N-803, such as capillary leak syndrome, pulmonary

dysfunction, acidosis, and gastritis, have been removed from the IB and are reflected in this protocol and its consent form.

Refer to the current Investigator Brochure (version 6) for additional information.

9 Adverse Event Monitoring, Documentation and Reporting

Toxicity and adverse events will be classified and graded according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

An exception to the use of CTCAE will be for the assessment of cytokine release syndrome (CRS). Individual adverse events which are associated with CRS will be graded per CTCAE; however the ultimate assessment will be made using a revised grading system for CRS as presented by Lee et al (24).

CRS Revised Grading System (replaces CTCAE v4 CRS grading)	
Grade	**Toxicity Description**
Grade 1	Symptoms are not life threatening and require symptomatic treatment only, e.g., fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention - Oxygen requirement < 40% or Hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity
Grade 3	Grade 3 Symptoms require and respond to aggressive intervention - Oxygen requirement ≥40% or Hypotension requiring high dose or multiple vasopressors or Grade 3 organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms - Requirement for ventilator support or Grade 4 organ toxicity (excluding transaminitis)
Grade 5	Death

Grades 2-4 refer to CTCAE v4.0 grading.

The following definitions of adverse events (AEs) and serious adverse events (SAEs) will determine whether the event requires expedited reporting via the SAE Report Form in addition to routine documentation in the AE case report form (CRF).

The reporting timeframes for SAEs and other reportable events are located in Section 9.6

Note: throughout this section the generic term “study drug” refers to the study related treatment (ALT-803).

9.1 Adverse Event Terminology

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Serious Adverse Event: An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Event: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

The following definitions are from the Masonic Cancer Center's Standard Operating Procedure (SOP) Deviation Reporting:

Major Deviation: A deviation or violation that impacts the risks and benefits of the research; may impact subject safety, affect the integrity of research data and/or affect a subject's willingness to participate in the research. Deviations that place a subject at risk, but do not result in harm are considered to be major deviations.

Minor Deviation: A deviation or violation that does not impact subject safety, compromise the integrity of research data and/or affect a subject's willingness to participate in the research.

9.2 AE Documentation and Reporting Requirements

Adverse event collection for the purposes of this study will focus on events felt to be related to ALT-803 or events that cannot be attributed to other causes (i.e.

underlying diseases). At each visit through the final treatment visit, a targeted toxicity worksheet (Appendix IV) will be completed to document select expected toxicities associated with ALT-803.

On days of ALT-803 administration, the worksheet will be completed:

- prior to ALT-803 administration
- At the end of dose monitoring period (as described in Section 6.1) with ±20 minute window for 2 hour monitoring or ±10 minute window for 30 minute monitoring
- Day 29 Treatment Course 1 only
- End of Treatment visit approximately 4 weeks after the last dose of ALT-803

In addition, the patient will be provided with an Injection Site Reactions Diary to be completed daily at home each day for 7 days after the each ALT-803 subcutaneous injection (Appendix V) or intraperitoneal infusion (Appendix VI). Unexpected events and expected events that are not listed in Appendix IV and Section 8.8, or the consent form must be documented.

Note: if a patient is not abiding by the standard of care study calendar (Section 7.1), collection of the corresponding targeted events (and research related samples) also may be altered or discontinued on an individual patient basis, as appropriate.

After the End of Treatment visit, monitoring for adverse events will become less frequent based on the schedule in Section 7.1 and only events that are unexpected and at least possibly related to ALT-803 will be documented upon knowledge.

9.3 SAE Documentation and Reporting Requirements

All SAEs are documented using the MCC OnCore SAE Report Form and reported. Any event that is both serious and unexpected and at least possibly related to the study treatment must be reported in an expedited manner.

9.4 Early Stopping Rule Events Documentation and Reporting Requirements

The following event counts toward an early study stopping rule and must be reported to the using the Event Form found OnCore under the reports tab:

- Grade 3-5 organ toxicity (cardiac, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic) not pre-existing within the 1st two months lasting more than 72 hours.

- Any grade 4 treatment emergent toxicity, grade 3 abdominal pain refractory to pain medication and persisting more than 72 hours or grade 3 or greater ascites

An event that counts toward an early stopping rule does not necessarily constitute a SAE and should be reported as such only if they meet the criteria for reporting as defined in Section 9.3.

9.5 Documentation of Death and Reporting Requirements

Deaths, including due to disease, will be recorded as an SAE. Deaths due to disease should be recorded as a Grade 5 Neoplasm and will be reported to the FDA as part of the IND annual report. In addition, the death date and cause must be recorded in the patient follow-up tab in OnCore using the comment field in the survival status section to record the cause.

9.6 Expedited Reporting the UMN IRB, FDA and Altor Bioscience

Agency	Criteria for reporting	Timeframe	Form to Use	Submission address/ fax numbers
U of MN IRB	Events requiring prompt reporting including, but not limited to unanticipated death of a locally enrolled subject(s); new or increased risk; any adverse event that requires a change to the protocol or consent form or any protocol deviation that resulting in harm For a complete list refer to http://www.research.umn.edu/irb/guidance/ae.html#.VC7xraI0-sh	Within 5 business days of event discovery	RNI	Ethos
	Deviation reporting per current IRB reporting requirements.	Per current IRB requirements	Deviation report	
FDA	Unexpected and fatal or unexpected and life threatening suspected adverse reaction	no later than 7 Calendar Days	MCC SAE	Submit to FDA as an amendment to IND with a copy to SAE.Reporting@Nantbio.com or Fax: (800) 853-3497
	1) Serious and unexpected suspected adverse reaction or 2) increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure or 3) findings from other sources (other studies, animal or in vitro testing)	no later than 15 Calendar-Days		
Altor BioScience	Any SAE report regardless of attribution or FDA reporting requirements	Within 24 hours of receipt	MCC SAE	SAE.Reporting@Nantbio.com or Fax: (800) 853-3497
Masonic Cancer Center SAE Coordinator	Events that count toward the early study stopping rule.	At time of reporting	Event Form	SAE Coordinator mcc-saes@umn.edu, SAE.Reporting@Nantbio.com or Fax: (800) 853-3497

10 Study Data Collection and Monitoring

10.1 Data Management

This study will collect regulatory and clinical data using University of Minnesota CTSI's instance of OnCore®(Online Enterprise Research Management Environment).

The Oncore database resides on dedicated secure and PHI compliant hardware located in the University of Minnesota (UMN) datacenter (WBOB). All the data servers are managed by the Academic Health Center – Information Systems (AHC-IS) virtual servers which utilize clustered infrastructure to provide real-time failover of virtual servers. This real-time clustering is physically limited to the UMN data center. All relevant AHC IS procedures related for PHI compliant servers (as required by the Center of Excellence for HIPAA Data) apply to Oncore databases.

The integrated data will be stored in PHI compliant servers managed by AHC IS with access given to those authorized users in the Clinical and Translation Science Institute Informatics team (CTSI BPIC and MCC CISS). The data will be integrated and extracted to researchers through the CTSI Informatics team and will be delivered through secure and compliant mechanisms (e.g. AHC IE data shelter, BOX, sftp, etc). If data de-identification is needed, then compliant AHC IE data de-identification tools will be used. The informatics team will grant the IRB approved study team members access to data.

Additional immune monitoring data about correlative laboratory samples generated by the Masonic Cancer Center Translational Therapy Laboratory (TTL) from the protocol-directed correlative research samples is stored in their Laboratory Information Management System (LIMS).The LIMS database application is also stored on a production server located in the UMN datacenter (WBOB) and is managed by the Academic Health Center

Key study personnel are trained on the use of OnCore and will comply with protocol specific instructions embedded within the OnCore.

10.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRFs) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study's Principal Investigator and the Biostatistician prior to release for use. The Clinical Research Coordinator (PCRC) or designee will be responsible for registering the patient into OnCore at time of

study entry, completing e-CRFs based on the patient specific calendar, and updating the patient record until patient death or end of required study participation.

10.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the University of Minnesota Masonic Cancer Center's Data & Safety Monitoring Plan (DSMP), which can be accessed at http://z.umn.edu/dmsp

For the purposes of data and safety monitoring, this study is classified as high risk (under a locally held IND). Therefore the following requirements will be fulfilled:

- At least quarterly review of the study's progress by the Masonic Cancer Center Data and Safety Monitoring Council (DSMC)
- The PI will comply with at least twice yearly monitoring of the project by the Masonic Cancer Center monitoring services.
- The PI will oversee the submission of all reportable events per Section 9.6 to the Masonic Cancer Center's SAE Coordinator, the University of Minnesota IRB, and the FDA.

IND Annual Reports

In accordance with regulation 21 CFR § 312.33, the IND sponsor (Dr. Geller) will submit a progress report annually. The report will be submitted within 60 days of the anniversary date that the IND went into effect.

10.4 Record Retention

The investigator will retain study records including source data, copies of case report forms, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 6 years after the study file is closed with the IRB and FDA.

The Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient. Please contact the CTO before destroying any study related records.

11 Primary and Secondary Endpoints

11.1 Primary Endpoint

The primary endpoint of this phase II screening trial is to select a "winner" among the two methods of delivery for future study. Progression free survival (PFS) at 6

months will be used to determine if one method is clearly inferior over the other. Other factors will be considered if the differences between the routes are small in terms of PFS.

11.2 Secondary Endpoints

- Progression free survival by 1 and 2 years is defined as alive at 1 and 2 years without disease progression from the start of ALT-803 dosing
- Overall survival (OS) by 1 year and 2 years is defined as alive at 1 year and 2 years from the start of ALT-803 dosing
- ALT-803 associated toxicities when administered by intraperitoneal infusion will be documented using CTCAE v4 toxicity classification and grading
- The safety of ALT-803 will be documented by lack of Grade 3 and greater toxicity

12 Statistical Considerations

12.1 Study Design, Objectives and Endpoints

The primary objective of this phase II screening trial is to select a “winner” among the two methods of delivery for future study. The study is not intended to seek definite evidence that one method is superior to the other based on progression-free-survival alone by 6 months for which a properly powered phase III trial would be needed. Instead this trial is intended

(1) to ensure that if one of the two delivery methods is clearly inferior to the other in terms of the primary endpoint of progression free survival (PFS) by 6 months, there is a small probability that the inferior method will be carried forward to a more highly powered trial
(2) if the difference between the methods is small in terms of PFS, the selection of the method will be allowed to include other factors (attraction of lymphocytes to the peritoneal cavity, ease of the methodology and safety).

This study includes 2 randomized arms using intraperitoneal (IP) administered ALT-803 at 10 mcg/kg during the initial course and subcutaneous ALT-803 at 10 mcg/kg. No arm is expected to be more toxic than the other. At the end of the trial, we will need to select a “winner” for any subsequent comparative trials. Hence, we adopt the design for selection between multiple screening trials proposed by Sargent & Goldberg (25). Following the notations in Sargent & Goldberg, we set up the selection rule as follows. Let $\pi 1$ and $\pi 2$ denote the true PFS. Define $\delta = \pi 2 - \pi 1$ and let p1 and p2 denote the observed PFS of the two arms where p2 has the highest PFS. In our calculation, if the difference between the two rates is

greater than a threshold d (i.e. |p2 – p1| > d), the treatment with the higher PFS rate will be selected for use in a future trial; otherwise, the method, which has a higher attraction of lymphocytes to the peritoneal cavity, easier methodology or fewer toxicities may be selected. The goal is to find a sample size n that can ensure that "the probability of correct selection" (which is analogous to "power") exceeds a certain threshold (λ), that is

$$\Pr[p_2 - p_1 > d|\pi_1, \pi_2] = 1 - \Phi\left\{\frac{d-\delta}{\sqrt{\left(\frac{1}{n}\right)[\pi_1(1-\pi_1)+\pi_2(1-\pi_2)]}}\right\} > \lambda.$$

Secondary endpoints include:
Overall survival (OS) at 1 year
Progression free survival (PFS) at 1 year

Correlative endpoints include:
In both blood and the peritoneal wash
1. Change in total number of T cells and NK cells, as well as activated cells (CD69, HLA-DR, CD25), T cell subsets, and NK cell subsets
2. Change in NK cell function

Randomization will apply to the 1st treatment course only with the following arms:
Arm 1: ALT-803 SQ only – patient receives ALT-803 10 mcg/kg SQ weekly x 4 followed by 4 weeks of no treatment before continuing with treatment courses 2, 3, and 4 as described below
Arm 2: ALT-803 IP and SQ – patient receives ALT-803 10 mcg/kg IP weekly x 4 weeks followed by 4 weeks of no treatment before continuing with treatment courses 2, 3, and 4 as described below

Treatment courses 2, 3, and 4 are identical for all patients - ALT-803 10 mcg/kg SQ weekly x 4 with a 4 week rest (4 weeks on/4 weeks off).

12.2 Statistical Analyses

Primary analyses will follow the intent-to-treat principle where the effect will be measured according to how treatments were randomized. A secondary analysis will only include those patients who received at least two treatment courses of the assigned regimen. The endpoints of progression-free survival and overall survival will be estimated from Kaplan-Meier curves. Descriptive statistics and plots such as median, range and interquartile range and box-plots will be used to measure the change in the total number of cells. The general-Wilcoxon test will be employed across groups. Change in NK cell function will be measure with simple proportions.

The Chi-square test or Fisher's exact test will be employed to test NK cell function across groups depending on expected cell counts.

12.3 Sample Size

We expect that all patients will receive at least 2 treatment courses. But we are including enough patients to realize at least 80% power under the secondary analysis even if 3 patients in each arm do not receive at last 2 treatment courses. If the true PFS is 70% and 90% (i.e. 90% is the best survival and 70% is the expected PFS in the other arm) and we choose a selection threshold of d = 15%, a sample size of 14 patients in each arm will achieve at least 81% power under ITT and 11 patients in each arm will achieve at least 80% power under the non-ITT analyses. Power calculations are generated from partial code from X. Luo in R 3.0.2 (R Development Core Team, Vienna, Austria).

12.4 Stopping Rules

Stopping rules will be monitored for each arm separately. Stopping rules were developed based on an adaptation of the Pocock stopping boundaries (26).

1) **Grade 3-5 organ toxicity (cardiac, gastrointestinal, hepatic, pulmonary, renal/genitourinary, or neurologic) not pre-existing within the 1st two months lasting more than 72 hours**

   The goal is to construct a boundary based on excessive toxicity such that the probability of early stopping is at most 10% if the rate is equal to 5% and our sample size is 14. With these stipulations, the study will be stopped if there is excess toxicity in 2 out of 2 patients or 3 events at any time. If the actual probability of toxicity is 20% or 30%, the probability of reaching the boundary will be 64% and 88% respectively.

2) **Any grade 4 treatment emergent toxicity, grade 3 abdominal pain refractory to pain medication and persisting more than 72 hours or grade 3 or greater ascites**

   The goal is to construct a boundary based on excessive toxicity such that the probability of early stopping is at most 10% if the rate is equal to 5% and our sample size is 14. With these stipulations, the study will be stopped if there is excess toxicity in 2 out of 2 patients or 3 events at any time. If the actual probability of toxicity is 20% or 30%, the probability of reaching the boundary will be 64% and 88% respectively.

13 Conduct of the Study

13.1 Good Clinical Practice

The study will be conducted in accordance the appropriate regulatory requirement(s). Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

13.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, consent, written information given to the patients, safety updates, progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

14 References

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Appendix I –Patient Eligibility Checklist

Randomized Study of Single Course of Intraperitoneal (IP) ALT-803 Followed by Subcutaneous (SQ) Maintenance ALT-803 Versus Subcutaneous (SQ) Maintenance ALT-803 Only after 1st Line Chemotherapy for Advanced Ovarian, Fallopian Tube, and Primary Peritoneal Cancer (CPRC #2016LS034)

Patient Initials: _____ **Patient ID**: 16034-UMN-_____

Masonic Cancer Center, University of Minnesota
Comprehensive Cancer Center designated by the National Cancer Institute
CLINICAL TRIALS OFFICE

CPRC #: 2016LS034

Short Title: Randomized Study of Maintenance ALT-803 Therapy IP Followed by SQ Versus SQ Only

Protocol Version Date: May 21, 2019

Eligibility Checklist page 1

	Inclusion Criteria *An answer of "No" indicates patient is ineligible for study enrollment*	**Yes**	**No**	**N/A**
1.	Diagnosis of stage III or stage IV epithelial ovarian, fallopian tube or primary peritoneal carcinoma (appendix II), has received at least 3 cycles of first line IV/IP cisplatin and paclitaxel chemotherapy and has stable disease or better (Note: to be eligible for this study, the patient must receive a minimum of 3 cycles of IP therapy; however, patients may continue on IV only 1st line therapy for additional cycles as long as inclusion criteria # 2 is met)			
2.	Able to begin study therapy within 3 months of final dose of first line chemotherapy			
3.	Functioning intraperitoneal catheter			
4.	≥ 18 years of age			
5.	GOG performance status ≤ 2 (appendix II)			
6.	Adequate organ function within 14 days of study enrollment defined as: Test / Required Value / Date of Test Result hemoglobin / ≥ 8 g/dl / ☐☐/☐☐/☐☐☐☐ ANC / ≥ 1500/ul / ☐☐/☐☐/☐☐☐☐ platelets / ≥ 50 x 10^9/L / ☐☐/☐☐/☐☐☐☐ serum creatinine / ≤ 2.0 mg/d / ☐☐/☐☐/☐☐☐☐ SGOT / ≤ 3 x ULN / ☐☐/☐☐/☐☐☐☐ SGPT / ≤ 3 x ULN / ☐☐/☐☐/☐☐☐☐			
7.	Ability to be off prednisone and other immunosuppressive drugs for at least 3 days prior to and while receiving ALT-803			
8.	Voluntary written consent prior to the performance of any research related procedures			

	Exclusion Criteria *An answer of "Yes" indicates patient is ineligible for study enrollment.*	**Yes**	**No**	**N/A**
9.	Somatic or germline BRCA1 or BRCA2 mutations			
10.	Received any investigational agent within the 14 days before the start of ALT-803			
11.	Class II or greater New York Heart Association Functional Classification criteria (appendix II) or serious cardiac arrhythmias likely to increase the risk of cardiac complications of cytokine therapy (e.g. ventricular tachycardia, frequent ventricular ectopy, or supraventricular tachyarrhythmia requiring chronic therapy)			
12.	Marked baseline prolongation of QT/QTc interval (e.g. demonstration of a QTc interval greater than 500 milliseconds)			
13.	Uncontrolled bacterial, fungal or viral infections including HIV-1/2 or active hepatitis C/B - chronic asymptomatic viral hepatitis is allowed			
14.	Active autoimmune disease requiring immunosuppressive therapy			
15.	History of severe asthma and currently on chronic medications (mild asthma requiring inhaled steroids only is eligible)			
16.	Uncontrolled hypertension: defined as ≥2 readings over 160 mmHg systolic or 110 mmHg diastolic within month prior to enrollment despite optimal anti-hypertensive medication. Patients with high readings which improve to ≤160/110 after adjustment of medications will be eligible.			
17.	History of pulmonary disease or abnormal pulmonary function studies			
18.	History of narcolepsy or any neurological condition which may impair consciousness			

Having obtained consent and reviewed each of the inclusion/exclusion criteria, I verify that this patient is eligible

_____ _____

Signature of enrolling physician Date

Appendix II – FIGO Staging, GOG PS and NYHA Classification

The **FIGO staging systems** are determined by the International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique). In general, there are five stages:

stage 0: carcinoma in situ (common in cervical, vaginal, and vulval cancer)
stage I: confined to the organ of origin
stage II: invasion of surrounding organs or tissue
stage III: spread to distant nodes or tissue within the pelvis
stage IV: distant metastasis(es)

please refer to https://radiopaedia.org/articles/figo-staging-system for detailed primary specific staging.

ref: Prat J, FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynaecol Obstet. 2014 Jan. 124 (1):1-5.

GOG Score	Activity Level
0	Fully active, unrestricted activities of daily living
1	Ambulatory, but restricted in strenuous activity
2	Ambulatory, and capable of self care. Unable to work. Out of bed for greater than 50% of waking hours
3	Limited self care, or confined to bed or chair 50% of waking hours. Needs special assistance
4	Completely disabled, and no self care
5	Dead

New York Heart Association Functional Classification

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

Ref: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

Appendix III – RECIST version 1.1 With Updated CA-125 Criteria(27)

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be

recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers This study will use CA-125 response based on International Journal of Gynecological Cancer & Volume 21, Number 2, February 2011 (26), published after the current version of RECIST.

A CA 125 response is defined as at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA 125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

Progression or recurrence based on serum CA 125 levels will be defined on the basis of a progressive serial elevation of serum CA 125 according to the following criteria:

a. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 ≥2 times the upper limit of the reference range on 2 occasions at least 1 week apart or
b. Patients with elevated CA-125 before treatment, which never normalizes, must show evidence of CA-125 ≥ 2 times the nadir value on 2 occasions at least 1 week apart or
c. Patients with CA-125 in the reference range before treatment must show evidence of CA-125 ≥ 2 times the upper limit of the reference range on 2 occasions at least 1 week apart.

CA 125 progression will be assigned the date of the first measurement that meets the criteria as noted. A patient may be declared to have PD on the basis of either the objective RECIST 1.1 criteria or the CA 125 criteria. The date of progression will be the date of the earlier of the 2 events if both are documented.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in

the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Appendix IV – ALT-803 Targeted Toxicity Worksheet

See Section 9.2 for time points based on CTCAE v4

Patient Initials: _____ **Date of Assessment:** _____ **Assessment Time Point:** _____

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT-803 Injection site reaction	None	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Abdominal Pain (IP related)	None	Asymptomatic but distention	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	----------
Dyspnea	None or no change	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Hypoxia	None	……	Decreased O_2 saturation with exercise (e.g., pulse oximeter < 88%) intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter < 88% or $PaO_2 \leq 55$ mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
Fever	None	38.0 - 39.0◦ C (100.4 - 102.2◦ F)	> 39.0 - 40.0◦C (102.3 - 104.0◦F)	> 40.0 ◦ C (>104.0◦ F) for ≤ 24 hrs	> 40.0 ◦ C (>104.0◦ F) for > 24 hrs
Chills	None	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	……
Hypertension	None	Pre-hypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent ≥ 24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated.	Stage 2 hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated.	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated.
Hypotension	None	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated
Edema	None	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	……
Pneumonitis	None	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g. intubation or tracheotomy)
Headache	None	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	……
Confusion (Altered Mental Status)	None	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated
Rash	None	Covering < 10% body surface area (BSA)	Covering 10-30% body surface area (BSA)	>30% body surface area (BSA)	Generalized exfoliative, ulcerative, or bullous dermatitis
Gait Disturbance	None	Mild change in gait (eg, wide-based, limping or hobbling)	Moderate change in gait (eg, wide-based, limping or hobbling); assistance device indicated; limiting instrumental ADL	Disabling; limiting self care ADL	……

Person Completing Form: _____ ADL = activities of daily living

Appendix V – ALT-803 Injection Site Reactions Diary

The Diary is to be completed by the patient as a self-assessment after each dose of ALT-803.

A new diary must be started for each ALT-803 injection/IP infusion.

If the previous injection reaction has not resolved, continue to collect information on its diary based on the days from that injection. In other words if at Day 6 post-injection, an injection site reaction is still present continue to collect data for items 1-4 daily until the reaction resolves.

Note: patients assigned to intraperitoneal (IP) ALT-803 during the 1st treatment course will complete the modified Patient Diary found in Appendix VI.

Patient Number*		Date of Study Drug Injection*	_____/_____/_____	*To be completed by the site.

Please answer all questions below <u>daily</u> for 7 days, beginning with day of treatment. Be sure to bring back this completed diary to your next clinic visit.

	Instructions	Day of Study Drug Injection ___/___/_____	Day 1 Post Injection ___/___/_____	Day 2 Post Injection ___/___/_____	Day 3 Post Injection ___/___/_____	Day 4 Post Injection ___/___/_____	Day 5 Post Injection __/__/_____	Day 6 Post Injection ___/___/_____
1. Is there redness at the injection site?	Check: ☐Yes or ☐No If yes, measure longest diameter in cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm
2. Is there firmness or swelling at the injection site?	Check: ☐Yes or ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
3. Have you experienced any pain or itching at the injection site?	Check: ☐Yes or ☐No If yes, tell us if the pain and/or itching is mild, moderate or severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe
4. Have you taken or applied any medication for injection site pain or itching?	Check: ☐Yes or ☐No Provide name of medication(s)	☐Yes ☐No Name(s):	☐Yes ☐No Name(s):	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:
5. Have you experienced any chills?	Check: ☐Yes or ☐No If yes, tell us if the chills are mild, moderate or severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe
6. Record your daily temperature upon waking (do not drink anything 5 minutes before taking your temperature)	Check: ☐Yes or ☐No If your temperature is 101°F for more than 24 hours notify your study doctor or the research staff.	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM	☐Yes ☐No _____°F Time: ____:____ AM / PM

Grading Injection Site Pain or Itching
Mild – Noticeable, does not interfere with activity
Moderate – Interferes with activity, limiting activities of daily living
Severe – Severely limiting self-care activities of daily living, incapacitating

Grading Chills
Mild – Mild sensitive of cold, shivering, chattering of teeth
Moderate – Moderate tremor of entire body, medication taken
Severe – Prolonged or severe, does not respond to medication

Page 2 – Please continue to complete for Injection Site Reaction if ongoing after page 1 has been filled out.

Patient Number*		**Date of Study Drug Injection***	_____/_____/_____	*To be completed by the site.

Complete <u>daily</u> for 7 days or until the injection site has resolved (returned to normal) . Please bring back this completed diary to your next clinic visit.

	Instructions	**Day 7 Post Injection** ___/___/_____	**Day 8 Post Injection** ___/___/_____	**Day 9 Post Injection** ___/___/_____	**Day 10 Post Injection** ___/___/_____	**Day 11 Post Injection** ___/___/_____	**Day 12 Post Injection** __/__/_____	**Day 13 Post Injection** ___/___/_____
1. Is there redness at the injection site?	Check: ☐Yes or ☐No If yes, measure longest diameter in cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm
2. Is there firmness or swelling at the injection site?	Check: ☐Yes or ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
3. Have you experienced any pain or itching at the injection site?	Check the pain and/or itch box if present And tell us if the pain and/or itching is mild, moderate or severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe
4. Have you taken or applied any medication for injection site pain or itching?	Check: ☐Yes or ☐No Provide name of medication(s)	☐Yes ☐No Name(s):	☐Yes ☐No Name(s):	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:

Grading Injection Site Pain or Itching
Mild – Noticeable, does not interfere with activity
Moderate – Interferes with activity, limiting activities of daily living
Severe – Severely limiting self-care activities of daily living, incapacitating

Appendix VI – ALT-803 Intraperitoneal (IP) Reactions Diary

INTRAPERITONEAL (IP) INJECTION

Patient Number*		**Date of Study Drug IP Infusion***	_____/______/_____	*To be completed by the site.

Please answer all questions below daily for 7 days, beginning with day of treatment. Be sure to bring back this completed diary to your next clinic visit.

	Instructions	**Day of Study Drug IP Infusion** __/__/____	**Day 1 Post Infusion** __/__/____	**Day 2 Post Infusion** __/__/____	**Day 3 Post Infusion** __/__/____	**Day 4 Post Infusion** __/__/____	**Day 5 Post Infusion** __/__/____	**Day 6 Post Infusion** __/__/____
1. Have you experienced any abdominal pain?	Check: ☐Yes or ☐No If yes, tell us if the pain is mild, moderate or severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe
1. Have you experienced any abdominal distention?	Check: ☐Yes or ☐No If yes, tell us if the extent of the abdominal distention	☐Yes ☐No Asymptomatic (visually distended but not bothersome) Symptomatic: Severe discomfort	☐Yes ☐No Asymptomatic (visually distended but not bothersome) Symptomatic: Severe discomfort	☐Yes ☐No Asymptomatic (visually distended but not bothersome) Symptomatic: Severe discomfort	☐Yes ☐No Asymptomatic (visually distended but not bothersome) Symptomatic: Severe discomfort	☐Yes ☐No Asymptomatic (visually distended but not bothersome) Symptomatic: Severe discomfort	☐Yes ☐No Asymptomatic (visually distended but not bothersome) Symptomatic: Severe discomfort	☐Yes ☐No Asymptomatic (visually distended but not bothersome) Symptomatic: Severe discomfort
4. Have you taken any medication for abdominal pain?	Check: ☐Yes or ☐No Provide name of medication(s)	☐Yes ☐No Name(s):	☐Yes ☐No Name(s):	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:
5. Have you experienced any chills?	Check: ☐Yes or ☐No If yes, tell us if the chills are mild, moderate or severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe
6. Record your daily temperature upon waking (do not drink anything 5 minutes before taking your temperature)	Check: ☐Yes or ☐No If your temperature is 101°F for more than 24 hours notify your study doctor or the research staff.	☐Yes ☐No ________°F Time: ____:____ AM / PM	☐Yes ☐No ________°F Time: ____:____ AM / PM	☐Yes ☐No ________°F Time: ____:____ AM / PM	☐Yes ☐No ________°F Time: ____:____ AM / PM	☐Yes ☐No ________°F Time: ____:____ AM / PM	☐Yes ☐No ________°F Time: ____:____ AM / PM	☐Yes ☐No ________°F Time: ____:____ AM / PM

Grading Abdominal Pain
Mild – Noticeable, does not interfere with activity
Moderate – Interferes with activity, limiting activities of daily living
Severe – Severely limiting self-care activities of daily living, incapacitating

Grading Chills
Mild – Mild sensitive of cold, shivering, chattering of teeth
Moderate – Moderate tremor of entire body, medication taken
Severe – Prolonged or severe, does not respond to medication