PROTOCOL TITLE:	**A Randomized, Intra-patient Crossover, Safety, Biomarker and Anti-Tumor Activity Assessment of the Combination of Atezolizumab and Vigil in Patients with Advanced Gynecological Cancers**
PROTOCOL NUMBER:	**CL-PTL-126**
STUDY AGENT(S):	**Atezolizumab (TECENTRIQ™, MPDL3280A)** **Vigil (bi-shRNA^{furin} and GMCSF) Autologous Tumor Cell Immunotherapy**
SPONSOR:	**Gradalis, Inc.** **2545 Golden Bear Drive, Suite 110** **Carrollton, TX 75006** **Phone: (214) 442-8124** **Fax: (214) 442-8101**
PROTOCOL DATE:	**Amendment No. 3 dated September 26, 2018** **Amendment No 2. dated December 30, 2017** **Amendment No. 1 dated April 5, 2017** **Initial Protocol dated December 13, 2016**

INVESTIGATOR PROTOCOL SIGNATURE PAGE

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I have read and understand the contents of the indicated clinical protocol and will adhere to the trial requirements as presented, including all statements regarding confidentiality. In addition, should I choose to participate as an investigator, I and my sub-investigator(s) agree to conduct the study as outlined herein, in accordance with Good Clinical Practices (GCPs), the Declaration of Helsinki, in compliance with the obligations and requirements of clinical investigators and all other requirements listed in Title 21 Code of Federal Regulations (CFR) Part 312.

Name of Investigator (please print) _____ **Signature of Investigator** _____

Date _____

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ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine transaminase (also referred to as SGPT)
ANC	Absolute neutrophil count
APC	Antigen Presenting Cells
AST	Aspartate transaminase (also referred to as SGOT)
BUN	Blood urea nitrogen
CBC	Complete blood count
CD	Cluster of differentiation
cCR	Clinically defined Complete Response
CgA	Chromogranin A
CHD	Carcinoid heart disease
CMV	Cytomegalovirus
CO_2	Total carbon dioxide
CRF	Case report form
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DC	Dendritic cell(s)
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-Linked ImmunoSorbent Assay
ELISPOT	Enzyme-Linked ImmunoSorbent Spot
ER	Endoplasmic reticulum
FANG™	bi-shRNA^{furin} and GMCSF Augmented Autologous Tumor Cell Immunotherapy
FL	Flt-3-Ligand
GEP-NETs	gastroenteropancreatic neuroendocrine tumors
GMCSF	Granulocyte Macrophage-Colony Stimulating Factor
GMP	Good Manufacturing Practice
GVAX	GMCSF Secreting autologous or allogenic tumor vaccine
H2RA	H_2 receptor antagonist
HLA	Human Leukocyte Antigen
ID	intradermal
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IL	Infiltrating lymphocytes
IRB	Institutional Review Board

Abbreviation	Term
irRC	immune related Response Criteria
LAK	Lymphokine-activated killer
LAR	Long acting repeatable
LLC	Large latent complex
MHC	Major histocompatibility complex
MLR	Mixed lymphocyte reaction
MR	Mannose receptor
NCI	National Cancer Institute
NED	No evidence of disease
NET	neuroendocrine tumor
NK	Natural Killer
NKT	Natural Killer T cell(s)
NSCLC	Non small cell lung cancer
ORR	Overall Response Rate
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase chain reaction
PD	Progressive disease
PD-L	Programmed cell death protein ligand
PI	Principal Investigator
PNET	Pancreatic neuroendocrine tumor
PPI	Proton pump inhibitor
PR	Partial response
PS	Performance Status
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency ablation
SD	Stable disease
SLC	Small latent complex
SOC	Standard of care
SSR	Somatostatin receptors
STZ	streptozocin
TAA	Tumor Associated Antigens
TAP	transporter associated with Ag processing
TCR	T cell receptor
TGFβ	Transforming growth factor-β
TIL	Tumor infiltrating lymphocytes
TNF	Tumor necrosis factor
Treg	Regulatory T cell

Abbreviation	Term
TSH	Thyroid stimulating hormone
ULN	Upper limits of normal
USPI	U.S. Package Insert
VEGF	Vascular endothelial growth factor
WNL	Within normal limits

SYNOPSIS

Hypothesis:

The interferon gamma ELISPOT assay is a commonly used biomarker of T-cell activation in clinical trials of anti-viral and experimental anti-tumor immunotherapies. Vigil autologous tumor cell immune therapy has induced ELISPOT positivity in 100% (31 of 31) of patients treated in a Phase 2 clinical trial in ovarian cancer. Several immune checkpoint inhibitors have been tested for anti-tumor activity in advanced ovarian cancer and induce responses in approximately 15%-20% of patients. These relatively low response rates may be a consequence of a low rate of immune activation in ovarian cancer in general. By safely combining Vigil therapy with immune checkpoint inhibitors we may broaden and potentially deepen the responsiveness of tumors which are largely unresponsive to checkpoint inhibitors alone.

Summary:

This is a 3-part safety study of Vigil in combination with checkpoint inhibitor atezolizumab, in patients with treatment refractory or recurrent epithelial ovarian cancer, or other gynecological cancers (i.e. cervical, uterine).

This study is intended as a companion study to protocol CL-PTL-119, A Randomized, Double Blind, Placebo-Controlled Phase 2 Trial of Vigil Engineered Autologous Tumor Cell Immunotherapy in Subjects with Stage IIIb-IV Ovarian Cancer in Clinical Complete Response following Surgery and Primary Chemotherapy, otherwise known as the VITAL study. Patients who have tumor harvested at surgery and Vigil successfully manufactured, but then are ineligible for randomization onto the VITAL study or previously randomized to placebo, will be offered the opportunity to participate in this protocol.

Subjects enrolled will either be:

- Patients with recurrent ovarian cancer. Furthermore, subjects who have previously received Vigil on this study may be considered for re-procurement for manufacture of Vigil (after consultation and approval from Sponsor) and re-enrolled into Part 2 (see below).

  OR
- Patients with ovarian cancer who failed to meet the eligibility criteria for Protocol CL-PTL-119 because of failure to achieve a complete clinical response following primary debulking surgery and standard paclitaxel/carboplatin therapy,

  OR
- Patients who failed to meet the eligibility criteria for Protocol CL-PTL-119 because of a histologic diagnosis of another gynecological cancer (i.e., cervical, uterine) and not ovarian cancer.

  OR
- Patients who were randomized on Protocol CL-PTL-119 and were subsequently unblinded at recurrence and were assigned to the placebo arm.

The primary objective of the study is to determine the safety of the Vigil and atezolizumab combination. Secondary objectives include determination of the immune response rate to Vigil alone, atezolizumab alone and the combination of the two agents. In patients with measureable disease, anti-tumor activity as assessed by RECIST 1.1 criteria, will also be summarized and correlated to baseline tumor mutation burden, baseline PD-L1 expression, post treatment TIL infiltration, change in PD-L1 expression and circulating tumor cell response. Overall assessment of time to progression and survival will also be summarized for each cohort. Assuming no untoward adverse effects from the combination of Vigil with atezolizumab, the treatment of 20-25 patients should be sufficient to assess safety and provide an estimate of the immune response rate and RECIST response rate.

Part 1

The first part will be a safety run-in where the initial 3 subjects registered will receive the combination of Vigil plus atezolizumab. Part 1 will evaluate the safety of Vigil in combination with atezolizumab.

Vigil immunotherapy will be administered at a concentration of $1x10^7$ cells/dose given via intradermal injection every 3 weeks for a minimum of 4 doses and a maximum of 12 doses. Atezolizumab will be administered at the FDA approved dose and schedule as described in the U.S. Package Insert (USPI). Thus, atezolizumab is to be administered at a dose of 1200mg as an intravenous infusion every 3 weeks. The initial dose is to be administered over one hour and if well tolerated, subsequent infusions may be administered over 30 minutes. Vigil should be administered first, followed 30 minutes later by atezolizumab.

The first subject to receive the combination of Vigil plus atezolizumab must complete the first 21-day cycle of combination therapy without serious, unexpected toxicity before the enrollment of any patients into Part 2 can occur.

Part 2

Part 2 is a randomized, open label intra-patient crossover study of Vigil, the checkpoint inhibitor atezolizumab and the combination of the two agents. Eligible patients will be randomized to receive two cycles of Vigil alone or two cycles of atezolizumab alone, followed by combination treatment with both agents.

Vigil immunotherapy will be administered at a concentration of 1×10^6 or $1x10^7$ cells/dose given via intradermal injection every 3 weeks for a minimum of 4 doses and a maximum of 12 doses.

Atezolizumab will be administered at the FDA approved dose and schedule as described in the U.S. Package Insert (USPI). Thus, atezolizumab is to be administered at a dose of 1200 mg as an intravenous infusion every 3 weeks, with a maximum of 12 doses. The initial dose is to be administered over one hour and if well tolerated, subsequent infusions may be administered over 30 minutes. When combined, Vigil should be administered first, followed 30 minutes later by atezolizumab.

Atezolizumab related safety events, include, but are not limited to immune related pneumonitis, hepatitis, colitis, endocrinopathies, meningitis/encephalitis, neuropathies and

pancreatitis are to be managed per the guidelines in the USPI. For combination treatment, the occurrence of a Grade 3 or 4 toxicity attributed to Vigil will result in the cessation of Vigil dosing and continuation of single agent atezolizumab only.

Part 3

Part 3 is an expansion cohort that allows for subjects who have completed all cycles of Part 2 as noted above to continue on atezolizumab alone, after Cycle 12. Eligible subjects will be pre-approved by Sponsor for inclusion into Part 3. Subjects may continue on single agent atezolizumab until disease progression.

Atezolizumab will be administered at the FDA approved dose and schedule as described in the U.S. Package Insert (USPI). Thus, atezolizumab is to be administered at a dose of 1200 mg as an intravenous infusion every 3 weeks.

Atezolizumab related safety events include, but are not limited to immune related pneumonitis, hepatitis, colitis, endocrinopathies, meningitis/encephalitis, neuropathies and pancreatitis are to be managed per the guidelines in the USPI.

Part 1, radiological assessment of tumor response will be performed at baseline and every third cycle thereafter. Tumor biopsy for correlative studies including scoring of tumor infiltrating lymphocyte (TIL) and PD-1 / PD-L1 expression analysis will be obtained at tissue procurement and at any time after the end of cycle 3. Whole blood for correlative studies (immune function) will be obtained at baseline, prior to study agent administration at the start of cycle 3 and every third cycle thereafter.

Part 2, radiological assessment of tumor response will be performed at baseline, at the end of cycle 2 of single agent therapy, and every third cycle thereafter. Tumor biopsy for correlative studies including scoring of tumor infiltrating lymphocyte (TIL) and PD-1 / PD-L1 expression analysis will be obtained at tissue procurement, prior to the start of combination therapy and at any time after the end of cycle 3. Whole blood for correlative studies (immune function) will be obtained at baseline, prior to study agent administration at the start of cycle 3 (the first cycle of combination therapy) and every third cycle thereafter.

Part 3 schedule of assessments are noted in Appendix C. The schedule will continue from Part 2 in which the following will be assessed every third cycle: radiological assessments, tumor biopsy (if available), and whole blood collection for correlative studies.

The safety evaluation will include AEs, SAEs, and changes from baseline in laboratory evaluations, vital signs, electrocardiograms, and physical examinations. The number and percentage of subjects reporting treatment-emergent AEs will be summarized overall and by the worst Common Terminology Criteria for Adverse Events (CTCAE) grade, system organ class, and preferred term. Similarly, the number and percentage of subjects reporting treatment-emergent AEs considered related to investigational product will be summarized. At each level of subject summarization, a subject will be counted once using the highest grade and level of causality if one or more occurrences of the same system organ class/preferred term is reported. Adverse events will be graded according to the National Cancer Institute

(NCI) CTCAE v4.03 and coded using the Medical Dictionary for Regulatory Activities. Laboratory abnormalities will be graded according to the NCI CTCAE v4.03, if applicable.

Objective(s):

Primary Objective(s):

- To evaluate and characterize the tolerability and safety profile of Vigil combined with atezolizumab.

Secondary Objective(s):

- To determine immune response rate and duration of conversion in subjects who are treated with Vigil, Atezolizumab and the combination of the two agents.
- To determine the ORR by RECIST 1.1 in subjects who are treated with the combination of Vigil and atezolizumab.
- To determine PD-L1 signal expression at baseline and follow up tumor biopsy (when available).
- To determine TIL infiltration at baseline and follow up tumor biopsy (when available).
- To determine PFS and estimate OS in treated patients.

Number of Patients:

Approximately 20-25 subjects will be enrolled.

Tissue Procurement Inclusion Criteria:

Subjects will be eligible for tissue procurement for the Vigil manufacturing process, if they meet all of the following criteria:

1. Histologically confirmed Stage IIIb, IIIc or IV high-grade papillary serous, clear cell, or endometrioid ovarian, fallopian tube or primary peritoneal carcinoma
2. Age ≥ 18 years.
3. Estimated survival ≥ 6 months.
4. ECOG Performance Status ≤ 1
5. Metastatic disease
6. Planned standard of care surgical procedure (e.g., tumor biopsy or palliative resection or thoracentesis) and expected availability of a cumulative soft-tissue mass of ~10-30 grams tissue (“grape” to “golf-ball” size) or ascites fluid estimated volume ≥ 500mL (from a primary or secondary paracentesis, yielding in a high volume of tumor cells) for immunotherapy manufacture.
7. Tumor intended for immunotherapy manufacture is not embedded in bone and does not contain luminal tissue (e.g. bowel, ureter, bile duct).
8. Ability to understand and the willingness to sign a written informed protocol specific consent for tissue harvest or a parental/guardian informed consent and pediatric assent when appropriate.

Tissue Procurement Exclusion Criteria:

Subjects meeting any of the following criteria are not eligible for tissue procurement for the Vigil manufacturing:

1. Medical condition requiring any form of chronic systemic immunosuppressive therapy (steroid or other) except physiologic replacement doses of hydrocortisone or equivalent (no more than 30 mg hydrocortisone or 10 mg prednisone equivalent daily) for < 30 days duration.
2. Known history of other malignancy unless having undergone curative intent therapy without evidence of that disease for ≥ 3 years **except** cutaneous squamous cell and basal cell skin cancer, superficial bladder cancer, *in situ* cervical cancer or other *in situ* cancers are allowed if definitively resected.
3. Brain metastases unless treated with curative intent (gamma knife or surgical resection) **and** without evidence of progression for ≥ 2 months.
4. Any documented history of autoimmune disease with exception of Type 1 diabetes on stable insulin regimen, hypothyroidism on stable dose of replacement thyroid medication, vitiligo, or asthma not requiring systemic steroids.
5. Known HIV or chronic Hepatitis B or C infection.
6. Known history of allergies or sensitivities to gentamicin.
7. History of or current evidence of any condition (including medical, psychiatric or substance abuse disorder), therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.
8. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) less than 21 days prior to tissue procurement.

Study Enrollment Inclusion Criteria:

Subjects will be eligible for registration into the trial if they meet all of the following inclusion criteria:

1. Successful manufacturing of at least 4 vials of Vigil.
2. One of the following:
    a. Failure to meet the eligibility criteria for Protocol CL-PTL-119 due to i) histology of ovarian cancer and failure to achieve a complete clinical response following primary debulking surgery and standard paclitaxel/carboplatin therapy OR, ii) a histologic diagnosis of another gynecologic malignancy which is not ovarian cancer.
    b. Recurrent ovarian cancer.
    c. Randomized on Protocol CL-PTL-119 and were subsequently unblinded at recurrence and were assigned to the placebo arm.
3. ECOG performance status (PS) ≤ 1 (or ≤ 2 due to carcinoid syndrome)

4. Estimated survival ≥ 6 months.
5. Measurable per RECIST 1.1 or evaluable disease.
6. Adequate organ and bone marrow function as defined below:
    a. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L (1500 per mm^3)
    b. Platelets ≥100 × 10^9/L (100,000 per mm^3)
    c. Hemoglobin ≥9.0 g/dL (5.59 mmol/L)
    d. Creatinine clearance (CrCL) >50 mL/min by the Cockcroft-Gault formula or by 24-hour urine collection for determination of creatinine clearance:

       Females:

       $$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

    e. Serum bilirubin ≤1.5 × upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of evidence of hemolysis or hepatic pathology) who will be allowed in consultation with their physician.
    f. AST and ALT ≤2.5 × ULN in patients with no liver metastasis
    g. AST or ALT ≤5 × ULN in patients with liver metastasis
    h. TSH within institutional limits. *If TSH is greater or less than institutional limits patients may participate if their T4 is within normal limits (WNL); patients may be on a stable dose of replacement thyroid medication; dose adjustments are allowed if needed*
7. Subject has recovered to CTCAE Grade 1 or better from all adverse events associated with prior therapy or surgery (or ≤ 2 due to carcinoid syndrome)
8. Pre-existing motor or sensory neurologic pathology or symptoms must be recovered to CTCAE Grade 2 or better
9. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by the IPs (Vigil and/or atezolizumab) may be included (e.g., hearing loss) after consultation with the Principal Investigator
10. Subjects who are not rendered surgically sterile as a result of surgery for ovarian cancer, must have, negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a negative serum test will be required for study entry.
11. Ability to understand and the willingness to sign a written informed protocol specific consent.
12. Willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
13. Patients must have fully recovered from chemotherapy associated toxicities prior to starting treatment on this protocol.

    Palliative radiotherapy is permitted provided:
    a. More than 3 weeks have elapsed between the end of radiotherapy and the first dose of study therapy, AND
    b. The irradiated lesion(s) (unless measurable progression after irradiation) cannot be used as target lesions.

Study Enrollment Exclusion Criteria:

In addition to the procurement exclusion criteria, subjects (both with Vigil manufactured and undergoing procurement) will NOT be eligible for study registration and enrollment if meeting any of the following criteria:

1. Participation in another clinical study with an investigational product within the last 3 weeks prior to study start.
2. Receipt of steroid therapy within the 2 weeks of the first dose of study therapy.
3. Live vaccine used for the prevention of infectious disease administered < 30 days prior to the start of study therapy. NOTE: Subjects, if enrolled, should not receive live vaccine during the study and for 5 months after the last dose of atezolizumab.
4. Post-surgery complication that in the opinion of the treating investigator would interfere with the subject's study participation or make it not in the best interest of the subject to participate.
5. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.
6. Female subjects who are pregnant, breast-feeding or of reproductive potential who are not employing an effective method of birth control defined in the protocol. Effective contraception is required for women receiving atezolizumab for 5 months after the last dose.
7. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
8. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) less than 21 days prior to the first dose of study drug or less than 6 weeks for nitrosourea or mitomycin C.
9. Receipt of any anti-cancer therapy between tissue procurement on CL-PTL-126 and first dose of study drug.

Medication and Dose(s):

Part 1

The first three subjects will receive Vigil in combination with atezolizumab on Day 1 every 3 weeks.

Part 2

Subjects will be randomized to receive two cycles of Vigil alone or two cycles of atezolizumab alone, followed by combination treatment with both agents.

- Vigil immunotherapy will be administered at a concentration of 1 x 10^6 or 1 x 10^7 cells/dose via intradermal injection every 3 weeks for a minimum of 4 administrations and a maximum of 12 administrations (depending on the quantity of Vigil manufactured from surgical specimens).

- Atezolizumab will be administered at the FDA approved dose and schedule as described in the U.S. Package Insert (USPI). Thus, atezolizumab is to be administered at a dose of 1200 mg as an intravenous infusion every 3 weeks. The initial dose is to be administered over one hour and if well tolerated, subsequent infusions may be administered over 30 minutes.
- When administered in combination on the same day (Day 1), Vigil should be administered first, followed 30 minutes later by atezolizumab.

Duration:

Patients should continue the combination of Vigil with atezolizumab until disease progression (by RECIST 1.1) is documented, or toxicity supervenes. Depending on the number of doses of Vigil manufactured, it is expected that 4 to12 doses of Vigil will be administered. Once Vigil doses are exhausted, subjects whose disease is stable or responding may continue to receive single agent atezolizumab until disease progression.

Efficacy Assessments:

- Immune activation will be assessed at the start of Cycle 3 and every third cycle thereafter.
- Durability of immune response will also be assessed.
- Anti-tumor activity will be assessed via RECIST 1.1 criteria as determined by the investigator at Cycle 3 and every third cycle thereafter.
- In consenting patients with tumor accessible for biopsy, the change in TIL infiltration and PD-L1 expression will be assessed by comparing tumor specimens from pre-study procurement to biopsy material obtained after at least one cycle of combination therapy with Vigil plus atezolizumab.

Safety Assessments:

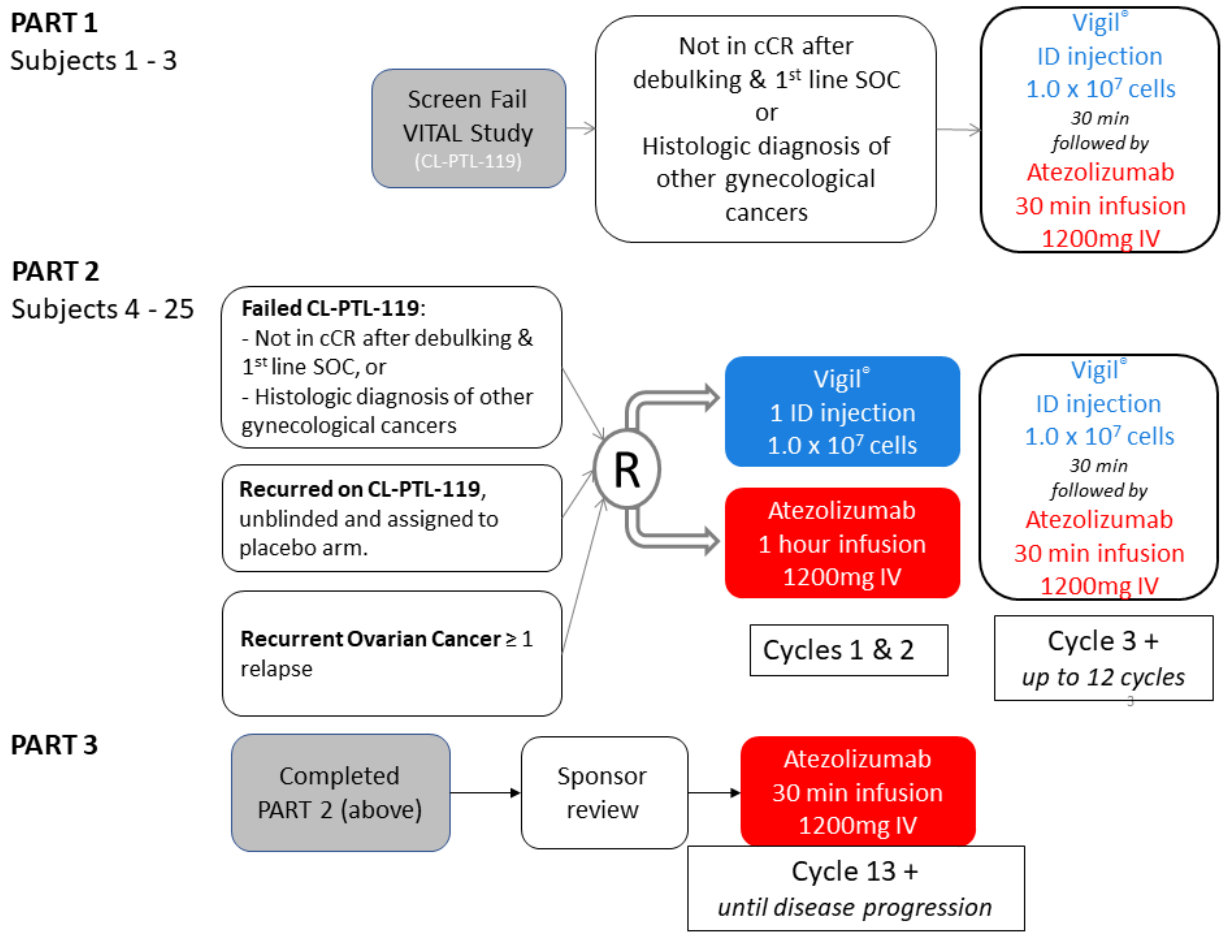
The safety evaluation will include AEs, SAEs, AESIs and changes from baseline in laboratory evaluations, vital signs, electrocardiograms, and physical examinations.

Adverse events will be recorded from time of first dose of Vigil and/or atezolizumab, throughout the treatment period and including the follow-up period.

- 30 days following the last study treatment or until another therapy has been initiated, whichever is earlier, regardless of causality.
- SAEs and AESIs are to be followed for 30 days after the last dose of study drug or the initiation of new therapy, whichever is earlier.

STUDY SCHEMA

21-day cycle



1.0 BACKGROUND

1.1 Unmet Medical Need in Ovarian Cancer

The majority of women diagnosed with cancer of the ovary present in an advanced stage (Jemal, Siegel et al. 2009) with 5-year survival rates of 59% for Stage IIIa, 52% for Stage IIIb, 39% for Stage IIIc (Heintz, Odicino et al. 2006), and 17% for Stage IV (American Cancer Society).

The established standard of care for newly diagnosed ovarian cancer is maximal de-bulking surgery followed by 6 months of chemotherapy with paclitaxel and carboplatin. About 75% of patients will be in complete remission following this front-line management.

Unfortunately, approximately 75% of the women with Stage III/IV ovarian cancer who achieve a complete clinical response will relapse, as will 50% of those achieving pathologic complete response, with a median time to relapse of 16-24 months following chemotherapy, depending on risk factors (Gadducci, Sartori et al. 1998; Markman, Liu et al. 2003; Gadducci, Cosio et al. 2005). Once relapsed, ovarian cancer is incurable, and the goals of treatment are primarily to prevent further disease progression and to palliate symptoms of advancing cancer.

A variety of treatment options are available for relapsed ovarian cancer. The type of treatment offered depends on the timing of relapse. Women who relapse 6 months or more after completion of chemotherapy are generally considered platinum sensitive and are treated with platinum doublet regimens such as carboplatin plus paclitaxel or carboplatin plus gemcitabine. Women who progress while receiving platinum doublet therapy or relapse in less than 6 months after completion of platinum doublet chemotherapy are considered platinum resistant. These patients generally receive sequential single agent chemotherapy with drugs such as pegylated liposomal doxorubicin, topotecan, weekly paclitaxel or the targeted agent olaparib, used only in patients whose tumor expresses BRCA mutations.

The anti-angiogenic agent bevacizumab has been found to improve relapse free and progression free survival when combined with initial chemotherapy or with chemotherapy following relapse. Dosing recommendations for bevacizumab in ovarian cancer allow for the continuation of single agent bevacizumab following the completion of chemotherapy until such time as the patient's disease progresses or toxicity intervenes.

A number of studies have attempted to improve outcome in ovarian cancer by administering maintenance therapy after patients have achieved a complete response following standard paclitaxel/carboplatin combination therapy. None of these studies have demonstrated any advantage in relapse free (Sabbatini, Harter et al. 2013) or overall survival (Markman, Liu et al. 2009; Sabbatini, Harter et al. 2013) and (Burger, Brady et al. 2011; Perren, Swart et al. 2011). In addition, a meta-analysis of randomized controlled trials of maintenance chemotherapy in 1644 women accrued to 8 trials concluded no significant difference in three-, five- and 10-year OS or PFS (Mei, Chen et al. 2013). A subsequent, independent trial-sequential analysis of these same data reached the same conclusion (Messori, Fadda et al. 2013).

In summary, the poor survival in advanced ovarian cancer is due both to late diagnosis, as well as to the lack of effective therapy for patients who relapse. The clinical course of ovarian cancer patients is marked by periods of remission and relapse of sequentially shortening duration until chemotherapy resistance develops. Therefore, new treatment modalities and paradigms are needed in order to significantly improve the prognosis of women diagnosed with epithelial ovarian cancer.

1.2 Rationale for Immunotherapy in Ovarian Cancer

One promising avenue of clinical research in ovarian cancer is the use of immunotherapy, including immune checkpoint inhibitors and cellular immunotherapies. An increasing body of data indicates that antitumor immunity impacts the clinical outcome of ovarian cancer. Recent reports have detailed how ovarian cancer cells can acquire potential escape mechanisms to evade host immunity via several immunosuppressive factors, including a loss of MHC expression and the upregulation of immunosuppressive factors including TGF-beta, indoleamine 2,3-dioxygenase (IDO) and cyclooxygenase (COX-1 and COX-2).

Increased expression of immunosuppressive TGFβ isoforms in ovarian tumor as compared with normal ovarian tissue has been reported (Henriksen, Gobl et al. 1995; Bristow, Baldwin et al. 1999) with significant increases in TGFβ1 in both primary (2.9 fold; $p \leq 0.002$) and recurrent (4.4 fold; $p \leq 0.002$) ovarian cancer (Bristow, Baldwin et al. 1999). Secreted TGFβ from ovarian cancer cells generate immunosuppressive Treg cells (CD4+CD25+) from peripheral CD4+CD25- cells (Li, Ye et al. 2007). Both Treg tumor infiltration and the granzyme B+/FOX3p+ ratio are associated with poor outcome in patients with high-grade serous ovarian carcinoma treated with neoadjuvant chemotherapy (Polcher, Braun et al. ; Milne, Kobel et al. 2009). The CD8/Treg ratio is also a prognostic indicator (Sato, Olson et al. 2005).

An additional immunosuppressive mechanism shown to be active in the ovarian cancer tumor microenvironment is enhanced immune checkpoint signaling via B7/CTLA4 and PD-1/PD-L1. The increasing knowledge of these immunosuppressive mechanisms in ovarian cancer highlights the importance of developing new treatment strategies in ovarian cancer. This study aims to explore the application of one such novel strategy, the combination of immune checkpoint inhibitor therapy and autologous cellular immunotherapy.

Following their successful development in other solid tumors like melanoma and non-small cell lung cancer, several immune checkpoint inhibitors are now being developed as therapeutics in ovarian cancer. The immune checkpoint inhibitors target molecules which dampen the normal human immune response and prevent uncontrolled immune stimulation. In ovarian cancer, cancer cells and tumor associated myeloid cells have been found to over express the ligand PD-L1 (Curiel, Wei et al. 2003; Liu, Chen et al. 2008; Abiko, Mandai et al. 2013), and expression of PD-L1 has been associated with decreased tumor infiltrating lymphocytes (TILs) and poor overall survival (Hamanishi, Mandai et al. 2007). These immune inhibitory proteins are overexpressed in the tumor microenvironment and prevent normal immune surveillance.

By blocking these inhibitory molecules, anti-cancer immune responses are restored and enhanced. In animal models, blockade of PD-1 and PD-L1 has been shown to eradicate tumors

through reprogramming of tumor microenvironment (Duraiswamy, Kaluza et al. 2013). In Phase I/II studies with several of the immune checkpoint inhibitors directed against PD-1 or PD-L1, single agent response rates of approximately 6% to 20% were observed in patients with advanced, relapsed ovarian cancer. Durable partial responses as well as some complete responses were reported. As a result, several of these agents have progressed to Phase III clinical trials.

1.3 Vigil

Vigil immunotherapy is one of the more advanced cellular immunotherapies being studies in clinical trials. It is composed of autologous tumor cells harvested from the patient at the time of initial de-bulking surgery which are then transfected extra-corporeally, with a plasmid encoding for the gene for GM-CSF, an immune-stimulatory cytokine, and a bifunctional, short hairpin RNA which specifically knocks down the expression of furin, the critical convertase responsible for production of the two TGβ isoforms (TGFβ-1 and TGFβ-2). Following manufacture, Vigil is administered to the patient from whom the tumor was harvested, via intra-dermal injection, once per month. The rationale for the Vigil construct is outlined below.

Dendritic cells prime antigen-specific immune responses (Zeng, Wang et al. 2001) and express diverse receptors that allow for the recognition and capture of antigens in peripheral tissues like the dermis. They process this material efficiently into the MHC Class I and II presentation pathways, upregulate costimulatory molecules upon maturation, and migrate to secondary lymphoid tissues (Banchereau, Briere et al. 2000) where they present the antigens to T cells.

Increasing evidence suggests that GMCSF is involved in the augmentation of tumor antigen presentation by dendritic cells (DCs) (Dranoff, Jaffee et al. 1993; Huang, Golumbek et al. 1994). It has been shown to induce a subset of DCs that are superior for the phagocytosis of apoptotic tumor cells (Young and Inaba 1996; Pulendran, Lingappa et al. 1997; Shen, Reznikoff et al. 1997). It evokes higher levels of co-stimulatory molecules, which is characteristic of greater functional maturation and more efficient T cell stimulation, thereby broadening the arsenal of induced lymphocyte effector mechanisms (Murtaza, Kuchroo et al. 1999). GMCSF also promotes the presentation of lipid antigens by dendritic cells which in turn leads to activation of Natural Killer T cells (NKT cells) a population of lymphocytes that may be pivotal in both endogenous and therapeutic responses to tumors (Smyth, Crowe et al. 2002).

The immune suppressor functions of TGFβ are likely to play a major role in modulating the effectiveness of cancer immunotherapy. TGFβ inhibits GMCSF induced maturation of bone marrow derived dendritic cells (DCs) (Yamaguchi, Tsumura et al. 1997) as well as expression of MHC Class II and co-stimulatory molecules (Geissmann, Revy et al. 1999). It has been shown that antigen presentation by immature DCs result in T cell unresponsiveness (Steinman, Hawiger et al. 2003). TGFβ also inhibits activated macrophages (Ashcroft 1999) including their antigen presenting function (Du and Sriram 1998; Takeuchi, Alard et al. 1998). The ubiquitous expression of the TGFβ isoforms as well as the inhibitory effects of these isoforms have on GMCSF immune stimulatory function provide a strong rationale for combining TGFβ suppression and GMCSF upregulation within a single immunotherapeutic construct.

Within the Vigil construct, the suppression of TGFβ isoforms is achieved by knocking down the expression of furin. Furin is a member of the subtilisin-like proprotein convertase family, an upstream regulator of the TGFβ isoforms. Furin is required for proteolytic activation of both TGFβ-1 and TGFβ-2. High levels of furin mRNA and furin protein are widely expressed in human tumors and, specifically, in ovarian tumors (Page, Klein-Szanto et al. 2007) where the gene is differentially expressed (compared to normal human ovarian surface epithelium cell lines) and the level appears to be inversely correlated with survival (Page, Klein-Szanto et al. 2007). The presence of furin in tumor cells likely contributes significantly to the maintenance of tumor directed, TGFβ-mediated peripheral immune tolerance (Pesu, Watford et al. 2008). Down regulation of furin can be expected to simultaneously reduce TGFβ-1 and TGFβ-2 levels. Indeed, this has been demonstrated consistently in the manufacture of Vigil for completed and ongoing clinical trials.

1.4 Vigil Clinical Experience

Since the initiation of clinical trials with Vigil in 2009, over 160 patients have received treatment with the therapy and over 900 doses have been administered in completed and ongoing studies. The most frequently reported adverse reactions attributed to Vigil engineered cell administration are injection site reactions which are mild to moderate in intensity, consisting primarily of redness and swelling at the injection site. These occur in essentially all Vigil treated patients. To date, there have been no severe or life threatening (CTC Grade 3 or 4) adverse events attributed to Vigil treatment.

An early report (Senzer et. al. 2012) summarized the initial experience in 27 patients treated with the Vigil cellular immunotherapy construct (named FANG at the time), and in a matched control group of 18 patients. All patients underwent surgery for procurement of tumor tissue and manufacture of Vigil, however, the matched control group of 18 patients did not receive Vigil due to patient choice (14), failure to satisfy eligibility criteria (2) or failure of manufacture (2). Patient characteristics and dosing information are summarized in Table 1 below.

Table 1. Patient Characteristics

Characteristic	No Vigil (*n* = 18)	Vigil (*n* = 27)	All (*n* = 45)
Age (years)			
Mean	56	59	57
Median	56	62	57
Range	39–73	26–84	26-84
Gender			
Male	9	8	17
Female	9	19	28
Dose level			
1.0 × 10e7 cells/ml	8	10	18
2.5 × 10e7 cells/ml	8	17	25
Vaccine failure	2	N/A	2

Both GMCSF transgene expression and downregulation of expression of TGFβ1 and TGFβ2 were apparent in all successfully manufactured Vigil preparations. Mean post-transfection GMCSF expression increased from 7.3 to 1,108 pg/10^6 cells/ml. Mean TGFβ1 and β2 knockdown were 93.5% and 92.5%, respectively.

Of the Vigil treated patients, 4 out of 27 had rapidly progressive disease after 1 or 2 injections of Vigil and were removed from study. The remaining 23 patients had stable disease as their best response to therapy and received between 3 and 11 monthly injections of Vigil. Median survival of the Vigil treated patients was 554 days when measured from tissue procurement and was not reached when measured from start of Vigil treatment. The 18 patients who had tumor harvested but did not receive Vigil therapy survived a median of 132 days from tissue procurement ($p < 0.0001$). There were no apparent differences in response to treatment, survival or safety profile by dose level of the Vigil construct.

The interferon gamma ELISPOT assay was piloted as a clinical biomarker of immune activation in 18 of 27 Vigil treated patients on the study. Only 1 of 18 patients demonstrated immune activation at baseline. Nine of 18 patients converted to ELISPOT positivity by month 4 of Vigil treatment and remained positive throughout treatment and in some cases for up to 6 months afterwards. A tenth patient was noted to convert to ELISPOT positivity at 6 months after the start of Vigil. Interestingly, the survival of ELISPOT positive patients was significantly longer than that of patients who failed to convert to positivity ($p = 0.045$ from time of tissue procurement or $p = 0.025$ from start of Vigil treatment).

The association of TGFβ expression with poor outcome in ovarian cancer coupled with the safety, biomarker and survival correlations reported in the first-in-human study, provided the basis for a randomized Phase 2 study of Vigil Immunotherapy as maintenance therapy in women who achieved complete clinical response (cCR) following surgical de-bulking and standard, paclitaxel/carboplatin chemotherapy. Following surgery and chemotherapy, patients in the control arm underwent regular observation for recurrence, which is current standard of care (SOC). Patients randomized to the control arm were permitted to cross-over and receive their Vigil at the time of recurrence.

Eligible patients were initially randomized 2 (Vigil): 1 (SOC). Patients received 1.0 x 10^7 cells / intradermal injection of Vigil once per month for up to 12 doses as long as sufficient material was available. Tumor procurement needed to be sufficient to supply a minimum of 4 monthly injections in order for a patient to be entered into the study. Treatment was continued until disease recurrence or exhaustion of the patient's vaccine supply. Clinical adverse events, as reported by the patient, were assessed continuously. Other scheduled safety assessments included monthly physical examination, performance status, height, weight, vital signs and laboratory evaluations. The primary efficacy endpoint was recurrence free survival assessed radiographically by the investigators. CA-125 was monitored at baseline, monthly for the first year, every 3 months ± 2 weeks for the second and third year.

Serial immune function analysis including ELISPOT analysis of mononuclear cell function to pre-processed autologous tumor cells was monitored at baseline (screening), prior to Vigil injection and at Months 2, 4, 6 and at end of treatment (EOT). A positive response was defined as > 10 ELISPOTs induced per 10^6 peripheral blood mononuclear cells (PBMC) and twice baseline response.

Results are reported in a total of 42 patients, 31 in the Vigil arm and 11 in the control arm. The original randomized design was abandoned after 21 patients were randomized into the Vigil arm of the study and 11 to the control arm, when the sponsor decided to initiate a definitive Phase 3 study. At that time, an additional 10 patients who were completing chemotherapy were allowed to receive Vigil without randomization.

A total of 241 intradermal (ID) injections of Vigil were administered to the 31 patients. The most frequent treatment emergent adverse events, considered related to therapy were injection site reactions of CTCAE Grade 1 or 2, which occurred in essentially all Vigil treated patients. There were no CTCAE Grade 3 or 4 treatment related adverse events amongst the Vigil treated patients.

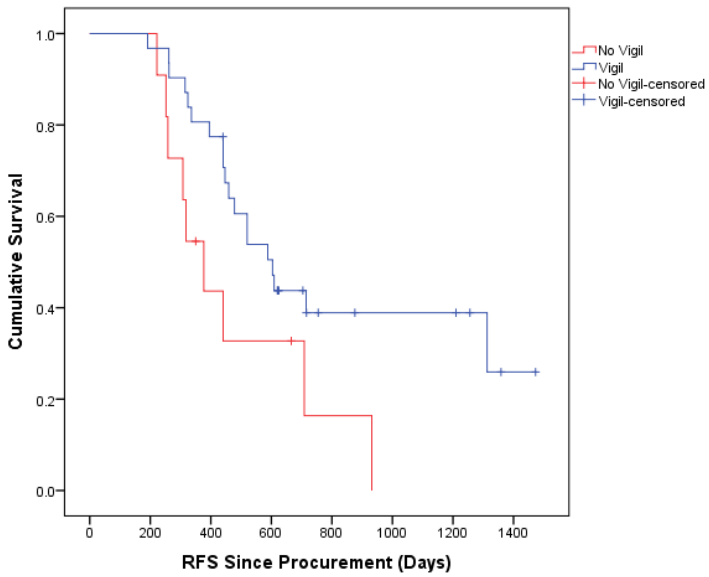
At baseline, 30 of 31 Vigil treated patients and 10 of 11 control patients demonstrated negative ELISPOT reactivity prior to Vigil treatment at time of randomization. One Vigil treated patient was actually ELISPOT positive at baseline and one control patient was inevaluable for ELISPOT reactivity. Following Vigil injection a positive ELISPOT response was observed in 31 of the 31 Vigil treated patients (median ELISPOT reactivity was 134; range, 12-448 spots). The positive responses were first observed at Month 2 (n=28), 3 (n=1), 4 (n=1) and 9 (n=1). In the control arm, 7 of the 8 patients who relapsed and elected to cross over to receive Vigil, were ELISPOT negative at the time of relapse and converted to positive ELISPOT by Month 2.

Comparison of RFS from time of procurement between Vigil or control patients following consolidation treatment with carboplatin/paclitaxel is summarized in Table 2 and shown in Figure 1. Control RFS is consistent with historical expectation (mean RFS 16 months/481 days). On the other hand, Vigil response data suggests improved RFS, 27 months/826 days by Kaplan Meier analysis (p=0.033, log-rank). Analysis of the high median ELISPOT positive population vs. low median ELISPOT population did not reveal a difference in time to relapse duration or overall relapse rate. RFS from time of treatment was a mean/median of 304/195 days in the control arm and 563/352 days in the Vigil arm (p=0.13)

Table 2. Relapsed Free Survival

Group	N	% of Recurrences	Mean RFS (days)	Median RFS (days)	p-value
Control	11	82%	15.8	12.4	0.033 log-rank
Vigil	31	61%	27.1	19.8	p=0.039 Cox HR 0.43 95% CI (0.19, 0.96)

Figure 1. RFS



On the basis of these results, a definitive comparison of maintenance Vigil vs. standard observation is underway in women with epithelial ovarian cancer who have achieved a complete clinical response following surgical de-bulking and standard paclitaxel/carboplatin chemotherapy (CL-PTL-119). The study, A Randomized, Double Blind, Placebo Controlled trial of Vigil Autologous Tumor Cell Immunotherapy in Subjects with Stage IIIb-IV Ovarian Cancer in Clinical Complete Response following Surgery and Primary Chemotherapy is otherwise known as the VITAL study.

This study is intended as a companion to VITAL for those women who fail to achieve a complete clinical response following standard chemotherapy and are thus ineligible for randomization.

2.0 STUDY RATIONALE

Early clinical results with both the checkpoint inhibitors and Vigil in ovarian cancer are promising. Given the complementary mode of action of the two agents, it is sensible to explore a combination of the two immunotherapy modalities.

3.0 OBJECTIVES

3.1 Primary objective(s)

To evaluate and characterize the tolerability and safety profile of Vigil combined with atezolizumab.

3.2 Secondary objective(s)

- To determine immune response rate and duration of conversion in subjects who are treated with Vigil, atezolizumab and the combination of the two agents.
- To determine the ORR by RECIST 1.1 in evaluable subjects who are treated with the combination of Vigil and atezolizumab.
- To determine PD-L1 signal expression at baseline and follow up tumor biopsy (when available).
- To determine TIL infiltration at baseline and follow up tumor biopsy (when available).
- To determine PFS and estimate OS in treated patients.

4.0 STUDY DESIGN

This is a 3-part safety study of Vigil in combination with checkpoint inhibitor atezolizumab, in patients with treatment refractory or recurrent epithelial ovarian cancer, or other gynecological cancers (i.e. cervical, uterine).

This study is intended as a companion study to protocol CL-PTL-119, A Randomized, Double Blind, Placebo-Controlled Phase 2 Trial of Vigil Engineered Autologous Tumor Cell Immunotherapy in Subjects with Stage IIIb-IV Ovarian Cancer in Clinical Complete Response following Surgery and Primary Chemotherapy, otherwise known as the VITAL study or previously randomized to placebo. Patients who have tumor harvested at surgery and Vigil successfully manufactured, but then are ineligible for randomization onto the VITAL study, will be offered the opportunity to participate in this protocol.

Subjects enrolled will either be:

- Patients with recurrent ovarian cancer. Furthermore, subjects who have previously received Vigil on this study may be considered for re-procurement for manufacture of Vigil (after consultation and approval from Sponsor) and re-enrolled into Part 2 (see below).

  OR
- Patients with ovarian cancer who failed to meet the eligibility criteria for Protocol CL-PTL-119 because of failure to achieve a complete clinical response following primary debulking surgery and standard paclitaxel/carboplatin therapy,

  OR
- Patients who fail to meet the eligibility criteria for Protocol CL-PTL-119 because of a histologic diagnosis of another gynecological cancer (i.e., cervical, uterine) and not ovarian cancer.

  OR
- Patients who were randomized on Protocol CL-PTL-119 and were subsequently unblinded at recurrence and were assigned to the placebo arm.

The primary objective of the study is to determine the safety of the Vigil and atezolizumab combination. Secondary objectives include determination of immune response rate to Vigil alone, atezolizumab alone and the combination of the two agents. In patients with measureable disease, anti-tumor activity as assessed by RECIST 1.1 criteria, will also be summarized and correlated to baseline tumor mutation burden, baseline PD-L1 expression, post treatment TIL infiltration, change in PD-L1 expression and circulating tumor cell response. Overall assessment of time to progression and survival will also be summarized for each cohort. Assuming no untoward adverse effects from the combination of Vigil with atezolizumab, the treatment of 20-25 patients should be sufficient to assess safety and provide an estimate of the immune response rate and RECIST response rate.

Part 1

The first part will be a safety run-in where the initial 3 subjects registered will receive the combination of Vigil plus atezolizumab. Part 1 will evaluate the safety of Vigil in combination with atezolizumab.

Vigil immunotherapy will be administered at a concentration of $1x10^7$ cells/dose given via intradermal injection every 3 weeks for a minimum of 4 doses and a maximum of 12 doses. Atezolizumab will be administered at the FDA approved dose and schedule as described in the U.S. Package Insert (USPI). Thus, atezolizumab is to be administered at a dose of 1200 mg as an intravenous infusion every 3 weeks. The initial dose is to be administered over one hour and if well tolerated, subsequent infusions may be administered over 30 minutes. Vigil should be administered first, followed 30 minutes later by atezolizumab.

The first subject to receive the combination of Vigil plus atezolizumab must complete the first 21-day cycle of combination therapy without serious, unexpected toxicity before the enrollment of any patients into Part 2 can occur.

Part 2

Part 2 is a randomized, open label intra-patient crossover study of Vigil, the checkpoint inhibitor atezolizumab and the combination of the two agents. Eligible patients will be randomized to receive two cycles of Vigil alone or two cycles of atezolizumab alone, followed by combination treatment with both agents.

Vigil immunotherapy will be administered at a concentration of 1×10^6 or $1x10^7$ cells/dose given via intradermal injection every 3 weeks for a minimum of 4 doses and a maximum of 12 doses.

Atezolizumab will be administered at the FDA approved dose and schedule as described in the U.S. Package Insert (USPI). Thus, atezolizumab is to be administered at a dose of 1200 mg as an intravenous infusion every 3 weeks, with a maximum of 12 doses. The initial dose is to be administered over one hour and if well tolerated, subsequent infusions may be administered over 30 minutes. When combined, Vigil should be administered first, followed 30 minutes later by atezolizumab.

Atezolizumab related safety events include, but are not limited to immune related pneumonitis, hepatitis, colitis, endocrinopathies, meningitis/encephalitis, neuropathies and pancreatitis are to be managed per the guidelines in the USPI. For combination treatment, the occurrence of a

Grade 3 or 4 toxicity attributed to Vigil will result in the cessation of Vigil dosing and continuation of single agent atezolizumab only.

Part 3

Part 3 is an expansion cohort that allows for subjects who have completed all cycles of Part 2 as noted above to continue on atezolizumab alone, after Cycle 12. Eligible patients will be pre-approved by Sponsor for inclusion into Part 3. Subjects may continue on single agent atezolizumab until disease progression.

Atezolizumab will be administered at the FDA approved dose and schedule as described in the U.S. Package Insert (USPI). Thus, atezolizumab is to be administered at a dose of 1200 mg as an intravenous infusion every 3 weeks.

Atezolizumab related safety events include, but are not limited to immune related pneumonitis, hepatitis, colitis, endocrinopathies, meningitis/encephalitis, neuropathies and pancreatitis are to be managed per the guidelines in the USPI.

Part 1, radiological assessment of tumor response will be performed at baseline and every third cycle thereafter. Tumor biopsy for correlative studies including scoring of tumor infiltrating lymphocyte (TIL) and PD-1 / PD-L1 expression analysis will be obtained at tissue procurement and at any time after the end of cycle 3. Whole blood for correlative studies (immune function) will be obtained at baseline, prior to study agent administration at the start of cycle 3 and every third cycle thereafter.

Part 2, radiological assessment of tumor response will be performed at baseline, at the end of cycle 2 of single agent therapy and every third cycle thereafter. Tumor biopsy for correlative studies including scoring of tumor infiltrating lymphocyte (TIL) and PD-1 / PD-L1 expression analysis will be obtained at tissue procurement, prior to the start of combination therapy and at any time after the end of cycle 3. Whole blood for correlative studies (immune function) will be obtained at baseline, at the start of cycle 3 (the first cycle of combination therapy) and every third cycle thereafter.

Part 3 schedule of assessments are noted in Appendix C. The schedule will continue from Part 2 in which the following will be assessed every third cycle: radiological assessments, tumor biopsy (if available), and whole blood collection for correlative studies.

The safety evaluation will include all adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs) as well as changes from baseline in laboratory evaluations, vital signs, electrocardiograms, and physical examinations. The number and percentage of subjects reporting treatment emergent AEs will be summarized overall and by the worst Common Terminology Criteria for Adverse Events (CTCAE) grade, system organ class, and preferred term. Similarly, the number and percentage of subjects reporting treatment-emergent AEs considered related to investigational product will be summarized. At each level of subject summarization, a subject will be counted once using the highest grade and level of causality if one or more occurrences of the same system organ class/preferred term is reported. Adverse events will be graded according to the National Cancer Institute (NCI) CTCAE v4.03

and coded using the Medical Dictionary for Regulatory Activities. Laboratory abnormalities will be graded according to the NCI CTCAE v4.03, if applicable.

5.0 STUDY POPULATION

5.1 Sample Size

Approximately 20-25 subjects will be enrolled.

5.2 Tissue Procurement Inclusion Criteria:

Subjects will be eligible for tissue procurement for the Vigil manufacturing process, if they meet all of the following criteria:

1. Histologically confirmed Stage IIIb, IIIc or IV high-grade papillary serous, clear cell, or endometrioid ovarian, fallopian tube or primary peritoneal carcinoma
2. Age ≥ 18 years.
3. Estimated survival ≥ 6 months.
4. ECOG Performance Status ≤ 1
5. Metastatic disease
6. Planned standard of care surgical procedure (e.g., tumor biopsy or palliative resection or thoracentesis) and expected availability of a cumulative soft-tissue mass of ~10-30 grams tissue (“grape” to “golf-ball” size) or ascites fluid estimated volume ≥ 500mL (from a primary or secondary paracentesis, yielding in a high volume of tumor cells) for immunotherapy manufacture.
7. Tumor intended for immunotherapy manufacture is not embedded in bone and does not contain luminal tissue (e.g. bowel, ureter, bile duct).
8. Ability to understand and the willingness to sign a written informed protocol specific consent for tissue harvest or a parental/guardian informed consent and pediatric assent when appropriate.

5.3 Tissue Procurement Exclusion Criteria:

Subjects meeting any of the following criteria are not eligible for tissue procurement for the Vigil manufacturing:

1. Medical condition requiring any form of chronic systemic immunosuppressive therapy (steroid or other) except physiologic replacement doses of hydrocortisone or equivalent (no more than 30 mg hydrocortisone or 10 mg prednisone equivalent daily) for < 30 days duration.
2. Known history of other malignancy unless having undergone curative intent therapy without evidence of that disease for ≥ 3 years except cutaneous squamous cell and basal cell skin cancer, superficial bladder cancer, in situ cervical cancer or other in situ cancers are allowed if definitively resected.

3. Brain metastases unless treated with curative intent (gamma knife or surgical resection) and without evidence of progression for ≥ 2 months.
4. Any documented history of autoimmune disease with exception of Type 1 diabetes on stable insulin regimen, hypothyroidism on stable dose of replacement thyroid medication, vitiligo, or asthma not requiring systemic steroids.
5. Known HIV or chronic Hepatitis B or C infection.
6. Known history of allergies or sensitivities to gentamicin.
7. History of or current evidence of any condition (including medical, psychiatric or substance abuse disorder), therapy, or laboratory abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.
8. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) less than 21 days prior to tissue procurement.

5.4 Study Enrollment Inclusion Criteria

Subjects will be eligible for registration into the trial if they meet all of the following inclusion criteria:

1. Successful manufacturing of at least 4 vials of Vigil.
2. One of the following:
    a. Failure to meet the eligibility criteria for Protocol CL-PTL-119 due to i) histology of ovarian cancer and failure to achieve a complete clinical response following primary debulking surgery and standard paclitaxel/carboplatin therapy OR, ii) a histologic diagnosis of another gynecologic malignancy which is not ovarian cancer.
    b. Recurrent ovarian cancer
    c. Randomized on Protocol CL-PTL-119 and were subsequently unblinded at recurrence and were assigned to the placebo arm.
3. ECOG performance status (PS) ≤ 1 (or ≤ 2 due to carcinoid syndrome).
4. Estimated survival ≥ 6 months.
5. Measureable per RECIST 1.1 or evaluable disease.
6. Adequate organ and bone marrow function as defined below:
    a. Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L (1500 per mm^3)
    b. Platelets ≥100 × 10^9/L (100,000 per mm^3)
    c. Hemoglobin ≥9.0 g/dL (5.59 mmol/L)
    d. Creatinine clearance (CrCL) >50 mL/min by the Cockcroft-Gault formula or by 24-hour urine collection for determination of creatinine clearance:

        Females:

        $$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

    e. Serum bilirubin ≤1.5 × upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of evidence of hemolysis or hepatic pathology) who will be allowed in consultation with their physician.
    f. AST and ALT ≤2.5 × ULN in patients with no liver metastasis

g. AST or ALT ≤5 × ULN in patients with liver metastasis
h. TSH within institutional limits. *If TSH is greater or less than institutional limits patients may participate if their T4 is within normal limits (WNL); patients may be on a stable dose of replacement thyroid medication; dose adjustments are allowed if needed*

7. Subject has recovered to CTCAE Grade 1 or better from all adverse events associated with prior therapy or surgery (or ≤ 2 due to carcinoid syndrome).
8. Pre-existing motor or sensory neurologic pathology or symptoms must be recovered to CTCAE Grade 2 or better
9. Patients with irreversible toxicity that is not reasonably expected to be exacerbated by the IPs (Vigil and/or atezolizumab) may be included (e.g., hearing loss) after consultation with the Principal Investigator
10. Subjects who are not rendered surgically sterile as a result of surgery for ovarian cancer, must have, negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a negative serum test will be required for study entry.
11. Ability to understand and the willingness to sign a written informed protocol specific consent.
12. Willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
13. Patients must have fully recovered from chemotherapy associated toxicities prior to starting treatment on this protocol.

    Palliative radiotherapy is permitted provided:
    a. More than 3 weeks have elapsed between the end of radiotherapy and the first dose of study therapy, AND
    b. The irradiated lesion(s) (unless measurable progression after irradiation) cannot be used as target lesions.

5.5 Study Enrollment Exclusion Criteria

In addition to the procurement exclusion, subjects (both with Vigil manufactured and undergoing procurement) will NOT be eligible for study registration and enrollment if meeting any of the following criteria:

1. Participation in another clinical study with an investigational product within the last 3 weeks prior to study start.
2. Receipt of steroid therapy within the 2 weeks of the first dose of study therapy.
3. Live vaccine used for the prevention of infectious disease administered < 30 days prior to the start of study therapy. NOTE: Subjects, if enrolled, should not receive live vaccine during the study and for 5 months after the last dose of atezolizumab.
4. Post-surgery complication that in the opinion of the treating investigator would interfere with the subject's study participation or make it not in the best interest of the subject to participate.
5. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.
6. Female subjects who are pregnant, breast-feeding or of reproductive potential who are not employing an effective method of birth control defined in the protocol. Effective contraception is required for women receiving atezolizumab for 5 months after the last dose.

7. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
8. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) less than 21 days prior to the first dose of study drug or less than 6 weeks for nitrosourea or mitomycin C.
9. Receipt of any anti-cancer therapy between tissue procurement on CL-PTL-126 and first dose of study drug.

Patients should continue the combination of Vigil with atezolizumab until disease progression is documented, or toxicity supervenes. Depending on the number of doses of Vigil manufactured, it is expected that 4 to12 doses of Vigil will be administered. Once Vigil doses are exhausted, subjects whose disease is stable or responding, may continue to receive single agent atezolizumab until disease progression.

5.6 Withdrawal from Study Treatment

Subjects will be taken **off study treatment** if any of the following occur:

1. An AE that, in the opinion of the Investigator or the Sponsor, contraindicates further dosing.
2. Patients with disease progression assessed by RECIST 1.1 criteria as determined by the investigator will not receive further Vigil or atezolizumab treatment.
3. The patient experiences unacceptable (≥Grade 3) toxicity felt to be related to treatment with Vigil, atezolizumab, or study related procedure that persists for >2 weeks.
4. Persisting Grade 3 or 4 toxicity unrelated to treatment, defined as failing to normalize within 4 weeks.
5. ≥ Grade 3 allergic reactions related to Vigil or atezolizumab.
6. Grade 2 autoimmune reactions unless there is evidence of clinical benefit.
7. ≥ Grade 3 autoimmune reactions.
8. An intercurrent illness, which would in the judgment of the investigator, affects assessments of clinical status to a significant degree or requires discontinuation of study treatment.
9. Non-protocol therapy is administered during study treatment.
10. Non-compliant with protocol or treatment.
11. Patient refuses to continue treatment.
12. Sponsor discontinuation of the protocol.

The date of and reason for discontinuation must be noted in the subject's source document. Every effort should be made to complete the appropriate assessments.

At any time, subjects are free to discontinue Vigil and/or atezolizumab without prejudice to further treatment. A subject who decides to discontinue Vigil and/or atezolizumab will always be asked about the reason(s) for discontinuation and the presence of any AE. If possible, they will be seen and assessed by an Investigator. Adverse events will be recorded from time of first dose of Vigil and/or atezolizumab, throughout the treatment period and including the follow-up period:

- 30 days following the last study treatment or until another therapy has been initiated, whichever is earlier, regardless of causality.
- SAEs and AESIs are to be followed for 30 days after the last dose of study drug or the initiation of new therapy, whichever is earlier.

The Study Physician should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

The date of and reason for discontinuation must be noted in the electronic Case Report Form (CRF). Every effort should be made to complete the appropriate assessments.

6.0 INVESTIGATIONAL PLAN

6.1 Subject Screening and Registration

Written documentation of full, unconditional IRB approval of the protocol and consent document must be on file before a subject can be screened. Study participation begins once written informed consent is obtained.

The Research Nurse or Clinical Research Coordinator will register the subject via email addressed to the Sponsor.

Please allow 48 hours for subject registration as the subject's source documents will be reviewed to ensure they meet the inclusion/exclusion criteria. Once confirmed, the site will be notified of eligibility by the Sponsor.

6.2 Study Treatment Administration

Treatment will be administered on an outpatient basis.

6.2.1 Schedule, Dose and Administration

Subjects will receive Vigil and atezolizumab according to the schedule outlined in Appendix B.

A study cycle is defined as 21 days (3 weeks).

Vigil immunotherapy will be administered at a concentration of 1×10^6 or 1×10^7 cells/dose given via intradermal injection every 3 weeks for a minimum of 4 doses and a maximum of 12 doses.

Atezolizumab will be administered at the FDA approved dose and schedule as described in the U.S. Package Insert (USPI). Thus, atezolizumab is to be administered at a dose of 1200 mg as an intravenous infusion every 3 weeks. The initial dose is to be administered over one hour and if well tolerated, subsequent infusions may be administered over 30 minutes.

The sites of injection for Vigil will be rotated between the right and left upper arms. If the ipsilateral axillary lymph nodes were radiated or surgically removed during prior therapy, alternative sites will be used. Subjects receiving Vigil will be observed for at least 30 minutes following administration.

Investigational treatment may continue unless documented disease progression, discontinuation for toxicity, withdrawal of consent, or meeting other criteria for withdrawal from study detailed in Section 5.6.

6.2.2 Dose Reduction / Escalation

Dose reduction or dose increase is not allowed for Vigil or atezolizumab.

Dose Holding Criteria

Both atezolizumab and Vigil should be held for any of the following AEs. Cycles held for toxicity should be made up (that cycle number is delayed rather than skipped). Atezolizumab and Vigil held may be resumed in patients whose AEs recover to Grade 0-1, with the exception of rash, which should recover to Grade 2 or better.

- Grade 2 pneumonitis
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Grade 2 or 3 diarrhea or colitis
- Symptomatic hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, or Grade 3 or 4 hyperglycemia
- Grade 2 ocular inflammatory toxicity
- Grade 2 or 3 pancreatitis, or Grade 3 or 4 increases in amylase or lipase levels (greater than 2.0 times ULN)
- Grade 3 or 4 infection
- Grade 2 infusion-related reactions
- Grade 3 rash
- Grade 2 nephritis

Based on the mechanism of action of atezolizumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune related colitis, pneumonitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of colitis, pneumonitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Study Regimen Delay

- Cycles held for toxicity should be made up and not deleted.
- Dosing of atezolizumab and Vigil may be restarted when toxicity is ≤ Grade 1 severity with the exception of rash which may be ≤ Grade 2.
- In case of immune related adverse events, treatment with atezolizumab and Vigil may be delayed for up to 15 weeks (12 weeks for steroid therapy plus 3 weeks for gradual steroid tapering to a dose of ≤ 10 mg/day of prednisone.
- Subjects who delay treatment for more than 15 weeks due to toxicities will be considered off study treatment (see Section 6.3 Withdrawal).
- Treatment delay not related to toxic events (including subjects unable to adhere to dose schedule) may not extend for more than three days unless due to symptoms related to disease or infection in which case up to a 4-week delay is allowed.
- If ≥ one 2-week delay due to disease or infection occurs, subject status must be reviewed by sponsor.

Atezolizumab should be permanently discontinued for any of the following AEs:

- Any life-threatening or Grade 4 AE
- Grade 3 or 4 pneumonitis
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >5 times upper limit of normal or total bilirubin >3 times upper limit of normal
- Diarrhea with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (Grade 4) stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
- Grade 4 hypophysitis
- Myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis (all grades)
- Grade 3 or 4 ocular inflammatory toxicity
- Grade 4 or any grade of recurrent pancreatitis
- Grade 3 or 4 infusion-related reactions
- Grade 4 rash
- Grade 3 or 4 nephritis
- Myocarditis (all grades)

For combination treatment, the occurrence of a Grade 3 or 4 toxicity attributed to Vigil will result in the cessation of Vigil dosing and continuation of single agent atezolizumab only.

Please reference https://www.gene.com/download/pdf/tecentriq_prescribing.pdf for full prescribing information regarding atezolizumab.

6.3 Toxicity

Toxicities will be graded and reported according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03 as linked in Appendix C. This document can also be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page <http://ctep.cancer.gov>.

Adverse events will be summarized using the MedDRA coding system or higher. The NCI-CTCAE will be used for AE grading. All AEs, regardless of severity, will be followed by the Treating Physician until resolution is satisfactory.

6.4 Treatment beyond Initial Progression in Select Cases

There is accumulating evidence that some subjects treated with immune system stimulating agents may appear to demonstrate progression of disease by conventional response criteria before demonstrating clinical objective responses and/or stable disease and ultimately survival benefit. This phenomenon has been observed in studies with inhibitors of both the CTLA-4 and PD-1/PD-L1 pathways. It may be that enhanced inflammation within tumors initially leads to an increase in tumor size or newly visible small lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals the kinetics of tumor growth may initially outpace anti-tumor immune activity followed, with sufficient time, by clinically apparent anti-tumor activity. Therefore, select subjects may be allowed to continue study therapy after investigator-assessed RECIST 1.1 progression and with agreement by the study Medical Monitor if the subject is determined to be deriving clinical benefit, tolerating study drug and meeting the following criteria:

1. Absence of symptoms and signs indicating clinically significant PD indicating disease progression.
2. No decline in ECOG performance status.
3. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

If subsequent imaging shows an objective response or stable disease relative to baseline, treatment with study agents will continue. If subsequent imaging again shows PD, patients will be discontinued from study therapy.

6.5 Schedule of Assessments

The schedule of assessments for the trial is shown in Appendix B. If a required observation or procedure is missed, documentation is required in CRF and in the subject's source documents, to explain the reason for this protocol deviation.

Based on findings during the study or during the follow up portion of the trial, Gradalis may request for additional blood and / or tissue samples from subjects during a routine blood draw or scheduled biopsy. Collection of whole blood (40ml) and / or tissue samples (via biopsy or clinically indicated surgical removal) will be **optional** and used to study the effects of the study agent (included, but not limited to testing of biomarkers, predictors or biological responses, toxicity, relationship between genotype and study agent responses).

Should Gradalis request for additional blood or tissue, the clinical site will present the option of the procurement to the participant and obtain written informed consent.

6.6 Part 3, Continuation with Single Agent Atezolizumab

Subjects who complete Cycles 3 – 12 of the combination study regimen, may continue administration of atezolizumab as long as they are in stable disease or better. Subjects may continue atezolizumab monotherapy until disease recurrence / progression. The schedule of assessments for subjects continuing with single agent atezolizumab is shown in Appendix C.

7.0 CONDUCT OF THE STUDY

7.1 Ethics and Regulatory Considerations

This study must have the approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Before the investigational product is shipped to the investigator, the investigator will provide Gradalis, Inc. with an electronic copy of the IRB or IEC approval letter stating that the study protocol and informed consent forms have been reviewed and approved.

7.2 IRB/IEC

This trial can be undertaken only after review and full approval of the protocol and Subject Informed Consent Forms have been obtained from a properly constituted IRB/IEC. This written approval must be dated and it must clearly identify the protocol, any amendments, the Subject Informed Consent Forms, and any applicable recruiting materials and subject compensation programs approved.

The decision concerning the conduct of the study will be made in writing to Gradalis, Inc. Copies of this decision and of all IRB/IEC correspondence will be kept on file at the study site; copies will be provided to the Sponsor for storage in the electronic Trial Master File.

During the trial, the PI is required to send various documents to the IRB/IEC for review in accordance with site institutional policies:

- All protocol amendments and Subject Informed Consent Form revisions.
- Reports of Serious Adverse Events.
- Protocol Deviations as required by IRB Guidelines

The PI provides Gradalis, Inc. with the necessary assurance that an IRB/IEC is responsible for the initial and continuing review and approval of the proposed clinical study in accordance with 21 CFR 312.60. At least once a year, the IRB/IEC will be asked to review and re-approve the clinical trial protocol; the request must be documented in writing. At the end of the trial, the PI will notify the IRB/IEC that the trial has been completed.

7.3 Written Informed Consent

The informed consent document should meet the requirements of the latest version of the Declaration of Helsinki and any applicable regulations and guidelines. It must be approved by an IRB or IEC.

Prior to entry into the trial and before any protocol-required procedures are performed, the Investigator must explain the nature of the trial, its intended purpose, and the implications of participation to potential subjects or to their legal representatives. They will be told about the possible risks and benefits, and the possible adverse experiences. They will be informed that subjects' participation is voluntary, and that they may withdraw consent to participate at any time. They will also be informed that if subjects choose not to participate in the trial alternative treatments are available; such refusal will not prejudice further treatment of their disease. Potential subjects or their legal representatives must be given the opportunity to ask questions about the trial protocol and the procedures involved.

Finally, each subject will be told that his or her records may be accessed by authorized personnel of Gradalis, Inc. and other authorized individuals without violating the subject's confidentiality, to the extent permitted by the applicable laws and/or regulations. By signing the written Subject Informed Consent Forms, the subject or his or her legal representative is authorizing such access. Following this explanation and prior to entry into the trial, the written, dated, and signed Subject Informed Consent Form must be obtained from each subject or his or her legal representative; a copy will be given to the person signing the form.

7.4 Confidentiality of Records

The Investigator is required to retain, in a confidential manner, sufficient information on each subject (i.e., full name, current address, and social security number) so that the subject may be contacted by the FDA, Gradalis, Inc., or by their affiliates should the need arise.

7.5 Modification of Protocol

Any changes to this protocol that affect study objectives, study design, study procedures, subject population, or significant administrative procedures will require a formal amendment to the protocol. Any proposed protocol amendments must be sent in writing to the applicable IRB. Prior to implementation, an amendment must be approved by the Gradalis, Inc., and approved by the applicable IRB or IEC.

General administrative changes to the protocol are minor corrections and/or clarifications that do not affect the manner in which the study is to be conducted. Such administrative changes will be agreed upon by the Gradalis, Inc., and will be documented in a memorandum. The applicable IRB or IEC will be notified of administrative changes according to applicable IRB guidelines.

7.6 Protocol Questions and Deviations

When evaluating a potential subject or while a subject is on study, protocol questions can be directed to the Gradalis Medical Monitor via email or phone using the contact information provided in the Contact Information section of the Study Reference Manual.

8.0 EVALUATION OF TUMORS

8.1 Tumor Measurements and Response (RECIST 1.1)

Response and progression will also be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. The guidelines are available online at: European Organization for Research and Treatment of Cancer (EORTC) RECIST Web page, https://www.eortc.be/Recist/documents/RECISTGuidelines.pdf

9.0 ATEZOLIZUMAB INVESTIGATIONAL PRODUCT

Atezolizumab will be provided by Roche / Genentech and distributed by Gradalis, Inc.

Atezolizumab is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless to slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8 (Phase III formulation).

Atezolizumab must be refrigerated at 2−8 °C (36−46 °F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in atezolizumab drug product; therefore, the vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

9.1 Preparation of atezolizumab

Atezolizumab in formulation F03 (1200 mg per vial) will be administered in 250 mL 0.9% NaCl IV infusion bags and infusion lines equipped with 0.2 µm in-line filters. The IV bag may be constructed of PVC or PO; the IV infusion line may be constructed of PVC or PE; and the 0.2 µm in-line filter may be constructed of PES. The use of administration supplies composed of materials other than those listed should be avoided if possible. Atezolizumab must be prepared and diluted under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user. The dose solution prepared for IV bag

delivery may be stored at 2−8 °C (36−46 °F) and/or at room temperature for up to a total in-use storage time of 8 hours.

The initial dose of atezolizumab will be delivered over 60 (± 15 minutes). If the first infusion is tolerated without infusion-associated adverse events, then the second infusion may be delivered over 30 (± 10 minutes). If the 30-minute infusion is well tolerated, then all subsequent infusions may be delivered over 30 (± 10 minutes).

The subject's vital signs (heart rate, respiratory rate, blood pressure, temperature, and O2 saturation) should be determined up to 60 minutes before each atezolizumab infusion. Vital signs should also be obtained during or after the atezolizumab infusion if clinically indicated. No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for subsequent infusions at the discretion of the treating physician after consultation with the Medical Monitor.

Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The dose solution prepared for IV bag delivery may be stored at 2−8 °C (36−46 °F) and/or at room temperature for up to a total in-use storage time of 8 hours.

Compliance

The administration of all study drugs (including Vigil and/or atezolizumab) should be recorded in the appropriate sections of the CRF. Treatment compliance will be assured by site reconciliation of the medication dispensed and returned.

Accountability

The study drug provided for this study will be used only as directed in the study protocol. Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site, for all unused study drugs, and for appropriate destruction of study drugs. Certificates of delivery, destruction, and return should be available.

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to the product manufacturer. All unused investigational product will be returned to a product manufacturer's authorized depot or disposed of upon authorization by product manufacturer.

10.0 VIGIL PRODUCT INFORMATION

10.1 Vigil Investigational Product

Vigil is made up of irradiated autologous tumor cells which have been electroporated *ex vivo* with the Vigil plasmid designed to suppress expression of both the TGFβ1 and TGFβ2 proteins while simultaneously expressing rhGMCSF protein.

10.2 Safety Analysis

Vigil plasmid employed in the generation of this product has been tested for identity, sterility, purity and strength.

Irradiated Gene Modified Tumor Cells

To ensure safety, all gene-modified tumor cells to be used in Vigil administrations must be irradiated with a dose of 10,000 cGy prior to freezing. This is the same irradiation process as for the TAG vaccine, BB-IND 13650 and prior vaccines (Belagenpumatucel-L and GVAX® published trial results and BB-IND 13401 and BB-IND 12118) (Kumar 2009; Maples PB 2009; Maples PB 2009). The selection of this radiation dose is based on the desire to utilize the lowest possible radiation dose for the transfected cells to optimize the level and duration of bifunctional shRNA^{furin} transcription and GMCSF protein production and maximize the safety of vaccine cell injections at the same time. In addition, investigators have demonstrated that irradiating cultured tumor cells of different histologic origins at 10,000 cGy completely arrests tumor colony formation.

Preparation

Reference the Pharmacy Reference Manual for preparation and handling information.

Vigil concentrate: 1.0 x 10^6 or 1.0 x 10^7cells per injection in a volume of 1mL.

Route of administration: Intradermal injection

Storage and Shipping

Frozen, unopened vials are stored in the vapor phase of Liquid Nitrogen below -150° C at Gradalis. Each Vigil concentrate will be shipped individually in a portable liquid nitrogen tank. This shipping container will be able to sustain temperature fluctuations for up to 10 days. This will enable sufficient time to reach the different clinical site pharmacies.

Request for investigational product for Day 1 administration must occur via email or phone at least 1 week prior to the anticipated visit date. Gradalis designated quality assurance personnel will confirm feasibility of release and transport the product. Subjects will be randomized up to 14 days prior to the subject receiving their first dose of atezolizumab or Vigil administration.

Vigil Transfer

All manufactured Vigil will be stored and shipped in the vapor phase of liquid nitrogen until ready for use. The site will request for Vigil shipment via email when the study agent is needed for subject administration.

Once the Vigil request is made, the Gradalis QA staff will confirm that eligibility criteria have been met and approved by the Medical Monitor. Gradalis QA staff will coordinate shipment of the product with the site.

At the site, investigational product preparation must be prepared by the Pharmacist or designee.

Please reference the Pharmacy Reference Manual for preparation and handling information.

11.0 CONCOMITANT THERAPY

All concomitant treatments taken during study participation, including blood and blood products, must be reported on the source documentation.

EMLA® may be utilized at the injection site prior to Vigil administration.

The following medications and interventions, unless otherwise specified, are prohibited from the time of study screening until the End of Treatment visit:

Systemic anti-cancer therapy, including chemotherapy, radiotherapy, or endocrine therapy other than those required per protocol are prohibited from the time of study screening until the End of Treatment visit.

Any investigational drug or device other than Vigil is prohibited from the time of study screening until the End of Treatment visit.

Systemic—oral, IV, injectable—corticosteroids (e.g., dexamethasone) should be avoided in subjects who receive Vigil. If deemed by the investigator to be necessary, short term (<30 days) systemic steroids ≤ 0.25 mg/kg (max 10mg) prednisone-equivalent per day and inhaled steroids are permitted while on protocol. Other steroid regimens and/or immunosuppressives are prohibited.

Subjects should be provided with full supportive care measures, as clinically indicated, and in accordance with institutional standards. Such care includes medication for pain control and symptom management, antibiotics, bisphosphonates, antiemetics, colony stimulating factors, and transfusions of blood or blood products. Treatment for drug-related adverse events should be administered at the discretion of the investigator.

Localized radiotherapy is permitted for palliation of painful lesions at the investigator's discretion. However, medical management in place of radiation therapy should be used if clinically appropriate.

Inactivated influenza and pneumococcal vaccines are allowed on study, if deemed appropriate by the investigator. Live vaccines are prohibited while on study.

12.0 BLOOD DONATION

Subjects should not donate blood while participating in this study or for at least 90 days following the last infusion of atezolizumab or until 28 days after the last dose of Vigil, whichever occurs longest.

13.0 OCCUPATIONAL SAFETY

Study medications are not expected to pose significant occupational safety risks to investigational staff under normal conditions of use and administration. However, precautions should be taken to avoid direct contact with study medication. Biosafety Level 1 practices shall be employed with this study medication. Reference the Pharmacy Reference Manual.

14.0 ADVERSE EVENTS

Adverse Event and Serious Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Serious Adverse Event

An AE (experience) or reaction occurring at any dose should be classified as a serious adverse event (SAE) if any of the following occur:

- Initial or prolonged hospitalization
- A life-threatening condition (i.e. an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Significant disability/incapacity (i.e. the AE resulted in a substantial disruption of the subject's ability to carry out normal life functions)
- Congenital anomaly/birth defect
- It does not meet any of the above serious criteria, but may jeopardize the subject or may require surgical or medical intervention to prevent one of the outcomes listed above.
- Death

Definition of Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the atezolizumab and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for atezolizumab include but are not limited to events with a potential inflammatory or immune-related mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with atezolizumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-related mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to exclude alternate etiologies and support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Medical Monitor.

AESIs for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
    - Treatment-emergent ALT or AST $> 3 \times$ baseline value in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)

  - Treatment-emergent ALT or AST $>$ 3 $\times$ baseline value in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT $>$ 10 $\times$ ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade $\geq$ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)

Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug
- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

Unexpected Adverse Event

An unexpected event is any AE that is not identified in nature, severity or frequency in the Clinical Investigator's brochure or the drug package insert.

Grading Adverse Events

Adverse events (AEs) will be recorded throughout the trial. Toxicities and AEs will be graded and reported using the Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03 as linked in Appendix D.

Adverse events will be summarized using the MedDRA coding system or higher. The NCI-CTCAE will be used for AE grading. All AEs, regardless of severity, will be followed by the Treating Physician until resolution is satisfactory.

14.1 Attribution of Causality

The relationship of each event will be assessed by the Treating Physician and recorded on the CRF.

14.2 Atezolizumab Infusion Reactions

Severe infusion reactions have occurred in patients in clinical trials of atezolizumab. Infusion related reactions occurred in 1.3% (25/1978) of patients across clinical trials, 1.7% (9/523) of patients with urothelial carcinoma, and 1.6% (16/1027) of patients with NSCLC. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Permanently discontinue atezolizumab in patients with Grade 3 or 4 infusion reactions.

14.3 Risks Associated with Atezolizumab

Refer to the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Medical Monitor for additional recommendations.

14.4 Vigil Expected Side Effects

Vigil immunotherapy have been previously administered to patients with cancer. Side effects were minimal, the most frequent of which included local reactions at the site of injection. Potential adverse events are listed below.

Local skin reactions at the site of injection:

Erythema, tenderness, induration, urticaria/rash, pruritus.

Other expected adverse events:

Fever, myalgias/arthralgias, chills/rigors, nausea, fatigue, headache, thrombocytopenia and other cytopenias, hyperglycemia, vomiting, hypotension, infection at the immunization site.

In addition, there may also be a risk of autoimmune disease development, although to date no evidence of this has been seen in any vaccination study. There may also be worsening of tumor related symptoms secondary to immune related attack on subject's tumor.

14.5 Recording of an Adverse Event

Adverse events will be recorded for the duration of a subject's study treatment (following the first dose of Investigational Product, Vigil and/or atezolizumab), and for up to 30 days following the last study treatment or until another therapy has been initiated, whichever is earlier, regardless of causality.

SAEs and AESIs should be recorded for the duration of the study treatment and for up to 30 days following the last study treatment or the initiation of new therapy, whichever is earlier.

All AEs, regardless of causal relationship are to be recorded in the eCRF and source documentation. Additional information about each event, such as treatment required, eventual outcome, and whether or not therapy had to be interrupted or dosages reduced, will be noted in source documents and recorded on the eCRF.

Pre-existing conditions will be recorded at baseline on the Medical History Form. If a pre-existing condition does not change, it does not have to be reported as an AE on subsequent cycles.

14.6 Serious Adverse Event Reporting

All SAEs and AESIs will be reported within 24 hours of notification by the site via email or fax to Gradalis, Inc. This includes any death from any cause while a subject is receiving the study agent on this protocol, or ≤ 30 days following the last dose of the protocol study agent.

The site will supply as much information as is available at the time of the initial SAE or AESI reporting (study number, subject study number, onset date, relationship, subject demographics, event, dosing regimen of study agent). All SAEs or AESIs must be followed until resolution.

Gradalis, Inc. 2545 Golden Bear Drive, Suite 110 Carrollton, TX 75006 Vigil@gradalisinc.com	
Direct: (214) 442-8124	Fax: (214) 442-8101

Gradalis, Inc. and Genentech, Inc. will report adverse events to the FDA in compliance with 21 CFR 312.32.

14.7 Overdose

An overdose is defined as a subject receiving a dose of atezolizumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with atezolizumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and Sponsor Partner Patient Safety or designee using the designated Safety e-mailbox. If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of atezolizumab.

The investigator will use clinical judgment to treat any overdose.

15.0 SUBJECT COMPLETION AND WITHDRAWAL

15.1 Indication for Taking Subjects Off Study

The Investigator must notify the sponsor at any time following discontinuation of a subject on study for the occurrence of a serious or unexpected AE associated with the use of the study medication.

16.0 STATISTICAL CONSIDERATIONS

16.1 Safety Analysis

The safety evaluation will include AEs, AESIs, SAEs, and changes from baseline in laboratory evaluations, vital signs, electrocardiograms, and physical examinations. The number and percentage of subjects reporting treatment emergent AEs will be summarized overall and by the highest Common Terminology Criteria for Adverse Events (CTCAE) grade, system organ class, and preferred term, with a breakdown by dose and tumor type. Similarly, the number and percentage of subjects reporting treatment-emergent AEs considered related to investigational product will be summarized. At each level of subject summarization, a subject will be counted once using the highest grade and level of causality if one or more occurrences of the same system organ class/preferred term is reported. Adverse events will be graded according to the National Cancer Institute (NCI) CTCAE v4.03 and coded using the Medical Dictionary for Regulatory Activities. Laboratory abnormalities will be graded according to the NCI CTCAE v4.03, if applicable.

16.2 Efficacy Analysis

For each cohort, the ORR will be estimated, along with its two-sided exact binomial 95% confidence interval. The definitions of the response-related endpoints and corresponding time-to-event endpoints will be based on the programmatically-derived response from the investigator's recorded measurements and assessments for target, non-target, and new lesions according to RECIST 1.1. The distributions of PFS and OS will be estimated within each cohort using the Kaplan-Meier method.

16.3 Sample Size Justification

The sample size for this study is not based on statistical considerations. The results of this trial will be used to help design future studies.

17.0 STUDY RECORDS

17.1 Documentation

A log of all subjects evaluated for this protocol must be maintained at each site. Subjects excluded from admission will be provided with a clear explanation of the specific reasons why they have been excluded from the study. Subjects who have tumor tissue procured will be assigned a subject identification number.

For each subject treated with the study drug(s), the Research Coordinator is required to prepare and maintain case histories that include all observations and other data pertinent to the

investigation. This will include all source documents needed to verify the accuracy of all observations and other data contained in the eCRFs on each study subject.

The Investigator or his/her designee is required to retain the records related to the trial for a period of 2 years following the date a marketing application is approved for the indication being investigated. If no application is to be filed or if the application is not approved for such indication, the records must be retained until 2 years after the investigation is discontinued and the regulatory agencies are notified.

The Investigator shall retain study drug disposition records and source documents for the maximum period required by the country and institution in which the study will be conducted, or for the period specified by Gradalis, whichever is longer. The Investigator must contact Gradalis, Inc. prior to destroying any records associated with the study.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, IRB). Notice of such transfer will be given in writing to Gradalis, Inc.

17.2 Case Report Form Procedures

Data for this study will be captured in the CRFs. The investigator or his/her designee is responsible for recording all data relating to the trial on the eCRFs in accordance with the site's contract with Gradalis. The investigator must verify that all data entries on the CRFs are accurate and correct.

APPENDIX A: PERFORMANCE STATUS SCALE

ECOG Performance Status Scale	
Grade	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of light or sedentary nature—(e.g., light housework or office work).
2	In bed <50% of the time. Ambulatory and capable of all self care, but unable to carry out any work activities; up and about > 50% of waking hours.
3	In bed >50% of the time. Capable only of limited self-care, confined to bed or chair >50% of waking hours.
4	100% bedridden. Completely disabled; cannot carry out any self care; totally confined to bed chair.
5	Dead

APPENDIX B: SCHEDULE OF ASSESSMENTS

1 cycle = 3 weeks	**Pre-Study**[1]	**Screening**	**Cycle 1**	**Cycle 2**	**Cycles 3, 6, 9, 12**	**Cycles 4, 5, 7, 8, 10, 11**	**EOT** (30 days)[2]	**Response Follow-Up** (quarterly)[3]	**Survival** (3 years)[4]
Visit Window		***-2 weeks***			***±5 days***			***+/- 7 days***	***±4 weeks***
Informed Consent	X	*within 4 weeks*							
Medical History	X	X							
Physical Exam	X	X					X		
Symptom-Directed Physical Exam[5]			X	X	X	X	X		
Performance Status (ECOG)		X	X	X	X	X	X		
Vital Signs (including weight)[6]	X	X	X	X	X	X	X		
Toxicity (adverse events)			X	X	X	X	X		
Concomitant Medications		X	X	X	X	X	X	X[7]	X[8]
Radiological Tumor Assessment[9]		*within 4 weeks*			X[10]		X[11]	X	
Triplicate Electrocardiogram (ECG)		X			X		X		
CBC with differential	X	X	X	X	X	X	X		
Serum Chemistry[12]	X	X	X	X	X	X	X		

[1] Pre-Study assessments including medical history, physical exam, CBC and Serum Chemistry may be obtained from medical records from standard preoperative hematology and chemistry panels.
[2] End of Treatment visit will occur 30 days (± 5 days) after the last treatment or prior to commencement of subsequent treatment.
[3] Subjects that discontinue study treatment before disease progression will have radiological assessment of disease quarterly until disease progression.
[4] Assessment performed annually after disease progression.
[5] Symptom-Directed Physical Exam performed by a medical provider.
[6] Vital signs (including weight) must be obtained predose. Vital signs (heart rate, respiratory rate, blood pressure, temperature, and O_2 saturation) should also be obtained within 60 minutes prior to each atezolizumab infusion.
[7] Collect any post study therapies taken after participation in the study.
[8] Collect any post study therapies taken after participation in the study.
[9] Radiological Tumor Assessment to include chest, abdomen, and pelvis. Assessment will be done per RECIST criteria for measurable disease.
[10] Radiological Tumor Assessment will be performed at baseline and every third cycle thereafter.
[11] Radiological Tumor Assessment performed at End of TX if not done within the previous 45 days.
[12] Serum Chemistry to include creatinine, glucose, total protein, blood urea nitrogen, total carbon dioxide, albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase and/or alanine transaminase and electrolytes (total calcium, chloride, potassium, sodium).

1 cycle = 3 weeks	**Pre-Study**[1]	**Screening**	**Cycle 1**	**Cycle 2**	**Cycles 3, 6, 9, 12**	**Cycles 4, 5, 7, 8, 10, 11**	**EOT** (30 days)[2]	**Response Follow-Up** (quarterly)[3]	**Survival** (3 years)[4]
Visit Window		***-2 weeks***	***±5 days***					***+/- 7 days***	***±4 weeks***
CA-125[13]	X	X	X	X	X	X	X	X	X
TSH[14]		X			X				
Pregnancy Test (if applicable)		X							
Immune Function Analysis[15]	≤ 1 week of tumor procurement	X			X		X	X	
Tissue Procurement	X								
Vigil Administration[16]			Part 1: Both Part 2: Vigil or Atezolizumab		X	X			
Atezolizumab Administration[17]					X	X			
Site Injection Assessment[18]			X	X	X	X			
Tumor Biopsy					X[19]				
Phone Contact	X								X

[13] Obtain results from medical records when available.
[14] TSH will be collected at screening and every third cycle thereafter.
[15] Immune Function Analysis sample will be collected at baseline, prior to study agent administration at Cycle 3 and every 3 cycles thereafter.
[16] Vigil Administration every 3 weeks on Day 1 as long as sufficient material is available and patient is deemed appropriate to continue. When combined, Vigil should be administered first, followed 30 minutes (+/- 5 min) later by atezolizumab.
[17] Atezolizumab is to be administered at a dose of 1200 mg as an intravenous infusion on Day 1 every 3 weeks. The initial dose is to be administered over one hour and if well tolerated, subsequent infusions may be administered over 30 minutes.
[18] Assessment of injection site will occur during the Vigil post-dose observation period and through 24 hours after Vigil dosing through patient contact.
[19] Tumor biopsy for correlative studies including scoring of tumor infiltrating lymphocyte (TIL) and PD-1 / PD-L1 expression analysis will be obtained at tissue procurement, prior to Cycle 3 combination dosing (for individuals in Part 2) and at any time after the end of Cycle 3.

APPENDIX C: ATEZOLIZUMAB EXPANSION SCHEDULE OF ASSESSMENTS

1 cycle = 3 weeks	**Each Cycle**	**EOT** (30 days)[1]	**Response Follow-Up** (quarterly)[2]	**Survival** (3 years)[3]
Physical Exam		X		
Symptom-Directed Physical Exam[4]	X			
Performance Status (ECOG)	X	X		
Vital Signs (including weight)	X[5]	X		
Toxicity (AESI/SAEs)	X	X		
Concomitant Medications	X	X	X[6]	X[7]
Radiological Tumor Assessment[8]	X[9]	X[10]	X	
Triplicate ECG (recommended)	Recommended per use with checkpoint inhibitors[11]			
CBC with differential	X	X		
Serum Chemistry[12]	X	X		
TSH (recommended)	Recommended per use with checkpoint inhibitors[13]			
Immune Function Analysis[14]	X	X		
Atezolizumab Administration[15]	X			
CA-125[16]	X	X	X	X
Tumor Biopsy[17]	X	X		
Phone Contact				X

[1] End of Treatment visit will occur 30 days (± 5 days) after the last treatment or prior to commencement of subsequent treatment.
[2] Subjects that discontinue study treatment before disease progression will have radiological assessment of disease quarterly until disease progression.
[3] Assessment performed annually after disease progression.
[4] Symptom-Directed Physical Exam performed by a medical provider.
[5] Vital signs (heart rate, respiratory rate, blood pressure, temperature, and O_2 saturation) should be obtained within 60 minutes prior to atezolizumab infusion.
[6] Collect any post study therapies taken after participation in the study.
[7] Collect any post study therapies taken after participation in the study.
[8] Radiological Tumor Assessment to include chest, abdomen, and pelvis. Assessment will be done per RECIST criteria for measurable disease.
[9] Radiological Tumor Assessment will be performed every third cycle.
[10] Radiological Tumor Assessment performed at End of TX if not done within the previous 45 days.
[11] Due to potential risk of myocarditis associated with atezolizumab use, it is recommended that cardiac function be monitored prior to and periodically during treatment with atezolizumab. Triplicate ECGs performed periodically during treatment with atezolizumab may help identify potential cardiac events; however, Institutional standard practice for monitoring cardiac function during use of checkpoint inhibitors should be used throughout treatment with atezolizumab.
[12] Serum Chemistry to include creatinine, glucose, total protein, blood urea nitrogen, total carbon dioxide, albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase and/or alanine transaminase and electrolytes (total calcium, chloride, potassium, sodium).
[13] Per atezolizumab package insert (Section 5.4 – Thyroid Disorders); Thyroid function should be monitored prior to and periodically during treatment with atezolizumab. Package insert and institutional practice should be followed throughout treatment with atezolizumab.
[14] Immune Function Analysis sample will be collected every 3 cycles.
[15] Atezolizumab is to be administered at a dose of 1200 mg as an intravenous infusion (over 30 minutes) on Day 1 every 3 weeks.
[16] Obtain results from medical records when available.
[17] Tumor biopsy for correlative studies including scoring of tumor infiltrating lymphocyte (TIL) and PD-1 / PD-L1 expression analysis will be obtained at any time when available.

APPENDIX D: NCI COMMON TOXICITY CRITERIA FOR ADVERSE EVENTS (CTCAE), VERSION 4.0.

Publish Date: June 14. 2010

As of June 14, 2010, NCI has introduced version 4.03 of the Common Toxicity Criteria for Adverse Events. These may be obtained at the following web link http://ctep.cancer.gov.

DO NOT USE CTC VERSION 3.0 TO GRADE TOXICITIES IN THIS STUDY!

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