CLINICAL PROTOCOL

A randomized multicenter Phase II trial to evaluate the safety, efficacy and immunogenicity of vaccination with Folate Receptor Alpha peptides admixed with GM-CSF as a vaccine adjuvant versus GM-CSF alone in patients with Platinum Sensitive Ovarian Cancer and a response or stable disease to platinum therapy

Protocol Number**:**	FRV-004
Document Number:	FRV-011-004
Investigational Agent:	TPIV200 (FRα vaccine with GM-CSF adjuvant)
Sponsor:	TapImmune Inc. 5 West Forsyth Street; Suite 200 Jacksonville, FL 32202
Trial Registration Numbers	ClinicalTrials.gov # NCT02978222 BB IND #14546
Version and Date:	04, 12 Apr 2018

INVESTIGATOR AGREEMENT PAGE

As an Investigator, I agree to the following:

- Keep all documentation supplied to me or developed by me concerning this study, and that has not been previously published, in the strictest confidence. This documentation includes, but is not limited to, the protocol, the Investigator's Brochure (IB), and Case Report Forms (CRFs).
- That the study will not commence without prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol or consent forms without prior written approval of the Sponsor and the Institutional Review Board, except where necessary to eliminate an immediate hazard to patients.
- Implement and conduct the study diligently and in strict compliance with the protocol, good clinical practices, and all applicable laws and regulations.
- Accurately transfer all required data from each patient's source documentation to the CRFs. The original CRFs will be submitted to the Sponsor in a timely manner at the completion of the trial, or as otherwise specified by the Sponsor.
- Keep a complete and accurate accounting during and at the completion of the trial of all procedures performed with the drug provided by the Sponsor.
- Allow authorized representatives of the Sponsor or regulatory authority representatives to conduct on-site visits to receive, review, audit, and copy trial documents. I will personally meet with these representatives at mutually convenient times to answer any trial-related questions.
- Provide the Sponsor with an Investigator's summary within 90 days of completion of the final trial visit for the last patient enrolled, or as designated by Sponsor.
- Maintain all information supplied by the Sponsor in confidence and, when this information is submitted to an IRB or another group, it will be submitted with a designation that the material is confidential.

This protocol was designed and will be conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. Federal Regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonisation (ICH) of the Technical Requirements for Registration of Pharmaceuticals for Human Use (E6).

I have read this protocol in its entirety, including the preceding statements, and I agree to comply with all aspects of this trial.

Investigator Printed Name	Investigator Signature	Date

Institution Name

AGREEMENT TO THE PROTOCOL BY THE SPONSOR

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PROTOCOL REVISION HISTORY

Version	Date	Comment
01	15Aug16	Initial version
02	21Feb17	Revised the disease assessment and randomization paradigms, adjusted histological subtypes, extended follow-up for survival, updated statistical justification with increased study size, added an interim analysis, clarified SAE reporting, and administrative edits
03	2May17	1. Revised the population to target first remission and increased the total number of patients to 120 2. Added booster vaccine doses at each follow-up visit 3. Allow inclusion of patients with inactive auto-immune disease 4. Clarified the required tests and procedures
04	12Apr18	1. Removed ANA as a safety lab and entry criterion 2. Clarified prior cancer exclusion 3. Clarified thyroid antibody testing and administrative details

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ABBREVIATIONS

Acronym	Term
ADCC	Antibody-Dependent Cellular Cytolysis
AE	Adverse Event
AJCC	American Joint Committee of Cancer
ALT	Alkaline Phosphatase
ANA	Anti-Nuclear Antibody
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BC	Breast Cancer
BUN	Blood urea nitrogen concentration
CA125	Cancer Antigen 125
C/A/P CT	Chest / Abdomen / Pelvis Computerized Tomography Scan
CBC	Complete Blood Count
CD4	Cluster of Differentiation 4
CFR	Code of Federal Regulation
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTLA	Cytotoxic T Lymphocyte-associated Antigen
CR	Complete Response
CYP	Cyclophosphamide
DCIS	Ductal Carcinoma In Situ of the Breast
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DTH	Delayed Type Hypersensitivity
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eDCF	Electronic Data Clarification Form
EGFR	Epidermal Growth Factor
ELIspot	Enzyme-Linked Immunosorbent spot
ER	Estrogen Receptor
ERS	Electronic Registration System
FR	Folate Receptor
FRA or FRα	Folate Receptor Alpha
FRα-mAb	FRα specific monoclonal Antibody
GITR	Glucocorticoid-induced tumor necrosis factor receptor
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GMP	Good Manufacturing Practice
GPI	Glycosyl-Phosphatidylinositol
Her2-neu	Human epidermal growth factor receptor 2
hFR	Human Folate Receptor
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA-A2	Human Leukocyte Antigen Class I A2
HLA-DR	Human Leukocyte Antigen Class II DR
huFR	Human Folate Receptor

ICH	International Conference for Harmonization – Good Clinical Study
ICOS	Inducible Costimulatory Molecule
ID	Intradermal
IFN-γ	Interferon gamma
IHC	Immunohistochemistry
IL-2	Interleukin 2
IMGN853	Mirvetuximab Soravtansine from Immunogen
IR/SD	Incomplete Response / Stable Disease
IRB/IEC	Independent Review Board / Independent Ethic Committee
irRC	Immune-related Response Criteria
MDSC	Myeloid Derived Suppressor Cells
NA	No Applicable
NE	Not evaluable
NED	No Evidence of Disease
NCCN	National Comprehensive Cancer Network
NTL	Non Target Lesion
OCP	Worldwide Organization for Collaborations in the Pharmaceutical
ORR	Objective Response Rate
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PI	Principal Investigator
PR	Progestogen Receptor
PR	Partial Response
RFC	Reduced Folate Carrier
RFS	Relapse–Free Survival
ROS	Review of System
SAE	Serious Adverse Events
SGOT	Serum Glutamic Oxaloacetic Transaminase
SOC	Standard of Care
SOC	System Organ Class
SPECT	Single Photon Emission Computed Tomographic
SWFI	Sterile Water For Injection
TEAE	Treatment-emergent adverse event
TERT	Telomerase Reverse Transcriptase
TIL	Tumor-infiltrating lymphocytes
TL	Target Lesion
TNBC	Triple Negative Breast Cancer
Treg	Regulatory T-cell
TRAIL	TNF-related apoptosis inducing ligand
TSH	Thyroid Stimulating Hormone
TT	Tetanus Toxin
ULN	Upper Limit of Normal
WOCBP	Women of child bearing potential

1. SYNOPSIS

Title of Study:	A randomized multicenter Phase II trial to evaluate the immunogenicity and efficacy of vaccination with Folate Receptor Alpha peptides with GM-CSF versus GM-CSF alone in patients with Platinum Sensitive Ovarian Cancer and a response or stable disease to platinum therapy
Sponsor:	TapImmune, Inc.
Trial Sites:	Up to 24 sites in the United States
Trial Phase:	Phase 2
Investigational Drug Products:	TPIV200: Folate Receptor alpha (FRα) vaccine, composed of FR30, FR56, FR76, FR113, and FR238 peptides with Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) adjuvant GM-CSF: a hematopoietic growth factor that stimulates proliferation and differentiation of hematopoietic progenitor cells
Purpose & Study Rationale:	This exploratory study will investigate the safety and preliminary efficacy of a peptide vaccine in patients with platinum-sensitive ovarian cancer. Preclinical studies have demonstrated that dosing of TPIV200 can increase detectable FRα-specific T cells, increase tumor-infiltrating lymphocytes, and suppress tumor growth. The Phase 1 study demonstrated safety and immunogenicity in humans.

Main Objectives:

Primary Objectives:

- To determine the efficacy of a hu-FRα peptide vaccine with GM-CSF immune adjuvant compared to GM-CSF alone assessed by progression-free survival (PFS) by RECIST v1.1.
- To evaluate the safety and tolerability of a hu-FRα peptide vaccine with GM-CSF versus GM-CSF alone.

Secondary Objectives:

- To determine the efficacy of a hu-FRα peptide vaccine with GM-CSF immune adjuvant compared to immune adjuvant alone by assessment of:
  - Overall survival (OS)
  - Best overall response rate (CR+PR), and duration of response (DOR)
  - Disease control rate (CR+PR+SD)
  - Response rate by irRECIST criteria
  - Cancer Antigen (CA)-125 response (Gynecologic Cancer InterGroup [GCIG] criteria)
  - Progression free rate (PFR) at 6 months.

Exploratory Objectives

- Determine the ability of laboratory biomarkers to predict response:
  - Tumor tissue expression of FRα
  - Tumor tissue immune related gene signature and immune response
  - Circulating tumor biomarkers

Study Design:

This is a double-blind, randomized, parallel groups Phase II trial. Patients with platinum-sensitive advanced ovarian cancer, defined as a lack of progression by RECIST v1.1 criteria following completion of standard-of-care chemotherapy, including a minimum of 4 cycles of a platinum-containing regimen. Patients will be randomized to either the vaccine using GM-CSF as an adjuvant or the GM-CSF adjuvant alone as a control group. Treatment will be administered as a consolidation therapy within one year of the last administration of platinum, targeting the first remission.

The vaccine will be administered in two phases, a vaccination period and a booster period. The vaccination period will include 6 administrations of the study drug at 4-week intervals. The booster period will include administration of the study drug every 12 weeks during the 18-month follow-up period or until cancer recurrence. Treatment is not administered at the final safety visit. Whether they progress or discontinue, patients will be monitored for tumor response to subsequent chemotherapy and for remission, relapse or progression, as well as survival by quarterly contact with their physician until study completion.

The maximum duration of the patient's participation in the study will be 2 years. Assessment for tumor response, disease progression, and recurrence will be conducted every 12 weeks from the beginning of treatment until confirmed disease progression.

Vaccination will be administered via the intradermal (ID) route.

Number of Patients Planned:

Up to 60 patients will be enrolled in each group. Dropouts will not be replaced once treatment begins.

Diagnosis and Criteria for Inclusion:

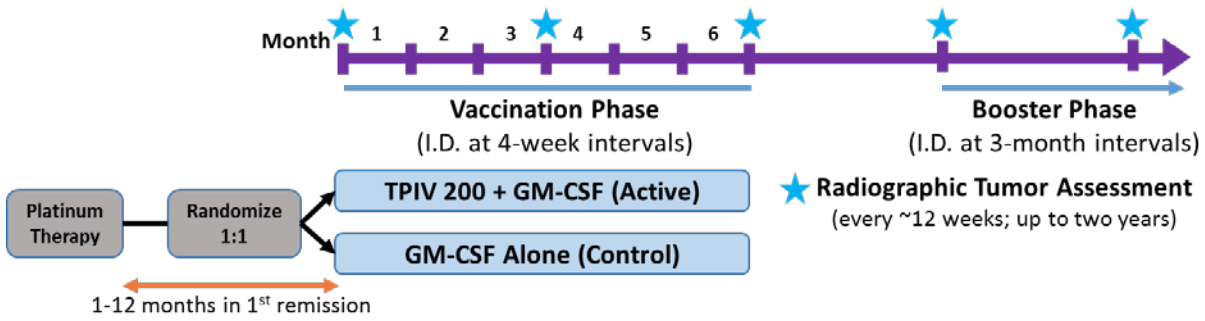
1. Female patient > 18 years.
2. Willing and able to give informed consent.
3. Stage III-IV platinum-sensitive (defined as a lack of progression by RECIST v1.1 criteria following completion of standard of care chemotherapy, including a minimum of 4 cycles of a platinum-containing regimen) epithelial ovarian, fallopian tube or primary peritoneal carcinoma in first remission.
4. Histologic documentation of diagnosis of carcinoma is required and the following histologic subtypes are eligible: high grade (grade ≥3+) serous or endometrioid carcinoma, carcinosarcoma, or poorly-differentiated adenocarcinoma, or mixed (including above subtypes). Note that synchronous serous or endometrioid uterine or fallopian cancers are allowed.
5. The patient must have demonstrated an objective response (PR or CR) or stable disease (SD) with the last chemotherapy prior to enrollment and this response must be stable (without progressive disease) until randomization.
6. Patients must receive their first dose of vaccine within 1 year of completion of their final dose of a chemotherapeutic agent of the platinum-containing regimen.
7. Adequate organ and marrow function without therapeutic intervention within 14 days prior to first vaccine administration:
   Absolute neutrophil count > 1.5 x 10^9/L
   Platelet > 100 x 10^9/L
   Hemoglobin > 9.0 g/dL
   Serum bilirubin < 1.5 times ULN (unless Gilbert's syndrome without concurrent clinically significant liver disease)
   AST/ALT < 2.5 ULN unless liver metastasis in which case it must be < 5 x ULN
   Serum creatinine CL > 40 mL/min by calculation
8. Female subjects must either be of non-reproductive potential (i.e. post-menopause by history: > 60 years old and no menses for > 12 months naturally or secondary to radiation/chemotherapy; OR serum FSH, LH and estradiol levels in the post-menopausal range; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of

bilateral oophorectomy), or must have a negative serum or urine pregnancy test upon study entry.
9. Life expectancy > 24 weeks.
10. ECOG performance status of 0 or 1.
11. Formalin fixed, paraffin embedded tumor sample from the primary cancer should be available for central testing.

Criteria for Exclusion:

1. Histology consistent with non-serous, non-endometrioid (i.e. mucinous or clear cell), or low-grade or borderline serous ovarian carcinoma.
2. Patients with a history of invasive cancers (other than non-invasive skin cancers) within the past 3 years.
3. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, targeted therapy, biological/cell therapy, tumor embolization, monoclonal antibodies, other investigational agent) < 28 days prior to the first dose of study drug.
4. Current or prior use of immunosuppressive medication within 28 days prior to the first dose of study drug with the exception of topical, intranasal or inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
5. Active autoimmune disease requiring therapy within the past 2 years Note: patients with vitiligo, Grave's disease or psoriasis not requiring systemic treatment within the past 2 years are not excluded.
6. History of hypersensitivity to GM-CSF.
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.
8. Symptomatic thyroid disease, unless negative for thyroid antibodies (typically including TSH receptor, thyroid peroxidase antibody, and/or thyroglobulin antibody).
9. Subjects who are pregnant or are breast feeding.
10. Subjects who or of reproductive potential, and are either:
    - Not abstinent;
    - Not in an exclusive relationship with a partner who is surgically sterile;
    - Not employing an effective method of birth control.
11. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
12. Symptomatic or uncontrolled brain metastasis requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
13. Subject with uncontrolled seizures.

Study Schema:



2. BACKGROUND AND RATIONALE

2.1. Ovarian Cancer is a Serious Condition associated with significant mortality

Ovarian cancer is the most lethal gynecologic malignancy, with a 5-year survival rate of 45% due to it being rarely diagnosed while the cancer is still localized [1]. Ovarian cancer patients are usually diagnosed with the disease in its most advanced state (i.e. stages III and IV). After initial surgical debulking, standard chemotherapeutic agents used include platinum/taxane combinations. Nearly 80% of patients with advanced stage disease respond to these drugs [1]. However, at least 70% of patients with an initial complete clinical response to treatment will subsequently experience recurrent disease. While second-line treatments are available and widely used, once ovarian cancer recurs it is not generally considered curable.

Thus, significant effort has been dedicated to improving the outcome of primary therapy to avoid recurrences, including increased intensity of primary chemotherapy, addition of new agents to the standard regimen, or continuation of primary therapy in the form of either consolidation or maintenance therapy. In general, consolidation therapy is designed to be a short-term treatment boost after initial therapy to consolidate the initial response to therapy. Maintenance therapy is designed to maintain the disease-free period as long as possible, while delivering a reduced dose of chemotherapy over a longer period of time (eg, 6 cycles or more). It has been speculated that continued reduction of residual cancer cells by extending the period of chemotherapy administration will diminish the risk of tumor regrowth. The concept of maintenance therapy has its roots in the experience extracted from the treatment of acute lymphoblastic leukemias, where post-remission therapy continued to reduce the burden of residual cancer cells, eventually yielding eradication of the disease.

2.2. An Unmet Medical Need Exists Despite Available FDA Approved Therapies to Treat Ovarian Cancer

While optimal debulking and chemotherapy results in complete clinical remission in the majority of patients, most will relapse due to tumorigenic tissue that resists conventional treatment. Thus, continued intervention during the tumor-free period to eradicate resistant deposits of tumor is essential to prevent recurrence.

The median overall survival for optimally debulked ovarian cancer patients has increased to more than 5 years, but less than 30% will remain disease-free following surgery and platinum-based chemotherapy [2]. Many patients will be highly responsive to additional chemotherapy at recurrence, and some can reenter successively shorter complete clinical remissions with additional treatment [3, 4]. Most studies of consolidation have been performed in the first clinical remission setting and include a variety of cytotoxic and immunologic strategies. No randomized study has provided a statistically significant improvement in overall survival [5-7].

Bevacizumab (Avastin®), a vascular endothelial growth factor-specific angiogenesis inhibitor, is now a well-established component of treatment programs for recurrent ovarian cancer [8]. Maintenance bevacizumab increases progression-free survival (PFS) when given after adjuvant chemotherapy in the upfront [9, 10] and recurrent platinum-sensitive [11] and platinum-resistant [12] settings. Bevacizumab is indicated in the subset of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.

Liposomal doxorubicin (Doxil®) is a standard anthracycline topoisomerase inhibitor encapsulated in long-circulating Stealth® liposome with surface bound methoxypolyethylene glycol (MPEG) [a process often referred to as pegylation], to protect liposomes from detection by the mononuclear phagocyte system (MPS)

and to increase blood circulation time for IV administration. Doxil® is also indicated in the subset of patients with platinum-resistant recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.

Olaparib (Lynparza®) is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germline *BRCA* mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

Niraparib (Zejula®) is another PARP inhibitor that was recently approved for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, whose tumors have achieved complete or partial response to platinum-based chemotherapy, irrespective of *BRCA* status. The median PFS for patients taking niraparib who had a germline *BRCA* mutation during their second remission was 21 months, compared to 5.5 months for the same patient population taking a placebo. The median PFS for patients taking niraparib who did not have a germline *BRCA* mutation was 9.3 months compared to 3.9 months for the same patient population taking a placebo.

These approved treatments are limited to patients with advanced disease. Efficacy of treatment has only been shown for time to progression and a minority of patients have a clinically significant tumor response (rate of CR <20%) and a short duration of response (median duration < 9-12 months) [12-14].

The notion of extended treatment is an active area of research extending far beyond the realm of traditional cytotoxic regimens. PARP inhibitors, immuno-vaccinations, endothelial and epithelial growth factor inhibitors, novel VEGF receptor inhibitors continue to be evaluated in ongoing clinical trials [5].

The proposed approach is to vaccinate patients with ovarian cancer at high risk of recurrence with the multi-epitope Folate Receptor Alpha peptide vaccine during their first remission following platinum-based chemotherapy. Vaccination may reduce the tumor burden (tumor shrinkage) and may prevent recurrence of the cancer (extension of the relapse free survival), reduce the requirement of toxic salvage cytotoxic therapies and extend overall survival.

2.3. Folate Receptor Alpha as an Immunotherapy Target

2.3.1. FRα as a vaccine target for ovarian cancer

The FRα receptor (also referred to as folate binding protein) is a glycophosphatidyl-anchored membrane glycoprotein that mediates cellular uptake of folate [15]. FRα attachment at the apical surface of cells situates it away from, and out of direct contact with folate in the circulation. In normal kidney cells, it functions in the absorption/re-absorption of folate from the luminal cavities. FRα has restricted expression in normal cells, but is highly expressed in various epithelial non-mucinous tumors [16]. This protein is overexpressed on greater than 90% of ovarian cancers at levels of up to 80-90-fold relative to the levels observed on normal tissues [17]. Furthermore, this expression is maintained in the majority of patients relapsing following conventional therapies (unpublished observations). It is overexpressed on ~ 50% of breast tumors [18]. It confers a growth advantage to the tumor by modulating folate uptake [19]. Increased growth and folate accumulation by cancer cells is associated with elevated FRα, suggesting that overexpression allows tumor cells to meet their folate needs [20]. It has recently been shown that FRα expression is common in metastatic foci present at the time of diagnosis of ovarian cancer as well as on recurrent tumors, indicating that FRα is a good tumor target regardless of whether the patient is newly diagnosed or experiencing disease recurrence [17].

2.3.2. The FRα may be an ideal target for a peptide vaccine targeting both T_h cell, CTL and antibody immunity

The FRα may be an ideal target for immunotherapy for a number of reasons. First, the fact that it is expressed in nearly all ovarian cancers strongly suggests that its expression confers a significant advantage to the tumor. In fact, in a study by Figini and colleagues, it was found that blockade of FRα function with intra-cellularly expressed FRα-specific antibodies prevented tumor cell growth in soft agar colony assays and reverted the transformed phenotype of ovarian cancer cell lines [21]. Studies have examined human tumor levels of FRα and patient survival. In non-mucinous epithelial ovarian carcinoma FRα-positive expression is associated with tumor progression [22] and platinum-therapy resistance, and poor prognosis in high-grade tumors [23]. Toffoli et al. investigated whether FRα in epithelial ovarian cancer specimens is a predictor of response to chemotherapy and survival. Among 58 patients with residual epithelial ovarian cancer after primary surgery, failure to respond to chemotherapy (complete or partial remission) was about 15-fold higher (95% confidence interval, 2.96–77.43) when tumors had elevated (>median) FRα levels following multivariable adjustment, although this estimate was based on 8 cases. Further, patient survival at 3 years was 30% among patients with high FRα (n = 30) compared to 62% among patients with tumors with low FRα levels (n = 28; p = 0.06). Among possible hypotheses to explain their findings included that FRα may increase folate uptake which could stimulate cells to repair DNA damage caused by platinum, or high level overexpression is significantly advantageous because both MHC class II and MHC class I epitopes (i.e. subdominant epitopes) within the FRα are expressed that would not ordinarily be processed and expressed in normal tissues.

Furthermore, the basal level of expression of the FRα in non-tumor tissues is very low, and therefore the potential for autoimmune toxicity is also low. Although it is found in the kidney, its expression on the luminal side of the proximal tubule would prevent it from being recognized by antibodies, which could potentially lead to autoimmunity. In contrast, FRα in cancer is highly overexpressed and accessible to folate in the circulation. The expression of FRα therefore appears to be restricted to immune privileged sites and immunity to the FRα appears not to be detrimental to normal host tissue because it can be detected in otherwise healthy women [24, 25].

2.3.3. Patients naturally develop immune responses to the FRα demonstrating the existence of a T cell repertoire.

From an historical perspective, the FRα was one of the first tumor antigens to be described for ovarian cancer [26]. Both Peoples and Knutson et al. found that patients with ovarian cancer develop endogenous immune responses to multiple targets within the FRα [26, 27]. FRα-specific lymphocytes that recognized several epitopes from FRα could be readily detected in the ascitic fluid of advanced ovarian cancer patients and CD8 T cells are among those localized to the tumor microenvironment [26]. This indicates that the FRα antigen is naturally recognized in patients with ovarian cancer.

This demonstrates that the ability to mount an immune response against FRα is intact and therefore should be able to be boosted.

To identify the vaccine constituents, we used the RANKpep algorithm and predicted fourteen potential MHC class II (HLA-DR) epitopes from the FRα. We chose peptides based on their potential to bind to at least three distinct HLA-DR alleles (i.e. degenerate epitopes). The peripheral bloods from 30 breast and ovarian cancer patients and 18 normal healthy volunteers were assessed for immune responses to each of the fourteen peptide epitope and the whole protein using T cell ELIspot assays and antibody ELISAs. Highly sensitive IFN-γELIspot analysis identified four peptides (FR30, FR56, FR 113, and FR238) that generated responses in more patients than in healthy donor counterparts. Overall, 70% of these patients showed FR-specific immunity to at least one epitope of FRα.

We also found that epitopes could potentially contain embedded MHC class I epitopes. Among patients who had helper T cell immunity to FR56, a majority also had CD8 T cell reactivity to the same peptide. FR56 contains predicted high affinity binders for HLA-A2 and –A3, and patients were genotyped with one of these class I molecules.

We also tested for the presence of increased levels of antibodies as compared to the normal healthy individuals. We chose to evaluate IgG immunity to FR76 since this 18-mer peptide contains a B cell epitope that is predicted as a top candidate using B cell epitope prediction algorithms, ABCpred and Antigenic (Data not shown). Patients demonstrated higher antibody immunity to this peptide compared to control ($p<0.0001$). Although patients did not demonstrate elevated preexisting T cell immune responses to this epitope, the fact that the peptide was a potential B cell target and demonstrated a high level of degeneracy with respect to predicted HLA-DR binding led to its inclusion in the vaccine as well. The tetanus toxin antibody response was similar amongst the 2 populations. There was no response by either group to control peptides (data not shown). In conclusion, these results indicate that some patients with FRα-expressing tumors have developed a coordinated multi-epitope immune response to the FRα, suggesting that the T cell and B cell repertoire are preserved and have not been subjected to tolerance. Furthermore, this body of information provided the basis for our final vaccine pool, which consisted of FR30, FR56, FR76, FR113 and FR238.

2.3.4. Scientific Rationale for Th peptides as Therapeutic cancer vaccines

The objective of administration of a therapeutic cancer vaccine to a patient is to induce or enhance an adaptive antitumor immunity, B cells or T cells against a tumor antigen present on tumor cells. In this trial the vaccine targets the FRα antigen [27]. Peptide based vaccines have been widely used in clinical trials to increase tumor specific immune response. Although therapeutic cancer vaccines have very good safety and tolerability, their observed clinical efficacy appeared weakened, probably on account of the immune-suppressive tumor microenvironment [28, 29].

Until recently, cytotoxic CD8 T cells have been considered to be the major component of anti-tumor immune response from cancer vaccines. More recently, it has been shown that CD4 T-cells may also be effective in mediating anti-tumor response [30-34]. This has been reviewed in detailed by Galaine et al. [35]. Several approaches have been developed to stimulate antitumor CD4 T cell immunity. In this trial we use the FRα peptide vaccine as a mix of 5 peptide sequences containing subdominant promiscuous Class II (Th) epitopes.

CD4 T cells orchestrate a broad range of immune responses and are equipped to differentiate into multiple sub-lineages, which can induce and maintain immune responses against tumor antigens. Although originally defined as Th1 and Th2 subsets, new Th CD4 T cells subsets have been characterized including suppressive regulatory T cells (Tregs) and pro-inflammatory Th17, and others [36, 37]. Among these various Th subpopulations, the Th1 subset that produces interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-γ) and interleukine-2 (IL-2) plays a clear antitumor role by orchestrating cell-mediated immunity against cancer cells [38, 39]:

- Successful generation of antitumor CD8+ T cell responses depend on the presence of CD4+ T cells;
- The induction of DC activation represents one major helper mechanism used by Th1 cells to sustain antigen presentation and to provide costimulatory signals such as CD40-CD40L to effector CD8 T cells;
- Th1 cells enhance the CD8+ T cells infiltration into the tumor.

CD4+ Th1 cells also exhibit direct (i.e. CD8+ T cell independent) antitumor activity. The IFN-γ secreted by Th1 cells exerts anti-proliferative, pro-apoptotic actions and inhibit angiogenesis in tumor cells and upregulate major histocompatibility complex (MHC) molecules on tumor cells leading to enhanced effector T cells recognition [40]. This mechanism enables MHC Class II restricted killing independently of B, NK or other T cells [41, 42]. Th1 cells also recruit and activate inflammatory cells (macrophages, granulocytes, eosinophils and NK cells) in around the tumor [37, 40]. Some CD4+ Th1 cells have also direct tumor-recognizing ability [43]. They are able to kill MHC-II+ tumors through perforine and granzyme, TNF-related apoptosis inducing ligand (TRAIL) receptor and Fas/Fas ligand (FasL) pathways.

In cancer patients, spontaneous CD4+ T cell responses against tumor antigens have been detected in several studies and a high density of tumor-infiltrating Th1 cells has been identified as a good prognostic marker in several human cancers [44, 45].

In recent randomized vaccine trials, melanoma patients were vaccinated with multi melanoma-derived cytotoxic T lymphocytes (CTL) peptides vaccine either in the presence of a tetanus-derived helper peptide or with melanoma-derived helper peptides [32, 46]. In contrast to the group that received CTL peptides and tetanus helper peptide, a high clinical objective response rate (ORR) was observed in patients treated with Melanoma-derived helper peptides [31, 47]. Interestingly, significant ORR was also observed when melanoma-helper peptides were used alone as compared to CTL-peptides vaccination. One possible explanation for these observations is that helper peptides unrelated to tumor antigens may be ineffective in guiding effector CD8 T cells within the tumor [48]. Results consistent with these observations are in line with previous reports by using tumor-derived helper peptides such as HER2-neu and hTERT [49, 50]. Hence, called GV1001 has been evaluated in many cancers [51]. In lung cancer patients an hTERT-derived helper peptide vaccine induced a durable T-cell memory response and increased survival in immune responders [50]. However, this hTERT vaccination failed to reach the main end point overall survival in pancreatic adenocarcinoma [52].

Finally, there is clear support for the epitope spreading, following immunization of cancer patients with tumor-reactive helper peptides [53, 54].

Based on the critical role of CD4+ Th1 cells in antitumor immunity, we believe that the induction of a FRα specific Th response will yield a favorable tumor microenvironment for the immune effector cells action (CD8+ T cells, NK cells and MAC macrophages) and a reduce the effect of the immune suppressive cells (Tregs, MDSC, etc.). The FRα Class II vaccine approach has several favorable features: i/ the Class II epitope selected are derived from overexpressed FRα tumor antigen [55]; ii/ the selected epitopes are promiscuous and immunize a large proportion of the US patient population [17, 27]; iii/ the FRα appears to have a crucial role in tumor cells as it affect TNBC patient's prognosis [56, 57] and is retained in tumor progression and metastasis indicating that it may avoid immune escape [17, 58]; iv/ vaccination with FRα Class II peptides induced a robust Th1 clonal response detected by IFNγ producing ELISPOT.

2.3.5. Clinical rationale for FRα vaccine strategy.

Ovarian cancer patients are usually diagnosed with the disease in its most advanced state (i.e. stages III and IV). While optimal debulking and chemotherapy results in complete clinical remission in the majority of patients, most will relapse due to tumorigenic tissue that resists conventional treatment. Thus, continued intervention during the tumor-free period to eradicate resistant deposits of tumor is essential to prevent recurrence. Efficacy of currently approved treatment is mediocre and few patients have a clinically significant tumor response (rate of CR <20%) and a short duration of response (median duration < 9-12 months) [12-14].

Our proposed strategy to eradicate residual tumor is to augment tumor antigen-specific immunity with the huFRα vaccine. Indeed, ovarian cancer is an immunologically active tumor and may be amenable to vaccination strategies. Over the past several years, many studies have demonstrated the importance of the immune system in affecting patient outcome. Notably, Zhang and colleagues published a study that demonstrated that the majority of patients had infiltrating CD3 T cells and that infiltration was positively associated with survival [59]. Patients with T cell infiltration had a 5-year overall survival rate of 38% compared with a 4.5% rate for those who lacked T cells [59]. Importantly, the presence of T cells was particularly beneficial for those individuals who demonstrated a complete clinical response to surgery and chemotherapy. The five-year survival for this group was 74% for patients with T cells compared to 12% for those without. Subsequent studies have refined our understanding of intra-tumoral T cells, notably CD8 cytotoxic T cells (CTL). Sato and colleagues showed that patients that had high levels of infiltrating CTL had a median survival of 55 months versus those with little or no CTL who had a survival of 26 months [60].

Furthermore, the basal level of expression of the FRα in other tissues is very low and therefore the potential for autoimmune toxicity is also low. Although it is found in the kidney its expression on the luminal side of the proximal tubule would prevent it from being recognized by antibodies, which could potentially lead to autoimmunity. The expression of FRα therefore appears to be restricted to immune privileged sites and immunity to the FRα appears not to be detrimental to normal host tissue because it can be detected in otherwise healthy women. This indicates that administration the FRα vaccine may have no unrelated organ toxicity and be well tolerated in patients who develop an immune response to the FRα vaccine.

The development of an ovarian cancer vaccine to prevent relapse after conventional treatment of primary tumor would be of enormous clinical value, may benefit most patients with ovarian cancer as an adjuvant to cytotoxic chemotherapy and may be better tolerated than standard chemotherapeutic interventions.

2.3.6. Booster Vaccination

An activated immune response maintained through booster vaccines can patrol for residual disease over an extended period. The selected booster regimen of an injection repeated every 3 months until recurrence or progression is similar to one developed for AE37, the li-Key hybrid peptide of HER2 776-790 (AE36), based on the result of a phase II trial of high-risk node negative breast cancer. In this study, peptide vaccine booster given every 6 months enhanced the immune response against HER-2 elicited during the primary vaccination series as evaluated by IFNγ ELISPOT and *in vivo* by intradermal reactions [61]. Safety and tolerability of booster dosing of TPIV200 is being evaluated in ongoing Phase 2 studies (NCT02593227 in TNBC and NCT02111941 in ovarian cancer). The 12-week schedule being used here is based on the more aggressive nature of ovarian cancer.

2.4. Previous clinical experience with FRα as a therapeutic target in ovarian cancer

There have been several therapeutic trials using an immune agent to target the FRα. The group of G. Peoples is currently evaluating E39 and J65, HLA-A2 restricted peptide vaccines in patients with ovarian and endometrial cancer (NCT02019524). Preliminary results of six monthly intradermal of E39 with GM-CSF indicate that the vaccine is well tolerated and elicit a strong in vivo immune response as assessed by DTH [62].

Several monoclonal antibodies targeting the FRα have also been tested in cancer patients. Farletuzumab, an anti-FRα MAb, shown to induce ADCC in preclinical models is currently in Phase III trial in subjects with low CA125 platinum-sensitive ovarian cancer (NCT02289950). In Phase II evaluation platinum-

sensitive ovarian cancer farletuzumab was well-tolerated as single agent, without additive toxicity when administered with chemotherapy. Of 47 subjects who received farletuzumab with chemotherapy, 38 (80.9%) normalized CA125 [63]. IMGN853 is a FRα-specific antibody-mytansoid conjugate. In a Phase I trial of IMNG853 in patients with recurrent ovarian cancer showed preliminary evidence of clinical benefit and levels of FRα measured by immunohistochemistry correlated with response. Although FRα can be detected in small amounts in healthy adult lung and kidney, pulmonary toxicities were rare and renal toxicity was not observed [64].

Furthermore, no significant pulmonary or renal toxicity was encountered in studies using farletuzumab, an anti-FRα MAb, shown to induce ADCC in preclinical models, despite radiolabeling studies confirming tumor-targeting; nor was such toxicity seen in clinical trials with vintafolide, a folate-vinca conjugate, also demonstrated to home to tumors by radio-imaging SPECT studies.

2.5. Preclinical cancer model with FRα peptide vaccine

The FRα vaccine was evaluated in an murine immunocompetent model for examining immune-based approaches to treating ovarian cancer [65]. Transplanted tumor cells generate tumors after intraperitoneal injection. 61 days following tumor challenge, tumors develop on the greater omentum (GO), the peritoneal lining, and organs. Ascites also develops in these mice.

As is the case in human ovarian cancer, murine ovarian tumors are immunogenic, overexpressing self-antigens such as FRα. Rather than using the human vaccine peptides animal testing requires a species-specific vaccine. Thus, the FRα vaccine for mouse was composed of native murine sequences containing Class I and II murine epitopes. Finally, the vaccination was done with the classical complete Freund's adjuvant (CFA) and incomplete Freund's adjuvant (IFA) rather than a murine GM-CSF as an immune adjuvant.

Naïve, non-tumor-bearing, healthy mice immunized with the pool of peptides in the presence of the adjuvant CFA had detectable FRα-specific T cells in the spleen toward each of the peptides by IFN-γ ELISpot analysis. Sera from the same immunized mice had elevated levels of tumor-specific IgG that bind to FRα+ tumor cells. ELISAs confirmed that IgG immunity targeted the FR9, FR74 and FR173 peptides.

In order to determine whether induction of immunity with FRα vaccine results in tumor reduction, tumor-bearing mice were vaccinated three times with the peptide pool along with CFA/IFA as adjuvant. After 40 days, the tumors were assessed for infiltration and weighed. As shown in Figure 1A, immunization resulted in influx of lymphocytes into the tumor, constituting about 50% of the total tumor mass as compared with control mice in which lymphocytes constituted about 10% of total tumor. Importantly, immunization with FRα peptide vaccine significantly prevented tumor growth (Figure 1B).

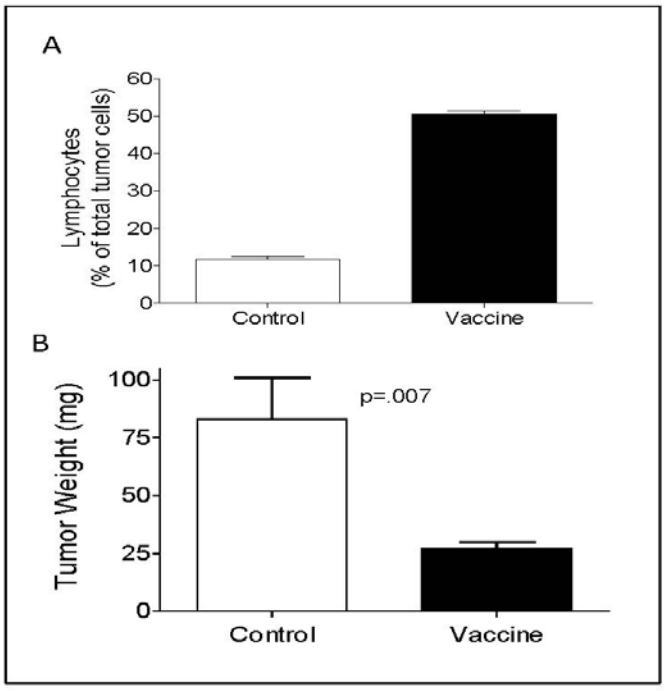
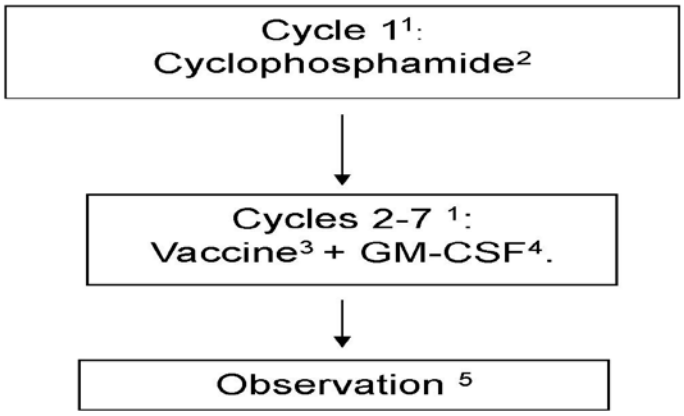


Figure 1: Immunization with FRα peptide vaccine augments lymphocyte infiltration into tumors and suppresses tumor growth. Mice (n=5) were challenged with tumor cells and 10 days later were immunized with the FRα multi-peptide three times with CFA/IFA as an adjuvant. On Day 40 following tumor challenge, the tumor were removed, weighted and assessed for lymphocytes as a fraction of total tumor cells as assess by flow cytometry. Each bar is the mean of 2 measurements from 2 different tumors. Panel B show the mean tumor burden in control and immunized mice. Each bar is the mean (+/- s.e.m.) of 5 mice.

2.6. Previous human experience.

The first in human evaluation of the FRα multi-epitope vaccine was conducted at the Mayo Clinic, Rochester MN. Patients were 18 years or older women, diagnosed with Stage II-III breast cancer or Stage II-IV ovarian, primary peritoneal or fallopian tube cancer. All patients had completed standard of care neo-adjuvant or adjuvant therapy at least 90 days prior to enrollment and were clinically without evidence of disease recurrence.



[1] Cycle length = 28 days ± 4 days
[2] Immune metronomic priming: 50 mgs bid total of 14 days over the cycle
[3] Dose = 500 mcgs per peptide
[4] Dose = 250 mcgs per injection
[5] 18 months of follow-up

The primary clinical endpoint of the study was the proportion of patients who experience severe toxicities (Grades 3-5 of the National Cancer Institute's Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events, version 4.0) attributable to therapy during the course of treatment. The primary translational endpoint was the evaluation of the vaccine-induced FRα-specific T cells immune response.

The study schema is outlined above. Following registration and consent, patients received a priming cycle with oral cyclophosphamide, followed by 6 monthly ID injections with the FRα vaccine mixed with GM-CSF as an immune adjuvant.

Vaccination of the first patient began in September 2012. The trial is fully accrued and as August 26, 2014, all patients have completed their vaccinations.

Eight women with HER2-negative breast cancer, thirteen with ovarian cancer and one with fallopian tube cancer were enrolled on study. Out of the 22 women enrolled, 3 with ovarian cancer relapsed early in the course of study. Although the phase I was not designed to evaluate patient benefit, at this time all of the other women remain free of disease relapse. Immune responses were measured, using IFN-γ ELIspot assays in the 21 patients who had given adequate numbers of specimens. Increased specific T cell immune responses were detected in all evaluable patients. All 5 of the constituent peptides were found to be immunogenic and all patients appeared to have developed immune responses to at least 2 and, in the majority, more than 3 of the vaccine peptides (Figure 2). Importantly, vaccination with peptide led to the generation of T cell that recognize naturally processed antigen. Lastly, 76% of patients achieved levels of FRα-specific T cells that were within 2 standard deviations of the mean levels of protective TT-specific immunity (not shown). Antibody responses have yet to be examined.

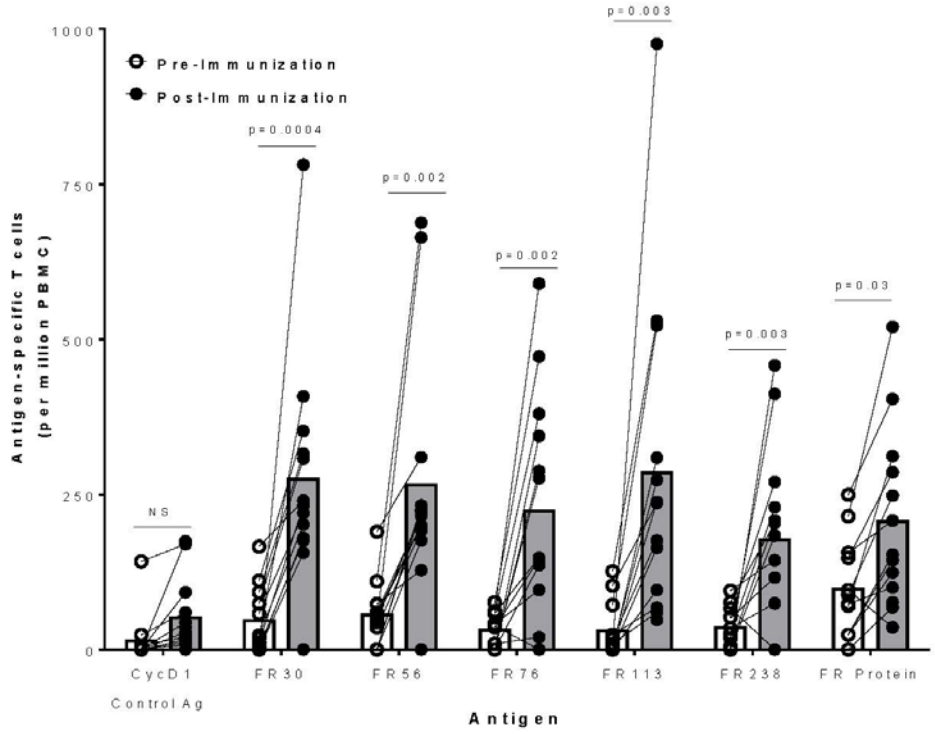


Figure 2: FRα vaccine generates immunity to the FRα in patients with breast and ovarian cancer. Shown are the frequencies of T cell specific for the vaccine peptides, whole FR protein and a pan DR binder from cyclin D1 as a control. Plotted are the pre-immunization levels and the maximum post-vaccine levels. Each dot represents a unique patient (calculated in replicate). P values are calculated from a student t test. Insert bars represent the mean.

The majority of the adverse events were grade 1 injection site reactions and other grade 1 toxicities. Two severe adverse events (grade 3-4) have been reported. One patient demonstrated grade 4 sepsis during priming with cyclophosphamide and another patient demonstrated a grade 3 injection site reaction.

Refer to the TPIV200 Investigator's Brochure for additional information on the FRα peptide vaccine including efficacy in the ID8 ovarian cancer mice model and toxicology evaluation during acute and sub-acute administration.

3. OBJECTIVES

3.1. Primary Objectives:

- To determine the efficacy of a hu-FRα peptide vaccine with GM-CSF immune adjuvant compared to GM-CSF alone assessed by PFS by RECIST v1.1.

- To evaluate the safety and tolerability of a hu-FRα peptide vaccine with GM-CSF versus GM-CSF alone.

3.2. Secondary Objectives:

- To determine the efficacy of a hu-FRα peptide vaccine with GM-CSF immune adjuvant compared to immune adjuvant alone by assessment of:
  - Overall survival (OS)
  - Best overall response rate (CR+PR), and duration of response
  - Disease control rate (CR+PR+SD)
  - Response Rate by immune-related RECIST (irRECIST) criteria
  - Cancer Antigen (CA)-125 response (Gynecologic Cancer InterGroup [GCIG] criteria)
  - Progression free rate (PFR) at 6 months

3.3. Exploratory Objectives

- Determine the ability of laboratory biomarkers to predict response:
  - Tumor tissue expression of FRα
  - Tumor tissue immune related gene signature and immune response
  - Circulating tumor biomarkers

4. MATERIALS AND METHODS

4.1. Study Design

This is a multicenter double-blind controlled randomized Phase II study to evaluate the activity of folate receptor alpha (FRα) peptide vaccine as a consolidation treatment following completion of no less than 4 cycles of a platinum containing regimen in patients with platinum-sensitive, non-mucinous ovarian, fallopian tube or primary peritoneal cancer.

The patients will have demonstrated a tumor response or stable disease upon their last regimen (per RECIST v1.1 and/or CA125 GCIG criteria) prior to enrolment in this study.

Following consent the patient eligibility will be confirmed. Patients will need to start treatment with study drug within one year of their last dose of a chemotherapeutic agent of a platinum-containing regimen. Patient randomization will be stratified based on:

1. The stage of disease at diagnosis and debulking status (stage III cancer and maximal residual lesion diameter ≤1 cm vs. stage III cancer and maximal residual lesion diameter >1 cm vs. stage IV cancer), and

2. Objective response to the last chemotherapy regimen prior to enrollment on the study: i/ CR (defined as normal radiological findings and CA125 within the normal range); ii/ PR (defined as a RECIST PR and/or GCIG CA125 response); iii/ SD (defined as RECIST SD [<30% decrease and <20% increase per RECIST v1.1] and/or lack of GCIG CA125 response/progression). Please refer to eligibility criteria and relevant literature [66, 67].

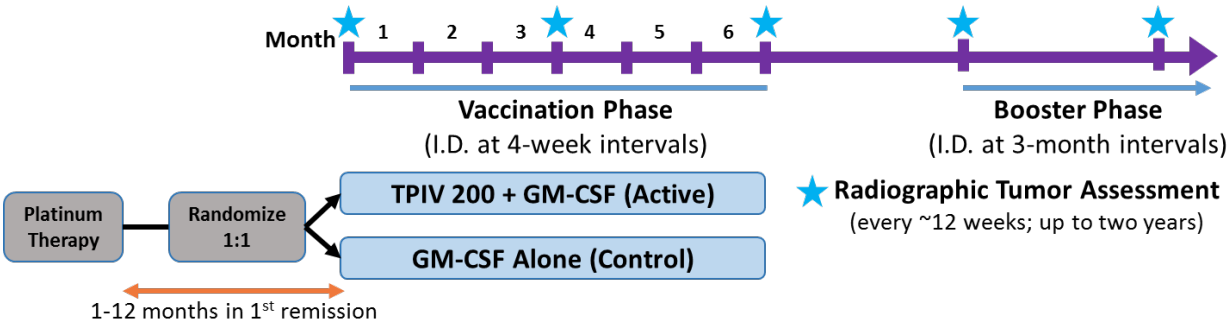
Following randomization, patients will be administered TPIV200 with GM-CSF as an adjuvant or GM-CSF control alone and will be followed up per the schedule of events (table 5.1). Patients will have booster doses and tumor assessments done every 12 weeks ± 1 week for up to 1.5 years, until objective disease progression or the patient withdraws consent. Tumor responses will be assessed at the study sites

by evaluating tumor images/scans according to RECIST v1.1. It is important to follow the assessment schedule as closely as possible. Staging scans will be collected for QC at the central facility and adjudication may be performed by blinded independent central review (BICR) following the same rules at a later date.

An interim analysis will be done and reviewed by the DSMB once 50 events or 50% total PD events are observed. Once a patient is off study and study drugs have been discontinued for more than 30 days, survival and cancer status will be followed by quarterly contact until study completion.

Safety will be evaluated with the monitoring of all serious and non-serious AEs, as well as AEs of Special Interest (AESIs), graded according to the current CTCAE v4.03. A safety-stopping rule will be used to terminate the study prematurely if excess toxicity is encountered.

Study Schema



4.2. Study Sites

Up to 24 clinical sites in the USA will participate in the trial and recruit patients.

4.3. Study Population

4.3.1. Patient Screening and Enrollment

Informed consent will be obtained from each potential patient during the prescreening period. Upon completion of the platinum-containing regimen, eligibility of the patient will be assessed by the site and the results will be reviewed and approved by the TapImmune Medical Monitor before randomization of up to 120 patients.

4.3.2. Criteria for Inclusion

1. Female patient ≥ 18 years.
2. Willing and able to give informed consent.
3. Stage III-IV platinum-sensitive (defined as a lack of progression by RECIST v1.1 criteria following completion of standard-of-care chemotherapy, including a minimum of 4 cycles of a platinum-containing regimen) epithelial ovarian, fallopian tube or primary peritoneal carcinoma in first remission.
4. Histologic documentation of diagnosis of carcinoma is required and the following histologic subtypes are eligible: high grade (grade ≥3+) serous or endometrioid carcinoma, carcinosarcoma, or poorly-differentiated adenocarcinoma, or mixed (including above subtypes). Note that synchronous serous or endometrioid uterine or fallopian cancers are allowed.

5. The patient must have demonstrated an objective response (PR or CR) or stable disease (SD) with the last chemotherapy prior to enrollment and this response must be stable (without progressive disease) before randomization.
6. Patients must receive their first dose of vaccine within 1 year of completion of their final dose of a chemotherapeutic agent of the platinum-containing regimen
7. Adequate organ and marrow function without therapeutic intervention within 14 days prior to first vaccine administration:
    - Absolute neutrophil count > 1.5 x 10^9/L
    - Platelet > 100 x 10^9/L
    - Hemoglobin > 9.0 g/dL
    - Serum bilirubin < 1.5 times ULN (unless Gilbert's syndrome without concurrent clinically significant liver disease
    - AST/ALT < 2.5 ULN unless liver metastasis in which case it must be < 5 x ULN
    - Serum creatinine CL > 40 mL/min by calculation.
8. Female subjects must either be of non-reproductive potential (i.e. post-menopause by history: > 60 years old and no menses for > 12 months naturally or secondary to radiation/chemotherapy; OR serum FSH, LH and estradiol levels in the post-menopausal range; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy), or must have a negative serum or urine pregnancy test upon study entry.
9. Life expectancy > 24 weeks.
10. ECOG performance status of 0 or 1.
11. Formalin fixed, paraffin embedded tumor sample from the primary cancer should be available and sent for central testing.

4.3.3. Criteria for Exclusion

1. Histology consistent with non-serous, non-endometrioid (i.e. mucinous or clear cell), or low-grade or borderline serous ovarian carcinoma.
2. Patients with a history of invasive cancers (other than non-invasive skin cancers) within the past 3 years.
3. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, targeted therapy, biological/cell therapy, tumor embolization, monoclonal antibodies, other investigational agent) < 28 days prior to the first dose of study drug.
4. Current or prior use of immunosuppressive medication within 28 days prior to the fist dose of study drug with the exception of topical, intranasal or inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
5. Active autoimmune disease requiring therapy within the past 2 years. Note: patients with vitiligo, Grave's disease or psoriasis not requiring systemic treatment within the past 2 years are not excluded.
6. History of hypersensitivity to GM-CSF.
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
8. Symptomatic thyroid disease, unless negative for thyroid antibodies (typically including TSH receptor, thyroid peroxidase antibody, and/or thyroglobulin).
9. Subjects who are pregnant or are breast feeding.
10. Subjects who or of reproductive potential, and are either:

- Not abstinent;
- Not in an exclusive relationship with a partner who is surgically sterile;
- Not employing an effective method of birth control.

11. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
12. Symptomatic or uncontrolled brain metastasis requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
13. Subject with uncontrolled seizures.

4.4. Patient Replacement

Once treatment is initiated, patients will not be replaced, even if they discontinue for reasons unrelated to progression or safety.

4.5. Description of clinical supplies

The TPIV200 peptides will be provided by TapImmune to the site research pharmacy. The site research pharmacy will be responsible for preparation of the vaccine for injection per the randomization schedule.

GM-CSF will be either sourced locally or provided by TapImmune.

4.5.1. FRα peptide vaccine

Formulation: TPIV200 peptides (composed of the five peptides formulated together) will be lyophilized and provided in a single glass vial. Each vial will contain 0.55 mg of each of the 5 peptides for a total of 2.75 mg. The peptides and formulation are GMP quality. The vial contains a 10% overage to account for volume loss during syringing. The nominal dose of 0.50 mg of each of the 5 peptides for a total of 2.50 mg is indicated on the label.

Storage: TPIV200 vials should be stored at -20ºC ±5 or 2 to 8 ºC using a controlled temperature freezer or refrigerator, respectively.

Refer to the TPIV200 investigator brochure for detailed information about the vaccine.

Dosage Preparation: Details on the preparation of TPIV200 are included in the Investigational Product Handling Manual.

4.5.2. Sargramostim (Leukine®, GM-CSF)

Background: Sargramostim stimulates proliferation, differentiation and functional activity of neutrophils, eosinophils, monocytes, and macrophages.

Formulation: Commercially available
Injection, powder for reconstitution: 250 mcg [contains mannitol 40 mg/mL and sucrose 10 mg/mL].

Storage: Store intact vials under refrigeration at 2 to 8 ºC (36 to 46 ºF); do not freeze.

Refer to the labelling information for Leukine®.

Dosage Preparation: Details on the preparation of GM-CSF are included in the Investigational Product Handling Manual.

4.6. Vaccination by ID injections

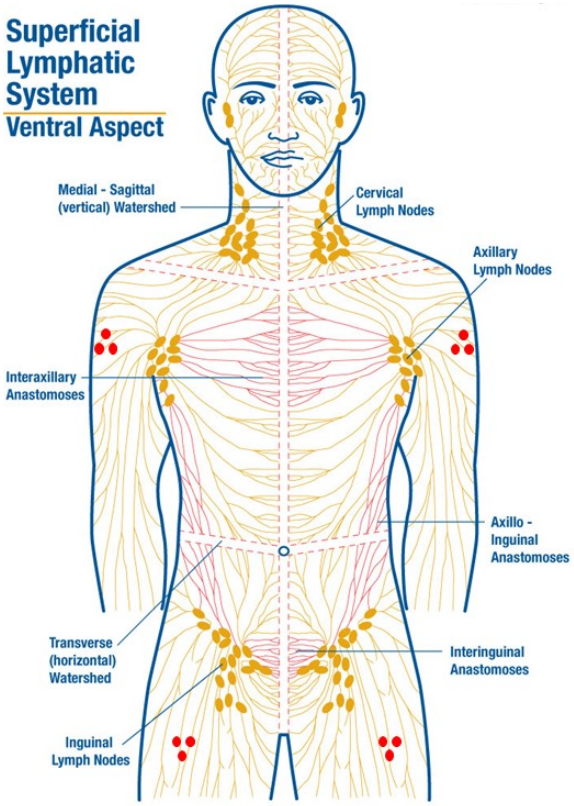
The ID syringes for injection of the TPIV200 with adjuvant (GM-CSF) or GM-CSF control will be prepared prior to each injection by unblinded personnel at the site pharmacy according to the instruction in the Investigational Product Handling Manual. The blinded syringes will then be delivered to the clinic for use as soon as practical but the drug must be administered no more than 6 hours after preparation.

If the prepared syringes cannot be administered rapidly after preparation (i.e. within approximately 1-2 hours) or need to be transported to an outside facility, then keep the vaccine/syringes refrigerated or on ice.

The vaccine mixture will be injected intradermally (ID) at three sites, spaced approximately 1 inch apart (shown as red dots below) on the upper leg or arm at about 3 inches below the inguinal crease or shoulder apex. Vaccination sites should be rotated to an alternate limb for subsequent doses.

Intradermal Injection Sites:

- One dose is delivered using 3 ID injections in one of 4 nodal regions
- Inject in the lateral upper arms or ventral upper thighs, about 10cm below the shoulder or groin
- Inject slowly to form a bleb - you may feel mild resistance
- Upon completion of injection, wait 3 seconds before removing the pressure on the needle
- Rotate between sites each dosing cycle
- Do not use an area that has decreased lymphatic flow



5. STUDY PLAN

5.1. Study Table

		Vaccination Period							Booster Period
Tests and Procedures	Screening/ Baseline [1]	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	28 Days post vaccination	Booster and Follow-up [2]
Informed Consent, I/E Criteria, Registration [3]	X								
Submission of most recent staging scans before the baseline set	X								
Submission of tumor specimen [4]	X								X
Weight	X							X	X
Demographics, Medical history, PE, Vitals, Disease staging, and Cancer treatment history	X								
Pregnancy test [5]	X	X	X	X	X	X	X		X
ECOG	X				X			X	X
Symptom directed physical examination, vitals		X	X	X	X	X	X	X	X
Adverse events [6]		X						X	X
Concomitant medications		X						X	X
CBC with diff and platelet count [7]	X		X		X		X	X	
Chemistry profile [7]	X		X		X		X	X	
TSH [8]	X				X			X	
CA125	X				X			X	X
Research Blood Samples for biomarker analysis [9]	X		X					X	X
Urinalysis for proteinuria [10]	X		X		X		X		
Radiographic disease assessment [11]	X				X			X	X
Randomization [12]	X								
Vaccination		X	X	X	X	X	X		X
Approximate blood volume (mL)	91		50		20		10	76	40
Cumulative blood volume (mL)	91		141		161		171	247	287

1. Screening studies must be done within 28 days of the first dose. Each cycle will be 28 days ± 4 days in length.
2. In the second phase of the study, patients will be followed in the clinic every 12 weeks (±1 week) for up to 1.5 years for booster injection and disease evaluation, unless they come off study due to progression or withdraw consent. No booster injection should be given at the last visit. Once a patient is off study, their survival and cancer status will be followed by quarterly contact with the referring provider until TapImmune notifies the study sites that all patients have completed the trial and the database is locked.
3. Once the enrollment tests are available, the completed Registration Form and supporting documents required will be sent to the TapImmune Medical Monitor for approval prior to randomization.
4. Biopsy testing for FRα antigen and tumor biomarkers does not need to be done prior to enrollment, although submission is mandatory. Biopsy should be obtained at recurrence, if feasible, and submitted as well.
5. Serum or urine pregnancy testing is required for women of child-bearing potential only. A negative result must be obtained <7 days prior to each treatment.
6. All AEs should be collected until 28 days after each dose and followed until resolution if related. SAEs are collected from the time the patient signs consent until they come off study, whether or not considered to be related to study drug, as booster doses will continue during follow-up. (see Section 10.1 for details).
7. Testing for CBC (with differential and platelet counts) and serum chemistries (BUN, creatinine [or clearance], sodium, potassium, chloride, CO2, calcium, total bilirubin [if >2xULN and no evidence of Gilbert's syndrome then fractionate into direct and indirect bilirubin], total protein, albumin, alkaline phosphatase, AST, ALT) must be done within 14 days of the first dose.
8. Thyroid antibody testing (typically including TSH receptor, thyroid peroxidase antibody, and thyroglobulin antibody) is only required for patients with systemically treated thyroid disease at baseline. Prior testing results should be recorded if available. If tested at baseline, follow-up testing performed during the study will be collected on the eCRF.
9. Samples will be collected at baseline, prior to dosing Cycle 2, 28 days after Cycle 6, and 12 months after enrollment. See Sections 5.5.2 and 6.1
10. All patients must have a urinalysis. If ≥ 2+ proteinuria, a 24-hour urine should be collected for protein quantification. Hold vaccine until 24-hour urine protein < 2.0 gm/24hrs. See Paragraph 5.5.6.
11. The imaging modalities used for RECIST assessment will be CT (preferably) or MRI scans of chest, abdomen, and pelvis (C/A/P) with other regions as clinically indicated for the assessment of disease. The tumor assessment must be performed no more than 28 days before the first dose of study medication. Follow-up assessments will be performed every 12 weeks +/-1 week relative to the date of the first dose during the study and interpreted according to the discussion in Section 9.4. Patients should be followed for survival regardless of whether study treatment is discontinued or delayed and/or protocol deviation – see Section 5.5.2.
12. Patients should be randomized no more than 4 days before the first dose of study drug.

5.2. Pre-treatment Period

5.2.1. Screening Procedures

To determine whether a patient meets the eligibility criteria, patient care providers will examine the patient and review medical records, including the ovarian cancer medical history and may contact patients who are currently treated with, or have recently completed, a platinum-containing regimen course. The Investigator will discuss the study with suitable participants. The specific items of this review may include:

a. Underlying disease
b. Ovarian cancer treatment history and staging (including chemotherapy, endocrine therapy, surgery, radiation, and immunotherapy)
c. Known chronic conditions that would exclude the patient
d. The patient mental status; ability to read and understand the consent
e. Medication record for drugs that would exclude the patient
f. Recent pregnancy test for female patients of childbearing potential

If the subject does not meet eligibility criteria, only the demographic data and reason for screen failure will be collected in the eCRF.

5.2.2. Informed Consent

Obtain written informed consent from the patient using the IRB-approved forms. If a screening consent is used, the main consent will need to be signed prior to performing any trial-mandated activities and tests.

Collect appropriate contact information to conduct follow-up assessment (i.e. name, mailing address, Email and phone number of patient, and as appropriate contact for caregiver and treating physicians). This confidential information should NOT be transmitted to TapImmune personnel and should be stored accordingly.

5.3. Method of Assigning Treatment Numbers to Patients

Before signing the consent, the patients can be identified by first, middle and last initials. If the patient has no middle initial, a dash is to be used.

After written informed consent has been obtained, the study site will add the subject to the IBM Clinical Development database. The system will automatically assign the patient a unique four-digit number. The first two digits will identify the site and the last two digits will be assigned sequentially to each new patient at the site. The same number will be used to randomize the patients in the EDC. The Investigator is responsible for assuring that results from all screening tests have been performed and that all eligibility criteria have been met before randomization.

Once the last cycle of chemotherapy is completed and enrollment tests are available, the information will be reviewed and approved by the TapImmune Medical Monitor. The study site can then randomize the patient within the EDC. The randomization information will be made available only to the unblinded pharmacy personnel at the corresponding site and appropriate measures will be in place to avoid unblinding the site personnel. TapImmune personnel will remain blinded to the patient's assigned randomization.

5.4. Patient Assessment at Baseline Prior to Vaccination

- Medical History, including all treatment received for ovarian cancer prior to enrollment
- Current medications

- Vitals including temperature, heart rate, and blood pressure
- Weight and height
- Physical examination and medical symptoms
- Radiographic tumor measurement (C/A/P CT [preferably] or MRI) with RESIST v1.1 scoring within 28 days of dosing
- Request archival tumor tissue (8-15 PPFE slides)
- Complete blood count (CBC) with differential and platelets (within 14 days of first dose)
- Chemistry profile (BUN, creatinine [or clearance], sodium, potassium, chloride, CO2, calcium, total bilirubin [if >2xULN and no evidence of Gilbert's syndrome then fractionate into direct and indirect bilirubin], total protein, albumin, alkaline phosphatase, AST, ALT) (within 14 days of first dose)
- TSH test (with negative anti-thyroid antibodies if thyroid disease is being treated systemically)
- Collect baseline research blood samples
- CA125
- Urinalysis
- Urine or serum pregnancy test (for women of child bearing potential)

5.5. Study Periods

5.5.1. Evaluation During the Vaccination Period

All assessments are described in the Study Table in Section 5.1. All assessments are to be performed pre-injection unless stated otherwise. Patients who complete the six cycles, as well as those who discontinue during the vaccination period, should return for a follow-up safety evaluation about 28 days after their last vaccination in the first portion of the study.

5.5.2. Booster Vaccinations and Evaluation During Study Follow-up

Patients will have a staging visit at 24 weeks, which is about 28 days after Cycle 6, then will be followed every 12±1 weeks for the next 18 months until study completion or progression. Patients who have not discontinued vaccination by the end of the initial vaccination period will receive a booster vaccination during these visits. Patients whose tumors progress will go off study, once the 28-day safety follow-up has been completed (note: a CA125-only progression is not a reason to discontinue vaccination – see Section 9.4.6 for a detailed discussion of the potential to keep a patient on study).

If any patient comes off study at any time during vaccination cycles 1-6, they should complete a safety visit at least 28 days after the last vaccination or prior to the start of a new treatment regimen, which ever comes first (the post 28 day cycle 6 visit procedures should be performed). If they come off study during the booster period, they should complete the last visit procedures and no booster injection should be given at the last visit. Once the patient is off study, their survival and cancer status will be followed by quarterly contact with the referring provider until TapImmune notifies the study sites that all subjects have completed the trial and the database is locked. Preparation of blinded study drug

The study drug will be prepared by unblinded research pharmacy personnel according to the procedures outlined in the Investigational Product Handling Manual. The procedure and instructions may be edited from time to time by way of an administrative change.

5.5.3. Methods for Unblinding of the Study

Individual treatment codes will be available to the investigator(s) from the EDC system for emergency unblinding. Routines for this will be described in the EDC user manual that will be provided to each center.

The treatment code must not be broken except in exceptional medical emergencies and only when the clinical management of the patient necessitates knowledge of the treatment randomization. If the treatment code is broken, then the investigator(s) must document and report to TapImmune. If time allows, discussion should be had with the TapImmune Medical Monitor before breaking the code.

The TapImmune Medical Monitor may break the code for SAEs that are unexpected and are suspected to be causally related to the study drug.

5.5.4. Dosing Schedule

Study Treatment will be administered as outlined in the tables below:

Vaccination

Agent	Doses (Blinded)	Presentation	Route	Start	Re-Treatment
TPIV200 FRα peptide vaccine With adjuvant	TPIV200 + adjuvant: -5 huFRα peptides, ~500μg each -GM-CSF (Leukine®) ~125 μg	3 ID syringes each with approx. 0.4mL	Intradermal injection at no less than 3 sites ~ 1" apart – on the upper leg or arm.	Day 1 of Cycle 1	every 28 days (±4 days) for 6 doses, then quarterly boosts until progression
	Adjuvant alone: -GM-CSF (Leukine®) ~125 μg				

The vaccine mixture should be injected about 3 inches below the inguinal crease or shoulder apex. Vaccination sites should be rotated to an alternate limb for subsequent doses.

5.5.5. Vaccine Schedule Modification and Discontinuation.

Allowable schedule modification: If a patient presents with an acute illness (cold, influenza, etc.), vaccination will be withheld until the illness has resolved. Subsequent cycles will be adjusted in consultation with the Medical Monitor to bring the dosing back in line with the original schedule. However, tumor reassessments will continue on the original schedule.

There will not be any modifications to the dose of vaccine used. There may be only allowances for the timing of the administration of vaccine to accommodate patient schedules or special circumstances. Such variations in the timing of vaccinations will be decided in advance after allowance by the study Medical Monitor on a case-by-case basis. Patient will be followed if study treatment is discontinued for toxicity.

Vaccine treatment will be discontinued for unacceptable toxicity that is possibly related to the study drug, as outlined in the following table.

CTCAE System/Organ/ Class (SOC)	ADVERSE EVENT	ACTION
Immune system disorders	Allergic reaction ≥Grade 2 Autoimmune disorder ≥Grade 2	Discontinue vaccination and go to observation phase Discontinue vaccination and go to observation phase
General disorders and administration site conditions	Injection site reaction manifesting as an ulceration- ≥Grade 3	Discontinue vaccination and go to observation phase
Renal and urinary disorders	Proteinuria ≥Grade 2 If 24-hour urine protein ≥ 2.0 gm/24hrs	Hold vaccine until 24- hour urine protein < 2.0 gm/24hrs Discontinue vaccination if urine protein does not recover to < 2.0 gm/24hrs after 4 weeks of vaccine interruption and go to observation phase
All other adverse events	Hematologic ≥Grade 3 Non-hematologic (excluding alopecia) ≥Grade 3 Neurologic ≥Grade 2	Hold vaccine. Repeat in 2-4 weeks. • If toxicity level normalizes vaccination may proceed. • If level remains positive or increase in severity, discontinue vaccination and patient goes to observation.

5.5.6. Criteria for discontinuation of vaccination

1. Request by the patient to discontinue study treatment
2. Unacceptable toxicity (see Section 5.5.6)
3. Treatment delay of > 6 weeks
4. Intercurrent illness or requirement for medication that, in the opinion of the clinical investigator, requires discontinuation of treatment
5. Symptomatic tumor progression or tumor recurrence per RECIST v1.1 criteria (Note: A CA125-only progression is not a reason to discontinue vaccination. Progression should be shown in the EDC as study completion, not discontinuation.)

Patients who discontinue vaccination after receiving at least one dose of vaccine will return for safety follow-up at least 28 days later unless they are discontinued from the study as detailed in Section 5.7. See also Section 5.5.2.

5.5.7. Accountability of Study Drug

The site personnel will maintain an accounting of TPIV200 deliveries and track preparation and dispensing of vaccine. Certificates of delivery must be retained in the pharmacy or investigator site files. At the end of the study it must be possible to reconcile delivery records with records of vaccine preparation.

There is no need to retain empty TPIV200 vials, these may be discarded per usual pharmacy practice.

5.6. Description of Adverse Events

The term "adverse event" could include any of the following events that develop or increase in severity during the course of the study:

1. Any signs or symptoms, regardless of severity, and whether or not ascribed to the test article;
2. Any clinically significant laboratory abnormality, and;
3. Any abnormality detected during physical examination.

The Principal Investigator will follow all subjects withdrawn from the study due to any adverse event, until the outcome is determined and where appropriate, additional written reports will be provided.

All treatment-emergent adverse events (TEAEs) are collected from the day of first vaccine administration until 28 days after each dose and recorded in the eCRFs. TEAEs considered to be possibly related will be followed until resolution, stabilization, or the Investigator determines that no further information can be obtained.

Adverse events are graded using the NCI CTCAE version 4.03 severity grading scheme. If CTCAE grading does not exist for an adverse event, the severity of mild (1), moderate (2), severe (3), life-threatening (4), and death related to an adverse event (5) will be used. Adverse event monitoring should be continued until adverse event resolution/stabilization (whichever is later).

Medical conditions/diseases present before consenting the patient are only considered adverse events if they worsen after receiving any study drug. All laboratory values are to be reviewed by the Investigator and medically relevant abnormal values will be graded according to the CTCAE Version 4.03 as well.

A laboratory abnormality is considered an adverse event if it results in

1. Discontinuation from study drug,
2. Necessitates therapeutic medical intervention,
3. If the Investigator assesses the abnormality as an adverse event, or
4. Any laboratory test that is clinically significant or meets the definition of an SAE

<u>Relationship of AEs to Study Drug</u>

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

- Definite - The adverse event *is clearly related* to the agent(s).
- Probable - The adverse event *is likely related* to the agent(s).
- Possible - The adverse event *may be related* to the agent(s).
- Unlikely - The adverse event *is doubtfully related* to the agent(s).
- Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably, or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

AEs and Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the type of cancer for which the study drugs are being studied. It may be an increase in the severity of the cancer or an increase in the symptoms of the cancer. Expected progression of the patient's cancer and/or expected progression of signs and symptoms of the cancer, unless more severe in intensity or more frequent than expected for the patient's condition, should not be reported as an AE. Any events that are unequivocally due to progression of disease must not be reported as an AE.

The development of new metastases, or progression of existing metastases to the primary cancer under study, should be considered as disease progression and not an AE. Signs and symptoms clearly associated with metastases present at study entry should not be reported as AEs unless they are newly emergent (i.e. not previously observed in the patient), judged by the Investigator to be unusually severe or accelerated, or if the Investigator considers deterioration of disease related signs and symptoms to be caused directly by the study medication.

Procedures for Recording AEs

1) TEAEs are to be assessed in all subjects and documented as events occur. Each treatment-emergent AE should be reported spontaneously or in response to general, non-directed discussion with the attending nurse or physician (e.g., has there been any change in subject status since the last assessment period?). For each TEAE, the investigator should obtain all the information required to complete the AE page of the eCRF, in accordance with the guidelines that accompany it.

2) All TEAEs, regardless of seriousness, severity, or presumed relationship to study therapy, must be recorded using medical terminology in the source document and graded according to the NCI CTCAE (version 4.03). Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. Investigators must record their opinion concerning the relationship of the AE to study therapy on the AE page.

3) All TEAEs considered to be possibly, probably, or definitely related will be followed until resolution, stabilization, or the Investigator determines that no further information can be obtained. Measures required for AE management and the ultimate outcome of the AE must be recorded in the source document and reported on the AE page.

5.6.1. Serious Adverse Event, Pregnancy and Adverse Events of Special Interest

Detailed procedures for reporting are in Section 10.

5.6.2. Concomitant Medications

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications received from the day of first vaccine administration until 30 days after the Cycle 6 administration will be recorded in the eCRFs.

The following medication are considered exclusionary during the study:

- Any investigational anticancer therapy other than specified in this protocol

- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), or therapy for cancer treatment, other than specified in this protocol. Concurrent use of hormones for non-cancer related conditions is acceptable. Local treatment of isolated lesions for palliative intent is acceptable (i.e. by local surgery or radiotherapy). Patients should not be enrolled, however, if there are plans for possible palliative localized treatment. Localized treatment should not be for progression of disease or the patient is deemed to have progressed and begins end of treatment assessments. Loss of lesion by localized treatment should not be the sole target lesion used for assessment of response and should be excluded in response assessments. Contact TapImmune medical monitor for further guidance.
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is however acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.) or for premedication prior to radiology.
- Live attenuated vaccines within 30 days of vaccination with study drug. Inactivated vaccines such as injectable influenza vaccine are permitted.

Rescue/supportive medication/class of drug	
	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited", as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc.])	Should be used when necessary for all patients

5.7. Criteria for Discontinuation

Subjects will discontinue vaccination for any of the following reasons:

1. The patient withdraws his/her consent.
2. The patient becomes pregnant.
3. The site PI determines it to be in the patient's best interest.
4. The patient is noncompliant.
5. The patient was ineligible for the study.
6. The Sponsor discontinues the study.
7. The patient dies.

5.8. Withdrawal of a Subject Prior to Study Completion

If for any reason, a subject is withdrawn before completing the study, the reason for withdrawal must be entered on the End of Study Form and other appropriate eCRFs must be completed. If the patient is not deceased, final

physical examinations and clinical laboratory assays will be performed. All data on the subject prior to discontinuation will be made available to TapImmune. Whether they progress or discontinue, patients will be monitored if possible for tumor response to subsequent chemotherapy and for remission, relapse or progression, as well as survival by quarterly contact with their physician until study completion.

6. BIOSPECIMENS FOR RESEARCH

6.1. Summary Table of Research Blood Specimens to be Collected

Assessment	Type of Blood Collection Tube (color of tube top)	Baseline (i.e. Day -28 to Day 1) [1]	Prior to vaccination of cycle 2 [2]	28 Days post vaccination cycle 6	12 months after 1st Dose	Temperature Conditions for Storage/ Shipping
Serum biomarkers	No additive (Red Top)	5 mL (one 5 mL red top tube)		5 mL (one 5 mL red top tube)		Room temperature shipment in containers provided by TapImmune.
Cytometry: circulating Treg and MDSC	Cyto-Chex BCT Tube (purple/black top) and an EDTA tube	11 mL (one 5 mL purple/black top tube and one 6 mL purple top tube)		11 mL (one 5 mL purple/black top tube and one 6 mL purple top tube)	-	
Cellular biomarkers (analyzed at baseline only) [3] And HuFR specific T cell immunity and additional exploratory correlative research	Sodium Heparin (green top) (Lithium heparin NOT accepted)	60 mL (Six 10 ml green top tubes)	40 mL (Four 10 ml green top tubes)	40 mL (Four 10 ml green top tubes)	40 mL (Four 10 ml green top tubes)	

1 Must be drawn after patient signs the main consent
2 Must be drawn prior to receiving vaccination to establish a baseline – but is not required to be on the day of vaccination
3 For exploratory correlative research (Section 9.5.6)

6.2. Collection and Processing

6.2.1. Collection will be done in the following order from a peripheral vein or port (where order is reversed):

- Red top tube for serum: 5mL tube, No Additive whole blood - No mixing required, but keep in upright position during transport.
- EDTA tubes for cytometry: 5 mL tubes - Immediately mix at least 10 times by gentle inversion.
- Green top tubes for PBMC and plasma: 10 mL tubes, heparin Na+ additive - Immediately mix at least 10 times (during sampling as necessary) by gentle inversion.

NOTE: Immediately mixing the tube at least 10 times by inversion or on a rocker for at least 10 minutes is critical to insure that PBMC may be purified properly by ficoll gradient after transport.

6.2.2. Processing, Shipping, and Handling

A detailed set of procedures will be provided by the respective central laboratories to each clinical site for processing, storage and shipment of blood and tissue samples.

6.2.3. Methodology

Refer to background and methods in Section 16.

7. PATHOLOGY CONSIDERATIONS/TISSUE BIOSPECIMENS

7.1. Research Tissue Specimens to be Collected for this Protocol

These samples will be collected from the site pathologist from the primary tumor and when feasible from the site of recurrence and/or metastasis. Note that shipment of the primary tumor is a requirement for enrollment in this trial. An adequately sized (minimum of 2 mm x 2 mm) tumor tissue paraffin block from resection (or a core biopsy for recurrence of metastasis) from the primary tumor or metastases should be provided. Sections mounted on glass slides prepared from the block can be provided as outlined below. This material may be used for, but not restricted to, the elucidation of mechanism of immune response to the vaccination and improving the understanding of markers of disease progression.

Correlative Study (Section for more information)	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	Prior to randomization	Analyze at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Determination of FRα-specific expression in primary tumor Additional exploratory correlative research	Formalin Fixed Paraffin Embedded From resection of primary tumor	8-15 slides, each with 2 or more 4-5 microns thick sections and 2 with a 10 micron section and One H&E stained slide Tumor content >30%	X	No	Ambient – using box provided by TapImmune. Ship within one week of sectioning
Determination of FRα-specific expression in recurrent tumor after vaccination (if available and if feasible – not mandatory)	Formalin Fixed Paraffin Embedded From resection or punch biopsy	8-15 slides, each with 2 or more 4-5 microns thick sections and 2 with a 10 micron section and One H&E stained slide	-		

7.2. Tissue Collection for IHC

The availability of tissue from the primary tumor for testing for the presence of huFRα is one of the criteria for inclusion of a patient into the study. Submit 8-15 slides according to the instruction in Section 17.

If available, at the time of recurrence submit 8-15 slides (4-5 microns on charged slides) from the recurrence or distant metastasis according to the instruction in Section 17

8. SAFETY STOPPING RULES

The Medical Monitor and the study statistician will review the study periodically to identify accrual, toxicity, and endpoint problems that might be developing. The study statistician will prepare a report containing accrual, adverse event, and any available unblinded efficacy data that will be submitted to an independent DSMB every 3 months until all patients have completed the initial vaccination period and every 6 months thereafter. The DSMB will include no less than 3 members (2 physicians and a statistician).

The DSMB will review unblinded data. At any point in the vaccination period after 10 or more patients have been enrolled in each group, if more than 20% of the enrolled patients develop a related grade 2 allergic reaction, grade 2 autoimmune reaction, grade 3 injection site reaction, or other grade 3+ toxicity, then enrollment to the trial may be suspended. All safety data will be reviewed; a trial recommendation will be formulated by the study team and presented to the independent DSMB.

The frequency of toxicities will be tabulated. If toxicities are observed, the DSMB may estimate an upper bound on the underlying toxicity rate using standard statistical methods. For example, assuming 22 patients have been enrolled, the upper bound of the 90% confidence interval based on an exact binomial test is as follows:

Number of patients observed with toxicity	0 (0%)	1 (4.5%)	2 (9.1%)	3 (13.6%)	4 (18.2%)
Upper bound of 90% confidence interval for the underlying toxicity rate	12.7%	19.8%	26.0%	31.6%	36.9%

9. ANALYSIS OF STUDY END-POINTS AND STATISTICS

9.1. Randomization and Stratification

This study will use an automated central randomization procedure to allocate patients in a 1/1 ratio to each of the two treatment groups. The randomization will be stratified based on:

- Stage of disease at diagnosis and debulking status
  - Stage III and maximal residual lesion diameter ≤1 cm
  - Stage III and maximal residual lesion diameter >1 cm
  - Stage IV
- Objective response to the last chemotherapy regimen prior to enrollment
  - Complete response (CR): defined as normal radiological findings
  - Partial Response (PR): deifned as RECIST PR
  - Stable Disease (SD): defined as RECIST SD [<30% decrease and <20% increase per RECIST v1.1], non-CR/non-PR for non-target only disease

The randomization will assign patients using a permuted block design with above stratification factors (9 stratum levels) and is detailed in a separate randomization plan.

9.2. Justification of Sample Size

The emphasis of this Phase 2 study is an exploratory estimation of effect size and incidence of adverse events; it is not considered as a pivotal trial for efficacy at this time. Therefore, a larger significance level (one-sided alpha=0.1) is used. The study is powered to detect a statistically significant hazard ratio (HR) of PFS of up to 0.64, assuming an estimated median time to progression of 9 months for the control group (based on estimates from the ICON7 trial [9]) and 14 months for treatment. The Lan-Demets alpha spending function was used to approximate the O'Brien-Fleming group sequential boundaries using an overall one-sided alpha = 0.10 to produce efficacy stopping rules of alpha < 0.02 for the interim analysis and <0.094 for the final analysis with a simulated power of approximately 80%. This assumes approximately an overall 100 PD events (120 patients) at the final analysis and the interim analysis will be performed when 50 PD events are observed.

The study is anticipated to enroll 120 patients over 12 months and patients will be followed for 24 months. The accrual rate is assumed to be approximately 0.5 to 1.0 patients per month per site, with sites being opened up over a 6-month period. The interim analysis would yield approximately a standard error (SE) of 0.2828 and upper one-sided 90% confidence intervals of potential HRs given on the left in the table below. By the end of the trial and assuming all enrolled and randomized patients had disease progression, are censored, died, or completed the trial, a SE of 0.2 is used to provide upper one-sided 90% confidence intervals of potential HRs given on the right in the table below.

Interim Estimated Hazard Ratio	One-sided Upper 90% Confidence Limit	Final Estimated Hazard Ratio	One-sided Upper 90% Confidence Limit
0.80	1.15	0.80	1.03
0.70	1.01	0.70	0.90
0.60	0.86	0.60	0.78
0.50	0.72	0.50	0.65
0.40	0.57	0.40	0.52
0.30	0.43	0.30	0.39
0.20	0.29	0.20	0.26

9.3. Data Collection

Patient records will be collected on the eCRFs from the baseline evaluation until completion of study follow-up or disease progression or withdrawal from the trial. Only authorized staff at the study site will conduct study assessments and procedures and they are responsible for the data entry. TapImmune or a delegated CRO will be responsible for the data management, including data quality insurance. eCRFs and query documentation will be maintained in the EDC system's audit trail. System backup for data stored in the EDC system will be conducted by the EDC vendor per the vendor standard procedures.

9.4. Efficacy Parameters

9.4.1. Radiological efficacy assessment

The RECIST v1.1 guidelines [66] for measurable, non-measurable, target and non-target lesions, and the objective tumor response criteria (CR, PR, SD, or PD) will be used to programmatically determine best overall response, PFS and duration of response. Patients with a CR and non-measurable disease at baseline are not excluded from this study. These patients should be followed up with the same assessment schedule as those with measurable disease at baseline, preferably using contrast enhanced CT or MRI where CT is not feasible. Patients with no measurable disease only will be assessed according to RECIST criteria for non-target and new lesions.

Baseline and follow-up contrast-enhanced CT of the chest, abdomen, and pelvis should be performed with other regions where clinically indicated for the adequate assessment of tumor burden.

All baseline radiological tumor assessments must be performed between completion of last platinum containing regimen and the start of study treatment. Scans that were performed as part of standard of care prior to signature of the informed consent form can be analyzed for the purposes of the study if they were performed within the correct time frame and of sufficient quality. Subsequent tumor assessments according to RECIST should be performed at the end of every 3 cycles (12 weeks +/-1 week) for up to 2 years according to the planned study schedule up to objective progression by RECIST. Any other sites at which new disease is suspected should also be appropriately imaged. Patients must be followed until RECIST disease progression.

Radiological examinations performed in the conduct of this study should be interpreted for a RECIST determination at the site, then forwarded to the central radiology vendor for QC and storage.

For patients with measurable lesions, all measurable lesions confirmed and assessed by radiological methods (CT or MRI scans) up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, recorded and measured at baseline, and at the time points specified in the protocol.

Non-target lesions will also be monitored throughout the study, and an overall assessment of response will be made regarding CR, incomplete response/SD or progression. Details of any new lesions will also be recorded.

Tumor assessment will be performed in accordance with the protocol schedule until evidence of one of the following:

- Progression of disease by RECIST v1.1
- Death without evidence of progression
- Withdrawal of consent

If a patient has any palliative radiotherapy to a lesion, that lesion should not be included in assessment of response, but should be assessed for progression.

A patient will be determined to have progressed if they have progression of target lesions, clear progression of existing non-target lesions, or the appearance of one or more new lesions.

Disease progression will be determined as the appearance of one or more new soft tissue and visceral lesions, including lymph nodes with SD> 1.5cm. Patients with appearance of new or worsening of any effusion including ascites will not be determined to have disease progression, unless this it is considered to be clinically significant by the investigator and confirmed on radiology.

Unequivocal malignant disease not identified prior to starting study treatment on additional anatomical imaging (eg, computed tomography (CT), magnetic resonance imaging (MRI) or bone scan confirmed by X-ray), prompted by symptoms is considered disease progression and should be recorded as new lesions.

If a patient demonstrates CA125 progression determined by a 2-fold increase from the baseline CA125 (if above the ULN at baseline) or 2-fold greater than the ULN (if below the ULN at baseline) on two occasions 7 or more days apart, the patient may have an unscheduled RECIST assessment (CT/MRI) to assess for objective disease progression by RECIST. If progression is not confirmed by RECIST the patient should continue on treatment until the next study assessment unless they fulfill another reason for withdrawal.

If a patient presents with disease related bowel obstruction they should be assessed by CT or MRI according to the RECIST criteria for tumor progression. If the CT or MRI findings are consistent with tumor progression in the view of the investigator, taking into account changes in CA125 levels indicative of progression according to the GCIG criteria, then this should be recorded as a new lesion, or captured appropriately for target or non- target lesions if present at baseline at this location.

If an unscheduled radiological and clinical tumor assessment is performed, and the patient has not progressed according to RECIST criteria, the next scheduled tumor assessment should still be performed at the planned time (as detailed in the study plan) relative to the date of the first randomized treatment dose and treatment should continue.

If at any time progression is uncertain and lesions are not symptomatic, patients may continue on treatment until the next scheduled assessment (ie, 12 weeks later +/- 1 week) or may have an unscheduled assessment earlier than this, if considered appropriate by the investigator.

Death will be regarded as a progression event in those patients who die before disease progression.

Lesions must be assessed using the same method and technique on each occasion. Lesions will be recorded on the CRF page in the same order as they were recorded at screening.

Details of any new lesions will also be collected. Response will be calculated in comparison to the baseline tumor measurements obtained before starting treatment. Progression will be calculated in comparison to when the tumor burden was at a minimum. Overall visit response will be recorded on the CRF.

9.4.2. Methods of assessment

Response will be assessed using RECIST v1.1 criteria in patients who have measurable disease. Categorization of overall visit response will be based on RECIST using the following response categories: CR, PR, SD, and PD. In the case of stable disease, measurements must have met the stable disease criteria at least once after study start for a minimum interval of 6 weeks.

Patients must have a CR/PR or SD prior to entry in the study. Therefore, the following criteria apply when assigning overall visit responses:

- Only patients with PR or SD and measurable disease at entry can achieve an overall visit response of CR or PR.
- Patients with a CR at entry or non-measurable disease only at entry cannot achieve an overall visit response of CR or PR.
- Patients with a CR at baseline will progress based on new lesions only.

To be assigned a status of PR or CR, changes in tumor assessments must be confirmed at the next scheduled tumor assessment no less than 4 weeks after the criteria for response were met.

Although CA125 is measured in this study it will not be directly used for assessing the primary objective response or progression and patients should be continued on treatment until confirmed RECIST progression.

9.4.3. Derivation or calculation of outcome variable

Best overall response will be calculated as the best response recorded from date of enrollment (taking as reference for progressive disease the smallest measurements recorded since the treatment started) for each patient, and will be used for the summaries of objective response. Best overall response will be determined programmatically based on the RECIST v1.1 criteria.

9.4.4. Tumor assessments for patients with non-measurable disease only at baseline

Patients with non-measurable disease only are not excluded from this study. These patients should be followed up with the same assessment schedule as those with measurable disease at baseline, preferably using contrast enhanced CT or MRI where CT is not feasible (see Appendix D for methods). Patients with non-measurable disease only will be assessed according to RECIST criteria for non-target and new lesions, as well as by the best overall response evaluated by CA125 as a secondary endpoint [66].

9.4.5. Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

CA125: CA125 alone cannot be used to assess response or progression, although CA125 response and progression information may be collected and separately analyzed and reported. If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

9.4.6. Response Criteria

Evaluation of Target Lesions:

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions:

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of CA125 level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

CA125 Progression:

CA125 progression will be determined by a 2-fold increase from the baseline CA125 (if above the ULN at baseline) or 2-fold greater than the ULN (if below the ULN at baseline) on two occasions 7 or more days apart. CA125 progression is a secondary analysis endpoint and should not be used to stop treatment or follow-up of patients until evidence of RECIST progression. If CA125 progression occurs, a follow-up RECIST scan should be performed.

Best Overall Response

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

Table for Patients with Measurable Disease

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Table for Patients with Non-Measurable Disease (i.e. Non-Target Disease)

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

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

Duration of Response

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

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

Permitted deviations from RECIST

The study's efficacy objectives will be evaluated according to the standard, unmodified RECIST v1.1 criteria as described above. Within the context of this protocol, the only purpose of the modifications to the criteria is to allow certain patients to continue the study treatment despite meeting RECIST criteria for progression of disease. Response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following [68-70]:

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after POD by conventional criteria
- The appearance of new lesions may not represent POD with immunotherapy
- SD while on immunotherapy may be durable and represent clinical benefit.

As long as they are receiving treatment on protocol, patients will be permitted to continue study treatment after RECIST v 1.1 criteria for PD are met if they meet all of the following criteria:

- Absence of symptoms and signs indicating unequivocal progression of disease
- No decline in ECOG performance status
- Absence of tumor growth at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

Patients for whom approved therapies exist must provide written consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial apparent progression. Patients in whom radiographic disease progression is confirmed at the subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above and have evidence of clinical benefit.

Modification of RECIST as described may discourage the early discontinuation of TPIV200 and provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria. Nonetheless, the primary efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST v 1.1 criteria.

Progression Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of study treatment to time of recurrence, progression, or death, whichever occurs first.

Survival

Survival is defined as the duration of time from start of treatment to time of death, or patients will be censored on the date of last contact. Survival will continue to be followed quarterly until study completion.

9.5. Data Analysis

All subjects who received one dose of study drug will be included in the analysis of safety and tolerability. Summary statistics for each endpoint will be provided for each relevant comparison group including the results

of statistical tests. All subjects who have a result for the baseline and a follow-up and who have received at least one dose of study drug will be included for the analysis of efficacy.

9.5.1. Demographics, Baseline and Other Characteristics

Subject characteristics (demographic information and pre-treatment measurements) will be summarized. All medical history and physical examination findings will be coded as appropriate and listed by subject. The results of the screening and final weight will be listed by subject.

9.5.2. Safety and Tolerability

Adverse events will be coded for purposes of summary by body system and preferred term. The incidence of TEAEs will be summarized for each treatment and tabulated by severity and attribution. Serious adverse events and those leading to study withdrawal will also be tabulated.

The results of laboratory tests results at each study visit will be listed by subject. Values outside the normal range will be identified, with special attention given to those values the PI or Medical Monitor flags as clinically significant. Shift tables or scatter plots of numeric laboratory parameters will be provided, depicting changes in values, as appropriate. Normal ranges will be incorporated. Laboratory data obtained at any time after the vaccination will not be used as Baseline data.

The incidence of Grade 3 and higher AEs will be compared across treatment groups.

9.5.3. Evaluation for Efficacy

The primary clinical efficacy endpoint is PFS (inclusive of recurrence or any death), where disease progression is determined per RECIST v1.1 criteria. The primary method for analysis will use Cox proportional hazards regression, adjusted for stage of disease at diagnosis and debulking status (stage III cancer and maximal residual lesion diameter ≤1 cm vs. stage III cancer and maximal residual lesion diameter >1 cm vs. stage IV cancer) and disease status (tumor response at the last platinum containing regimen [CR, PR, or SD]), to estimate the hazard functions for time to disease progression in each treatment group and compare them using HRs.

Cox models will be generated at an interim analysis when 50 PD events have occurred, and again at the end of the study when all patients are expected to have had disease progression or censorship or completed the study. The HRs will be evaluated using one-sided upper 90% confidence intervals and a p-value of <0.02 at the interim and a p-value of <0.094 for the final analysis will be considered statistically significant to define trial success of the primary efficacy endpoint. The DSMB will review the interim results to recommend whether the trial should be continued until all patients have been fully assessed. The model will be adjusted for potential confounding variables: stage of disease at diagnosis and debulking status and disease status. Additionally, the probability of disease progression will be estimated using Kaplan-Meier methods for each treatment group.

The above stopping rules will only serve as the guidance for decision-making during this exploratory phase of development. To support the best decisions based on the totality of efficacy evidence and benefit-risk evaluation, other methods including Bayesian approaches may also be utilized at interim and final analyses. Furthermore, when interim data becomes available, the sponsor may opt to discuss with the regulatory authorities regarding the possibility of extending the trial to a Phase 3 pivotal design.

Other secondary efficacy end-points are:

- Overall survival (OS) will be analyzed using a Cox model similar to that for PFS. The probability of death will be estimated using the method of Kaplan-Meier for each treatment group.

- Best overall response (CR+PR) will be treated as a binary endpoint. Response rates will be reported and 90% CI will be estimated using exact binomial proportions. Treatment groups will be compared using Fisher's exact test or other appropriate method.
- Duration of response will be summarized with descriptive statistics for subjects who have a baseline response or achieve a post-baseline response of CR or PR.
- Duration of stable disease will be summarized with descriptive statistics for subjects who achieve a post-baseline response of SD.
- Disease control rate (CR+PR+SD) will be analyzed like best overall response.
- Response by irRECIST criteria will be treated as a binary endpoint [69, 70]. Rates of response by irRECIST will be reported and 90% CI will be estimated using exact binomial proportions. Treatment groups will be compared using Fisher's exact test.
- Cancer Antigen (CA) 125 response (Gynecologic Cancer InterGroup [GCIG] criteria) will be analyzed like PFS.
- The progression free rate (PFR) at 6 months will be treated as a binary endpoint [71]. Response rates will be reported and 90% CI will be estimated using exact binomial proportions. Treatment groups will be compared using Fisher's exact test.

The PFR and OS for each group will be determined at the interim analysis and reported to the Sponsor, as they do not impact further hypothesis testing. A secondary efficacy variable is the PFS by CA125 [67].

Patients who have received at least one cycle of therapy and have has their disease re-evaluated at least once after baseline will be considered evaluable for response and PFS. Patients without a post-baseline assessment of response will be included in a sensitivity analysis as non-responders for response rate and PFS rate.

9.5.4. FRα tumor expression

Tumor membrane staining intensity will be scored by a pathologist as negative (0), weak (1+), moderate (2+), and strong (3+). The percent of cells within each tissue core stained at each intensity will be recorded to calculate an H-score. The H-score is a weighted score that captured both the proportion of positive staining and intensity for each tumor. H-score values can range from zero (no membrane staining) to a maximum of 300 (100% membrane staining at 3+). The mean H-scores across treatment groups will compared using the Mann-Whitney test.

9.5.5. Immune Monitoring

To evaluate each treatment arm with respect to change from baseline in T cell response, descriptive statistics will be provided and statistical inference will be performed using the Wilcoxon signed rank test. To compare the low versus high vaccine dose groups, the Mann-Whitney test will be used after aligning ranks within each cyclophosphamide level (priming or no priming). To compare priming versus no priming, the Mann-Whitney test will be used after aligning ranks within each vaccine dose level.

The emergence of a FRα-specific T cell responses (i.e. immune responder) will be defined as (1) a 2-fold or greater increase in FRα-specific T cell at the end of the vaccination period if pre-treatment levels are detectable, or (2) levels of FRα-specific T cells above the threshold of the assay at end of the vaccination period if pre-treatment levels are non-detectable.

A 90% binomial confidence interval will be constructed for percentage of patients who develop an immune response among those patients in each treatment groups and for the sub-group of patients in each H-score quartile.

9.5.6. Exploratory Correlative Research

The goal of the correlative studies is to determine whether serum biomarkers or immune measurement or tissue marker may be a predictor of a robust FRα specific T-cell response after vaccination. Such a predictor of immune response may be used clinically to rapidly assess whether or not immune protection against recurrence will be established. Surrogate markers could be used to assess the need for booster immunizations that may be required if immunity wanes.

The following markers may be evaluated as baseline predictors: i/ Tumor infiltration from immune-cell subsets such as TIL, CD4+ Treg, myeloid cells by immunofluorescence and expression of markers of T cell activations such as 4-1BB (CD137), OX40, GITR, CD40, and ICOS, as well as known pathway inhibitors such as PD-1/PD-L1, IDO, B7, LAG3, TIM-3, CTLA-4; ii/ Tumor cell markers such as Ki and EGFR [72]; iii/ Circulating inhibitory T cells such as Tregs and MDSC; iv/ Tumor genotyping to identify ovarian cancer subtypes.

10. MANAGEMENT AND REPORTING OF SAES AND SPECIAL SITUATIONS

10.1. Definition of Serious Adverse Events

A serious adverse event is defined in general as an untoward (unfavorable) adverse event which:

1. Is fatal or life-threatening (defined as an event in which the subject 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 were more severe);
2. Requires or prolongs hospitalization;
3. Is significantly or permanently disabling or incapacitating;
4. Constitutes a congenital anomaly or a birth defect; or
5. May jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).

Suspected transmission of an infectious agent (e.g., any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose of the peptides or dosing above the label dose of GM-CSF, and cancer (other than the pre-existing ovarian cancer) are not always serious by regulatory definition, these events must be handled as SAEs for data transmission purposes.

The following hospitalizations are not considered SAEs in TapImmune clinical studies:

1. A visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
2. Elective surgery, planned prior to signing consent
3. Admissions as per protocol for a planned medical/surgical procedure
4. Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
5. Medical/surgical admission for purposes other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
6. Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative).

10.2. Special Situations for Reporting

10.2.1. Adverse Events of Special Interest

While they may not be considered SAEs, certain situations require special documentation; these are called Adverse Events of Special Interest (AESIs). These can occur at any time during the trial and must be handled in the same manner as SAEs for data transmission purposes, whether they are considered related or not. Autoimmune diseases of new onset or that are exacerbated are a typical example for vaccine product development; a list of diseases that may be autoimmune related are included in Appendix 4. Any TEAE can be addressed in this fashion; the Sponsor will determine whether the event should be reported to FDA.

10.2.2. Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. All secondary malignancies that occur following treatment with the study drug during the follow-up must be must be handled in the same manner as SAEs for data transmission purposes.

10.2.3. Pregnancy

Although pregnancy is not considered an AE or SAE by regulatory definition, for this study pregnancies must be handled in the same manner as SAEs for data transmission purposes. In the event that a pregnancy complication occurs or elective termination of a pregnancy is required for medical reasons, then the complication will be recorded as an AE or SAE as appropriate.

While elective and uncomplicated induced abortion not required for medical reasons does not constitute an AE or SAE (even if the subject is hospitalized to undergo abortion), spontaneous abortion is considered a fatal event and must be reported as an AE and SAE as appropriate.

Any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or, if appropriate, as an SAE. A spontaneous abortion is always considered an SAE and should be reported as described below.

Women of childbearing potential enrolled in this study will have pregnancy tests administered during screening and before each treatment. Female subjects must either be of non-reproductive potential (i.e. post-menopause by history: >60 years old and no menses for >12 months naturally or secondary to radiation/chemotherapy; OR serum FSH, LH and estradiol levels in the post-menopausal range; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy), or must have a negative serum or urine pregnancy test upon study entry. Subjects who are pregnant or are breast feeding must not be entered into the study.

If any pregnancy and/or suspected pregnancy occurs during the study in a female patient or a female partner of a male patient should be reported. Any pregnancy and/or suspected pregnancy will be followed for outcome.

The Investigator must notify the Sponsor immediately after the pregnancy is confirmed. If the subject has received the investigational drug prior to becoming pregnant, the subject will continue the efficacy assessment and follow-up periods and measures of safety and efficacy will be obtained.

The subject will be followed until the outcome of the pregnancy is determined. It is the responsibility of the Investigator to obtain and document pregnancy information on the most recent InClin Pregnancy Report Form. Furthermore, any SAE occurring as outcome of the pregnancy must be reported to the Sponsor's Medical Monitor.

10.3. Reporting Procedures

SAEs are collected from the time the patient signs consent until they come off study, whether or not considered to be related to study drug, as booster doses will continue during follow-up. Deaths must all be reported to the Sponsor within 24 hours of knowledge of the event, whether or not considered to be related to study drug, although deaths due to ovarian cancer will not be considered as SAEs.

Any SAE that occurs greater than 30 days after the patient's last dose of study drug and is considered to be at least possibly related to the study drug requires reporting within 24-hours to InClin Drug Safety. Unrelated SAEs that occur more than 30 days after a dose of study drug should be reported as soon as is convenient. These events will be followed until resolution, stabilization or until the Investigator provides sufficient evidence that no further information can be obtained.

The Investigator or healthcare professional must send the InClin Serious Adverse Report Form by e-mail, e-facsimile or telephone to:

Contact Methods for SAEs & Pregnancy Reports	
E-mail: (primary)	drugsafety@inclin.com
eFacsimile: (back-up)	+1 (877) 669-1618
Telephone: (emergency)	+1 (415) 870-7682

Although not all information required for a complete InClin Serious Adverse Event Form may be readily available at the time of the event, the Investigator must include sufficient information on the InClin Serious Adverse Report Form to allow for a complete medical assessment. This should include at a minimum the subject number, site number, detailed description of the event, seriousness criteria, and causality/relationship to study drug.

The InClin Drug Safety Team will acknowledge the receipt of the SAE via e-mail to the clinical site. After submission of the initial report, the Investigator will provide follow-up information to the InClin Drug Safety Team as requested (eg, concomitant medications, hospital discharge summary) to further evaluate the event and assure that all appropriate information is received. Once all information is received and the SAE has been deemed appropriate for closure, the InClin Serious Adverse Report Form must be signed and dated by the Investigator.

The Investigator is responsible for informing the Institutional Review Board/Independent Ethics Committee (IRB/IEC) of the SAE in accordance with institutional policies and procedures including relevant initial and follow-up information about the SAE.

11. ETHICAL ASPECTS

11.1. Ethics and Good Clinical Practice

This trial will be conducted in compliance with the appropriate protocol, ICH GCP guidelines, the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local institutional review board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an

appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented.

11.2. Regulatory files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for regulatory compliance prior to study initiation, throughout the study, as well as at the study closure.

11.3. Confidentiality Regarding Study Subjects

Investigators must assure that the privacy of subjects, including their personal identity and all personal medical information, will be protected at all times, as required by law. Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance with HIPAA.

Participant records will be held confidential by the use of study codes for identifying participants on eCRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

11.4. Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 54, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will have an up-to date signed financial disclosure form on file with the sponsor.

11.5. Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed ICF, and other information provided to subjects must be reviewed by an IRB/IEC. A signed and dated statement that the protocol, and ICF, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects have been approved by the IRB/IEC must be given to TapImmune before study initiation. The name and occupation of the chairperson and the members of the IRB/IEC (preferred) or the IRB's Health and Human Safety Assurance number must be supplied to TapImmune or its designee. This committee, as required by local law or procedure, will approve any amendments to the protocol that need formal approval. The IRB/IEC will also be notified of all other administrative amendments (i.e., administrative changes). The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates. The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

11.6. Informed Consent

The informed consent form is a means of providing information regarding the trial to a prospective participant and allows for an informed decision about participation in the study. All participants must read, sign, and date a consent form(s) prior to undergoing any study-specific procedures and participating in the study. The informed

consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect study participation. A copy of the informed consent(s) form will be given to a prospective participant to review during the consent process and to keep for reference. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty. Study sites will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

12. ADMINISTRATIVE REQUIREMENTS

12.1. Monitoring Procedures

Investigators will host periodic visits by TapImmune or CRO Clinical Monitors who will ensure all study procedures are conducted and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, case report forms (CRFs), and corresponding source documents for each participant.

12.2. Protocol Deviation

A protocol deviation is any departure from procedures and requirements outlined in the protocol. Protocol deviations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) effects on the study objectives, to ensure that site performance does not compromise the integrity of the trial.

All protocol deviations will be recorded in the EDC via the Protocol Deviations eCRF. Additionally, each site is responsible for tracking and reporting Protocol Deviations to their IRB as required by IRB regulations. The TapImmune Clinical Monitor must be contacted immediately if an unqualified/ineligible participant is randomized into the study.

12.3. Investigational Site Training

TapImmune may provide investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedures, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP as applicable.

12.4. Recording of Data and Retention of Documents

Study sites will collect data on eCRFs. All information required by the protocol should be provided. These forms will be completed on an ongoing basis during the study. Instructions will be provided for the site personnel to instruct the participant in the use of the eCRFs. However, the local investigative team is responsible for maintaining accurate, complete and up-to-date records, and progress notes are required by the protocol and the SOPs. The investigative team is also responsible for maintaining any source documentation related to the study.

Essential documents, as listed below, will be retained by the Investigator for the maximum period required to comply with national and international regulations, or institutional procedures. The investigator must contact TapImmune prior to destroying any records associated with the study. If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to TapImmune.

Essential documents include:

1. Signed protocol and all amendments;
2. IRB/IEC approvals for the study protocol and all amendments;
3. All source documents and laboratory records;
4. Subjects' ICF/HIPAA authorization; and
5. Any other pertinent study documents.

12.5. Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information generated in connection with the study or provided by TapImmune or its designee in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC. Study documents provided by TapImmune (protocols, Investigators' Brochures, eCRFs, and other material) will be stored appropriately to ensure their confidentiality. Such confidential information may not be disclosed to others without direct written authorization from TapImmune, except to the extent necessary to obtain informed consent/HIPAA authorization from subjects who wish to participate in the study.

12.6. Discontinuation of Study

TapImmune reserves the right to discontinue any study for any reason at any time.

13. DATA MANAGEMENT

13.1. Data Collection

Electronic Data Capture (EDC) system will be deployed, eCRF will be completed by the authorized study site personnel. An electronic version of the final eCRF book for each subject will be forwarded to the study sites for record keeping at the study site closure.

13.2. Data clarification

Obvious eCRF data errors may be corrected by Data Management. Other errors, omissions, or requests for clarification will be queried; queries will be returned to the study site for resolution.

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15. APPENDIX 1: ECOG / KARNOFSKY PERFORMANCE STATUS

Grade

0	Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work (Karnofsky 70-80).
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50 percent of waking hours (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50 percent or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Dead

16. APPENDIX 2: IMMUNE MONITORING METHODS

16.1. Background

The goal of the immunologic studies is to determine whether the potential exists for an immune measurement or tissue marker to act as a surrogate marker of protection against disease recurrence in patients immunized with the FRα vaccine. While the clinical response (e.g. disease free period in the current proposal) remains the endpoint of choice for many different types of therapeutic modalities, validated surrogate endpoints are useful for vaccines for a number of reasons.

- Prediction of clinical benefit: Surrogate immunologic endpoints can be used clinically to rapidly assess whether or not protection against disease exists in the absence of clinical symptoms or other biologic features of infection or disease. Surrogates are used to determine protection following immunization against a number of infectious agents including Polio virus and Streptococcus pneumonia.

- Decisions for ongoing therapy: Surrogate markers could be used to assess the need for booster immunizations that may be required if immunity wanes.

- Vaccine improvements and lot variations

16.2. Methods

16.2.1. FRα-specific antibody enzyme-linked immunosorbent assay

The FRα vaccine in this protocol incorporates a known antibody recognition epitope of FRα. Testing will be done in an ELISA assay to detect response toward the FRα peptide-mix and/or FRα protein.

A vaccine-induced increase in FRα-specific antibody responses will be defined as (1) a 2-fold or greater increase in FRα-specific antibody at any point during treatment if there were detectable pre-treatment levels of FRα-specific T cells or (2) FRα-specific antibodies at any point during treatment if pre-treatment levels of FRα-specific antibodies are non-detectable.

16.2.2. Flow cytometric analysis of circulating regulatory T cells (Tregs) and MDSC

Treg and MDSC will be counted at baseline either from fresh blood (K3 EDTA tube) or from the PBMC obtained from the heparin tubes.

17. APPENDIX 3 – TISSUE IMMUNOCHEMISTRY METHODS

FRα expression in the tumor will be examined as previously described [17]. Samples will be examined for FRα expression by assessing triplicate slides made from a full paraffin block. Tissues will be stained with a IgG antibody specific for human FRα purified.

Five-micron sections will be cut and placed on positively charged slides. After rehydration, tissues will be subjected to antigen retrieval and blocking of endogenous peroxidases prior to staining with FRα Ab or a non-specific isotype matched antibody as a negative control for 30 min. After washing the slides, signals will be detected using the mouse MACH3 system (Biocare Medical, Walnut Creek, CA). Slides will be counterstained with Modified Schmidt's Hematoxylin and permanently mounted.

Slides will then be archived using digital imaging system. The staining intensity (strong, moderate, weak, or negative) and proportion of FRα-positive cells among the malignant cells and will be scored independently.

Other testing may be done to evaluate the local immune response, including standard or multiplex immunohistochemistry for CD4, CD8, and Treg cells or transcript analysis.

18. APPENDIX 4 - DISEASES THAT MAY BE AUTOIMMUNE RELATED

Acute disseminated encephalomyelitis Addison's disease Alopecia universalis Ankylosing spondylitis Antiphospholipid antibody syndrome Aplastic anemia Asthma Autoimmune hemolytic anemia Autoimmune hepatitis Autoimmune hypoparathyroidism Autoimmune hypophysitis Autoimmune myocarditis Autoimmune oophoritis Autoimmune orchitis Autoimmune thrombocytopenic purpura Behcet's disease Bullous pemphigold Celiac disease Chronic fatigue syndrome Chronic inflammatory demyelinating polyneuropathy Chung-Strauss syndrome Crohn's disease Dermatomyositis Diabetes mellitus type 1 Dysautonomia	Eczema Epidermolysis bullosa acquista Gestational pemphigoid Giant cell arteritis Goodpasture's syndrome Graves' disease Guillain-Barré syndrome Hashimoto's disease IgA nephropathy Inflammatory bowel disease Interstitial cystitis Kawasaki's disease Lambert-Eaton myasthenia syndrome Lupus erythematosus Lyme disease - chronic Meniere's syndrome Mooren's ulcer Morphea Multiple sclerosis Myasthenia gravis Neuromyotonia Opsoclonus myoclonus syndrome Optic neuritis Ord's thyroiditis Pemphigus Pernicious anemia Polyarteritis nodusa	Polyglandular autoimmune syndrome Primary biliary cirrhosis Psoriasis Reiter's syndrome Rheumatoid arthritis (but not osteoarthritis) Sarcoidosis Scleroderma Sjögren's syndrome Stiff-Person syndrome Takayasu's arteritis Ulcerative colitis Vitiligo Vogt-Kovanagi-Harada disease Vulvodynia Wegener's granulomatosis