PHASE I CLINICAL TRIAL OF ADOPTIVE TRANSFER OF AUTOLOGOUS FOLATE RECEPTOR–ALPHA REDIRECTED T CELLS FOR RECURRENT HIGH GRADE SEROUS OVARIAN, FALLOPIAN TUBE, OR PRIMARY PERITONEAL CANCER

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Main Investigational Product:	*MOv19-BBz CAR T cells*
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IND Number:	[redacted]
Sponsor Cell Manufacturing:	*Clinical Cell and Vaccine Production Facility (CVPF)* *University of Pennsylvania*
Correlative Laboratory:	*TCSL University of Pennsylvania*
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LIST OF ABBREVIATIONS

AE, adverse event
aFR, alpha folate receptor
CAR, chimeric antigen receptor
CCI, Center for Cellular Immunotherapies
CD137, 4-1BB costimulatory molecule
CFR, code of federal regulations
CRF, case report form
CRM, Continual Reassessment Method
CRS, Cytokine Release Syndrome
CTCAE, common terminology criteria for adverse events
CTL, cytotoxic T lymphocyte
CTRC, Clinical Translational Research Center at the University of Pennsylvania
CVPF, clinical cell and vaccine production facility at the University of Pennsylvania
CTL, cytotoxic T lymphocyte
CTX, cyclophosphamide
DSMB, data and safety monitoring board
DLT, dose-limiting toxicity
EOC, epithelial ovarian cancer
FDA, food and drug administration
GCP, good clinical practices
GMP, good manufacturing practices
HAMA, human anti-mouse antibody
HACA, human anti-CAR antibody
IBC, Institutional Biosafety Committee
i.p., intraperitoneal
IRB, Institutional Review Board
irRC, immune related response criteria
irRECIST, Immune-related Response Evaluation Criteria in Solid Tumors
MABEL, Minimum Anticipated Biological Effect Level
MAS, Macrophage Activation Syndrome
MOv19, alpha folate receptor-specific scFv
OBD, optimal biologic dose
PBMC, peripheral blood mononuclear cells
PDAE, protocol-defined adverse event
PDCS, Product Development and Correlative Sciences laboratory
PDSAE, protocol-defined serious adverse event
RECIST, Response Evaluation Criteria in Solid Tumors
ROA, route of administration
SAE, serious adverse event
SaFRP, soluble alpha folate receptor protein

TCR, T cell receptor
TCSL, Translational and Correlative Studies Laboratory
UADE, Unanticipated Adverse Device Effect
UPenn, University of Pennsylvania
VSV-G, vesicular stomatitis virus

STUDY SUMMARY

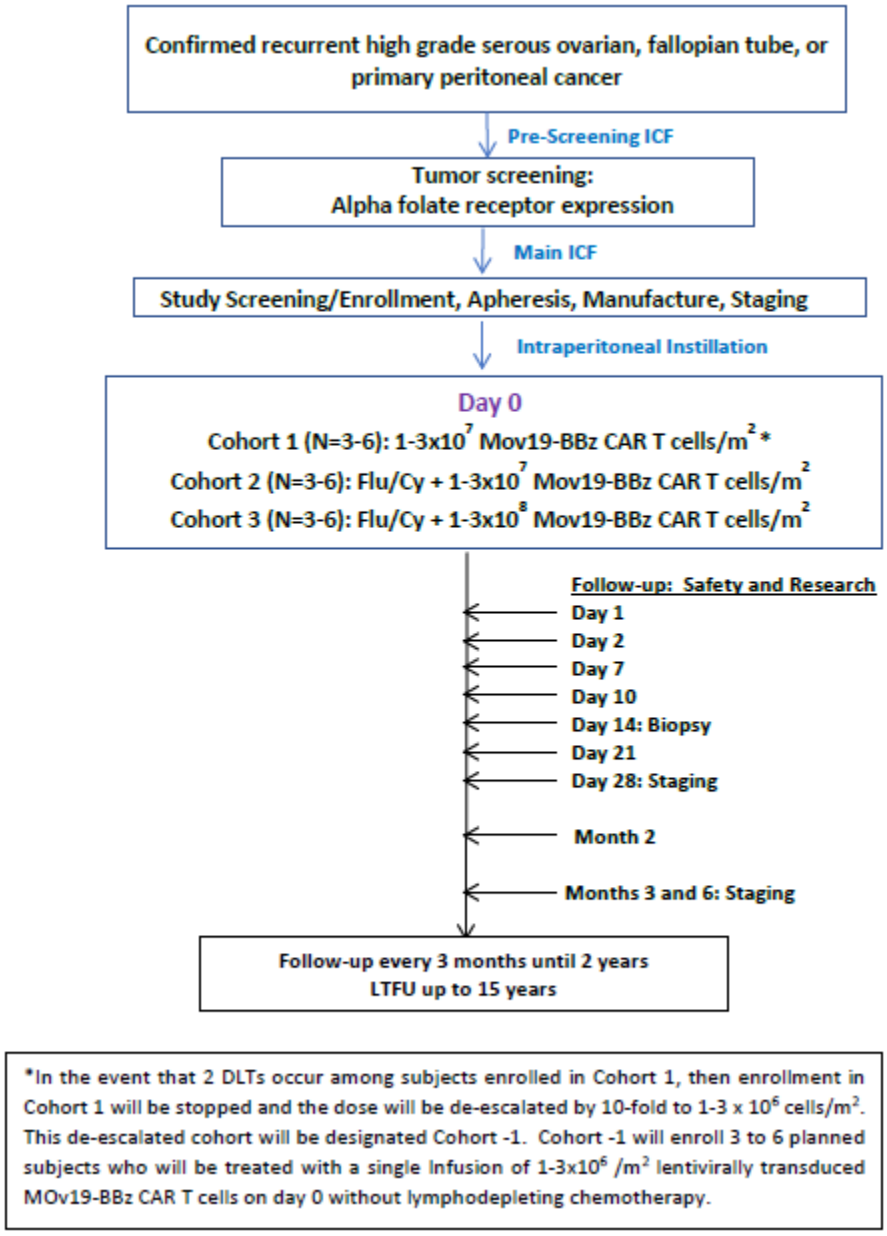
Title	Phase I Clinical Trial of Adoptive Transfer of Autologous Folate Receptor–alpha Redirected T Cells for Recurrent High Grade Serous Ovarian, Fallopian Tube, or Primary Peritoneal Cancer
Short Title	MOv19-BBz CAR T cells in aFR expressing recurrent high grade serous ovarian, fallopian tube, or primary peritoneal cancer
Protocol Number	UPCC 03818; IRB# 830111
Phase	Phase 1 - Safety and Proof of Concept
Methodology	Phase I study to establish safety and feasibility of intraperitoneally administered lentiviral transduced MOv19-BBz CAR T cells with or without cyclophosphamide + fludarabine as lymphodepleting chemotherapy.
Study Duration	The protocol will require approximately 18-24 months to complete enrollment. Each subject will be followed for up to 15 years from their MOv19-BBz CART cell infusion.
Study Center(s)	University of Pennsylvania
Number of Subjects	9 to 18 evaluable subjects.
Study Design	This is a Phase I study evaluating the safety and feasibility of intraperitoneally administered lentiviral transduced MOv19-BBz CAR T cells in 4 cohorts with or without cyclophosphamide + fludarabine in a 3+3 dose escalation design. The DLT observation period is 28 days post CAR T cell infusion. The Maximum Tolerated Dose (MTD) is defined as the dose at which 0 or 1 DLT occurs in 6 evaluable subjects tested within the dose range of this study. Evaluable subjects are defined as follows: • Subjects evaluable for DLT assessment are all those who receive the target dose of MOv19-BBz CAR T cell infusion based on cohort. • Subjects evaluable for safety include all those who receive a MOv19-BBz CAR T cell infusion. • Subjects evaluable for efficacy are all those who receive the target dose of MOv19-BBz CAR T cell infusion based on cohort. • <u>Cohort 1: (n= 3 to 6 subjects)</u>: Single infusion of 1-3x10^7 /m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 without lymphodepleting chemotherapy. o If 1 DLT/3 subjects occurs, the study will enroll an additional 3 subjects at this dose level. If 0 DLT/3 subjects or 1 DLT/6 subjects occurs, the study will advance to Cohort 2. If 2 DLT/3 subjects or 2 DLT/6 subjects occurs, then enrollment in Cohort 1 will be stopped and the dose will be de-escalated by 10-fold to 1-3 x 10^6 cells/m^2 (Cohort -1). o If the number of manufactured CAR T cells does not meet the protocol-specified minimum dose for Cohort 1 subjects of 1 x 10^7/m^2 cells, but does meet the protocol minimum dose requirement of at least 1 x 10^6/m^2 cells, then the subject may receive the cells, but will not be included in the DLT assessment for Cohort 1. Thus, the subject would be evaluable for safety, but would be replaced in this cohort for formal DLT assessment. If, however, the number of manufactured CAR T cells does not meet the minimum acceptable dose for infusion, then the cells will not be administered, and the subject will be replaced in the study.

	• Cohort 2: (n= 3 to 6 subjects): Single infusion of 1-3x10^7 /m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 beginning 3 days (+/- 1 day) after lymphodepleting chemotherapy with cyclophosphamide + fludarabine. o If 1 DLT/3 subjects occurs, the study will enroll an additional 3 subjects at this dose level. If 0 DLT/3 subjects or 1 DLT/6 subjects occurs, the study will advance to Cohort 3. If 2 DLT/3 subjects or 2 DLT/6 subjects occurs, further infusions within this cohort and subsequent dose escalation would be halted. If less than 6 subjects were infused in Cohort 1, up to 6 total subjects will be infused in Cohort 1 to establish the MTD. o If the number of manufactured CAR T cells does not meet the protocol-specified minimum dose for Cohort 2 subjects of 1 x 10^7/m^2 cells, but does meet the minimum dose requirement of at least 1 x 10^6/m^2 cells, then the subject may receive the cells but will not be included in the DLT assessment for Cohort 2. Thus, the subject would be evaluable for safety, but would be replaced in this cohort for formal DLT assessment. If, however, the number of manufactured CAR T cells does not meet the minimum acceptable dose for infusion, then the cells will not be administered, and the subject will be replaced in the study. • Cohort 3: (n=3 to 6 subjects): Single infusion of 1-3x10^8 /m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 beginning 3 days (+/- 1 day) after lymphodepleting chemotherapy with cyclophosphamide + fludarabine. o If 0 DLT/3 or 1 DLT/3 subjects occur, the study will enroll an additional 3 subjects to confirm tolerability and MTD. If 2 DLT/3 subjects or 2 DLT/6 subjects occurs, further infusions within this cohort will be halted. If less than 6 subjects were infused in Cohort 2, up to 6 total subjects will be infused in Cohort 2 to establish the MTD. o If the number of manufactured CAR T cells does not meet the protocol-specified minimum dose for Cohort 2 subjects of 1 x 10^8/m^2 cells, but does meet the minimum dose requirement of at least 1 x 10^6/m^2 cells, then the subject may receive the cells but will not be included in the DLT assessment for Cohort 3. Thus, the subject would be evaluable for safety, but would be replaced in this cohort for formal DLT assessment. If, however, the number of manufactured CAR T cells does not meet the minimum acceptable dose for infusion, then the cells will not be administered, and the subject will be replaced in the study. In the event that 2 DLTs occur among subjects enrolled in Cohort 1, then enrollment in Cohort 1 will be stopped and the dose will be de-escalated by 10-fold to 1-3 x 10^6 cells/m^2. This de-escalated cohort will be designated Cohort -1. • Cohort -1: (n= 3 to 6 subjects): Single Infusion of 1-3x10^6 /m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 without lymphodepleting chemotherapy. Up to 6 subjects will be infused in Cohort -1 with ≤ 1 DLT/6 subjects to establish the MTD.

	Subjects with accessible lesions will be subjected to a mandatory CT-guided needle biopsy of tumors or needle aspiration of malignant effusion pre-infusion and approximately Day +14 after T cell administration.
Objectives	**Primary objective:** Determine the safety and feasibility of intraperitoneal administration of lentivirally transduced MOv19-BBz CAR T cells in the target population. Intraperitoneal administration of MOv19-BBz CAR T cells is planned with and without cyclophosphamide + fludarabine as lymphodepleting chemotherapy. **Secondary objectives:** <u>Clinical objectives</u>: 1. Assess the clinical anti-tumor effect by standard criteria (RECIST 1.1) and immune-related response criteria (irRECIST). 2. Assess overall response rate (ORR), progression-free survival (PFS) and overall survival (OS). <u>Correlative objectives</u>: 1. Evaluate MOv19-BBz CAR T cells engraftment and persistence in peripheral blood and body fluids (including peritoneal fluid). 2. Determine the bioactivity of MOv19-BBz CAR T cells in peripheral blood and body fluids (including peritoneal fluid). 3. Evaluate the development of anti-CART immune responses favoring rejection of MOv19-BBz CAR T cells. 4. Evaluate the development of secondary anti-tumor immune responses as a consequence of epitope spreading. 5. Evaluate potential tumor biomarkers of anti-tumor activity. 6. Where tumor material or body fluids can be obtained: a. Measure trafficking of MOv19-BBz CAR T b. Evaluate aFR expression on tumor cells to assess for antigen-escape c. Analyze tumor microenvironment and cell interactions (if feasible)
Study Population and Main Inclusion Criteria	Subjects with histologically confirmed persistent or recurrent stage II to IV high grade serous epithelial ovarian, fallopian tube or primary peritoneal carcinoma that expresses aFR as assessed by immunohistochemistry. Inclusion criteria are designed to include subjects 18 years of age and older diagnosed with advanced high grade serous ovarian, fallopian tube, or primary peritoneal cancer that is incurable by presently available therapy, who have failed two or more prior chemotherapy regimens, and with ECOG 0-1 performance status.
Investigational Agent(s), Dose, Route, Regimen	<u>Investigational Agent(s)</u>: • MOv19-BBz CAR T cells: autologous T cells lentivirally transduced with chimeric anti-alpha folate receptor immunoreceptor MOv19 scFv fused to the 4-1BB and CD3ζ signaling domains. • Cyclophosphamide and Fludarabine: cytotoxic chemotherapy agents used for lymphodepletion prior to MOv19-BBz CAR T cell administration (Cohorts 2 + 3 only) <u>Dose</u>: • MOv19-BBz CAR T cells: ○ Cohorts 1 + 2: 1-3x10^7 MOv19-BBz CAR T cells/m^2 ○ Cohort 3: 1-3x10^8MOv19-BBz CAR T cells/m^2 ○ Cohort -1: 1-3x10^6 MOv19-BBz CAR T cells/m^2

	• Cyclophosphamide and Fludarabine: Cyclophosphamide 300mg/m^2 and Fludarabine 30mg/m^2 (Cohorts 2 + 3). Fludarabine doses will be rounded down to the nearest 50 mg vial size, if the rounded dose does not differ by > 10% of the original dose prescribed. Route of Administration: • MOv19-BBz CAR T cells: intraperitoneal instillation (all Cohorts) • Cyclophosphamide and Fludarabine: intravenous infusion (Cohorts 2 + 3) Regimen: • MOv19-BBz CAR T cells: single dose on Day 0 (all Cohorts) • Cyclophosphamide and Fludarabine: given over 3 days; scheduled so that the last day of chemotherapy falls 3 days (+/- 1 day) prior to the CAR T cell infusion (Day 0). Cohorts 2 + 3 only.
Reference Therapy	None
Statistical Methodology	This is a phase I safety and feasibility study. Adverse events will be collected and evaluated for all subjects during the protocol specified adverse event reporting period outlined in **Section9.1**. AEs will be graded for severity using the National Cancer Institute (NCI) – Common Terminology Criteria (v5.0). All adverse events will be described and exact 95% confidence intervals will be produced for adverse event rates, both overall and within major categories. The data will be monitored continuously for evidence of excessive toxicity. Results will be tabulated and summarized. Rates of clinical responses will be summarized in exact 95% confidence intervals. Distributions of progression-free and overall survival, and overall response rate will be presented graphically using Kaplan-Meier curves. Overall survival rates will also be presented. The statistical analysis will be primarily descriptive in keeping with the exploratory nature of the study. Descriptive statistics will be applied to determine the relative persistence and trafficking to blood (and optionally tumor) of the MOv19-BBz CAR T cells. Data regarding the number of CAR T cells in blood, and the tracking of soluble biomarker levels will be presented graphically. Correlations with radiographic and other standard measures of tumor burden will be determined. We will compute 95% confidence intervals for proportions and means.

Figure 1- Study Schema



*In the event that 2 DLTs occur among subjects enrolled in Cohort 1, then enrollment in Cohort 1 will be stopped and the dose will be de-escalated by 10-fold to 1-3 x 10^6 cells/m^2. This de-escalated cohort will be designated Cohort -1. Cohort -1 will enroll 3 to 6 planned subjects who will be treated with a single infusion of 1-3x10^6 /m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 without lymphodepleting chemotherapy.

1 INTRODUCTION

1.1 Background

1.1.1 Epithelial Ovarian Cancer

Subjects with recurrent ovarian cancer have been chosen as the study population here because of the frequent expression of the target antigen alpha folate receptor in this malignancy. Ovarian cancer is the 5th most common cancer in women and, in the United States in 2015, 21,290 women were diagnosed with ovarian cancer and 14,180 women died of the disease [1]. Despite efforts studying different cytotoxic and targeted agents to treat ovarian cancer, no major improvement in cure rates has been seen [2]. Surgery and platinum-based therapies are the current standard of care for ovarian cancer management. Thus, new approaches to ovarian cancer treatment are desired. As ovarian tumors have previously been shown to be immunogenic [3] immunotherapeutic strategies, including vaccines, adoptive cell transfer, and immunomodulatory drugs, have recently been presented as possible methods of combating ovarian cancer [4, 5].

Multiple lines of evidence indicate that T cells play a role in the control of ovarian cancer progression. For instance, T cell accumulation in ovarian cancer is a positive prognostic factor for ovarian cancer survival [3]. In an early T cell transfer trial by Fujita et al., administration of autologous tumor infiltrating lymphocytes (TILs) to ovarian cancer patients in the adjuvant setting (after surgical resection and subsequent cisplatin-chemotherapy) resulted in a prolonged disease-free survival and increased the 3-year survival rate, supporting the notion that T cell transfer can actively inhibit ovarian tumor growth [6]. Moreover, administration of TILs (alone or in combination with cisplatin-containing chemotherapy) after a single dose of cyclophosphamide was shown to induce objective cancer regressions in some patients with existent chemotherapy-naïve or recurrent ovarian cancer as well [7]. These reports rationalize the use of adoptive T cell therapy as a means to bolster anti-tumor immune responses, and control the progression of ovarian cancer.

1.1.2 Adoptive immunotherapy

Breaking tolerance to self-antigens is a major obstacle in the application of immunotherapy to solid malignancies. Vaccine strategies aimed at harnessing endogenous anti-tumor T cells are limited by the T cell receptor (TCR) repertoire which can be deleted within the thymus as part of central tolerance or rendered non-functional by post-thymic mechanisms of peripheral tolerance. One approach designed to overcome these obstacles is adoptive immunotherapy, a term used to describe the transfer of immune cells for the treatment of cancer or infectious disease [8]. This therapeutic approach is already demonstrating impressive early clinical results [9-11]. With adoptive immunotherapy, therapeutically effective T cells can be engineered to recognize tumors. For example, one strategy is to identify therapeutically effective T cell clones and then to clone the heterodimeric TCR and express it in other T cells, thereby creating bispecific T cells with reactivity defined by the original TCR and the clone TCR (reviewed in[12]). Kessels and coworkers demonstrated the potential of this approach using a mouse model of cancer. Mouse T cells engineered to express a defined TCR were shown to be fully functional; capable of protecting against tumor challenge; and effective at targeting metastatic lesions. Moreover,

the T cells were shown to expand more than 1000 fold after *in vivo* antigen encounter and to traffic to tumor sites [13].

An alternative strategy to produce genetically engineered T cells involves the development of 'T-bodies' or chimeric antigen receptors (CARs). CARs combine the effector functions of T lymphocytes with the ability of antibodies to recognize distinct surface antigens in a non-MHC restricted manner. For example, CARs usually encode an extracellular single chain variable fragment (scFv) antibody, containing the V_H and V_L chains joined by a peptide linker of approximately 15 amino acid residues. This extracellular domain is then linked to an intracellular signaling domain that mediates T cell activation (reviewed in[14]). As a result, CARs can be used to redirect T cells to recognize an intact membrane protein independent of antigen processing.

The *in vivo* persistence, expansion, and functional capacity of adoptively transferred engineered T cells is dependent on two discrete signals mediated by cell surface receptors. The primary "activation" signal is produced by ligation of the TCR with an MHC-peptide complex. The second "costimulatory" signal is generated by ligation of a costimulatory molecule on the T cell surface with its cognate ligand on the surface of an antigen presenting cell. Several T cell costimulatory molecules have been identified including members of the immunoglobulin superfamily (CD28) and members of the tumor necrosis factor (TNF) superfamily (e.g. CD40L, CD134 [OX-40], and CD137 [4-1BB])[15].

Because signaling through the cytosolic domain of the scFv-TCRζ single chain construct does not fully replicate the multichain TCR signaling complex, chimeric antigen receptors bearing only the TCRζ signaling modules are not sufficient to drive proliferation or cytokine production in peripheral T cells. However, 4-1BB, a T cell co-stimulatory receptor induced by TCR activation, is critical for long-term proliferation of CD8 cells whereas CD28 is essential for sustained CD4 cell proliferation [16, 17]. Consistent with this finding, we have found that "bipartite receptors" comprised of TCRζ and either CD28 or 4-1BB signaling modules substantially improve the function and proliferation of T cells *in vivo* [17]. Our team of PENN investigators has applied this strategy to the development of CAR T cells specific for CD19 (CART19) and demonstrated the long-lived persistence of CART19 cells in patients with treatment-refractory leukemia [9, 11]. In a proof-of-concept study, we have demonstrated that T cells expressing a CD19-specific CAR (CART19) can have potent anti-leukemic effects in patients with advanced, chemotherapy-resistant [9, 11, 18-20]. Using a patient's own T cells, we engineered autologous T cells to permanently express a CD19-specific CAR using a lentiviral vector [21]. We found that CART19 cells upon adoptive transfer by intravenous administration can persist for more than 5 years in some patients with advanced, chemotherapy-resistant leukemia. Importantly, the CART19 cells eliminated leukemic CD19+ B cells as well as normal CD19+ B cells in responding patients with a resultant hypogammaglobulinemia that was

an expected adverse event. In August 2017, the FDA approved CART19 cells (Kymriah) for the treatment of acute lymphoblastic leukemia.

We have also applied a similar approach to develop a CAR specific for alpha folate receptor [17]. Here, we have used the same type of lentiviral transduction system and the same type of CAR construct as used in the CART19 cells, comprised of an alpha folate receptor specific scFv fused to the 4-1BB and CD3z signaling domains, to generate MOv19-BBz CAR T cells. The main difference between the anti-CD19 CAR and anti-aFR CAR constructs rely on the origin of the scFv portion of the construct which is specific to the target protein.

1.1.3 α Folate Receptor (αFR)

The α-isoforms of the folate receptor (FR) is a glycosylphosphatidylinositol-anchored membrane proteins that bind folic acid with high affinity (Kd ~1 nM) and mediate the cellular uptake of this vitamin and drug conjugates thereof via receptor-mediated endocytosis. The significance of the α-isoform of folate receptor (aFR) as a tumor marker was discovered in 1991 when amino acid sequence analysis of a protein enriched on the surface of a human ovarian carcinoma cell line was shown to be the aFR [22]. Monoclonal antibodies (MOv18 and MOv19) that react with the aFR revealed that it was expressed on a majority of nonmucinous ovarian carcinomas; however, little to no reactivity was detected on nonepithelial tumors and normal tissues [22]. Subsequent analyses have shown elevated aFR expression in approximately 90% of ovarian carcinomas as well as numerous other cancers, including endometrial, kidney, lung, mesothelioma, breast, brain, and myeloid leukemia [23-33]. Of note, chemotherapy does not alter expression rates in the remaining vital tumor tissue, indicating that folate-targeted agents can have a place in the treatment for ovarian cancer, before as well as after chemotherapy [34].

By contrast, aFR low-level expression in normal human tissues is limited to the luminal surface of cells located in the bronchial epithelium, renal tubules and the choroid plexus, intestinal brush-border membranes, type 1 and type 2 pneumocytes of the lung, salivary glands, parathyroid and placental tissue [35-41]. It is notable that aFR is expressed on the luminal surface of epithelial cells and therefore generally not in contact with folate circulating in the blood. Because of this polarized luminal surface expression, the sites where FRα is expressed are not accessible by circulating antibodies or folate-chemotherapeutic agents, as revealed by PET imaging of radiolabeled antibodies and folates, which visualized only tumor sites (reviewed in [42]). Further, on-target toxicity has not been observed in animals or humans treated with aFR targeted agents [43], as detailed further below. Because of this polarized luminal surface expression, healthy tissue sites expressing low levels of aFR are also not expected to be attacked by T cells recognizing surface αFR protein via a CAR.

1.1.4 Rationale for using lentivirus vector

A self-inactivating lentiviral vector (LV) will be used to transfer the CAR constructs into autologous T lymphocytes by ex vivo transduction. Lymphocytes will be isolated from leukapheresis product by elutriation and transduced with the LV. Lentiviral vector-mediated transduction of T lymphocytes isolated from the peripheral blood has been previously tested in other clinical trials to date by our UPENN group and other investigators.

For an increased safety of T cell products modified by LV transduction, FDA recommends that patients with chronic infections (HIV, HBV, and HCV) be excluded. The main rationale for this exclusion was that these viruses may get co-activated during the manufacturing process and contaminate the T cell product; additionally, chronic infections can serve as trigger for autoimmunity and thus, ex vivo activation and expansion of T cells from patients with chronic infections may enhance the frequency of autoimmune T

cells in the T cell product and potentially result in autoimmunity. Developing autoimmunity may not be an important consideration in cancer patients; however, this would make efficacy data interpretation challenging (biased toward increased efficacy). Additionally, patients with chronic infections have compromised immune system and T cell biology, and we think this patient subpopulation would not accurately reflect the safety profile of genetically modified T cells. Moreover, this patient subpopulation may introduce outliers from the manufacturing feasibility perspective. The variations that these patients may introduce in the data analysis can be studied in a follow-up study following the establishment of the safety profile for CAR modified T cells.

In collaboration with VIRxSYS, UPENN investigators performed the first trials using autologous T lymphocytes transduced with LV in HIV subjects; these were carried out at the UPENN under the direction of Dr. Carl June. No serious adverse events related to the infusion of these modified cells were found during the studies [44, 45]. Moreover, no adverse events related to LV transduction were noted on long-term follow-up of 65 subjects administered 263 infusions with some being followed for over 8 years [46]. Another trial for HIV subjects and a number of others in cancer patients have been opened at UPENN and no adverse events related to the use of LV in T cells have been noted to date. To our knowledge, no such events have been reported by other investigators either.

1.1.5 Lymphodepletion

Adoptive immunotherapy strategies may be able to capitalize on homeostatic T cell proliferation [47], a recent finding that naive T cells begin to proliferate and differentiate into memory-like T cells when total numbers of naive T cells are reduced below a certain threshold [48, 49]. Lymphodepletion eliminates regulatory T-cells and other competing elements of the immune system that act as “cytokine sinks”, enhancing the availability of cytokines such as IL-7 and IL-15 [50]. This hypothesis has been tested clinically in patients with metastatic melanoma refractory of conventional treatments [51]. The patients received a lymphodepleting conditioning regimen consisting of cyclophosphamide (60mg/kg x 2 days) and fludarabine (25 mg/m2 x 5 days) prior to adoptive transfer of T cells. Patients with myeloma, NHL, and CLL have been treated with infusions of ex-vivo co-stimulated and expanded autologous T cells after lymphodepleting chemotherapy, and observed improved engraftment [9, 11, 20, 52, 53].

Although it is fairly well established that lymphodepleting chemotherapy aids in the engraftment of infused T cells, it is not clear that lymphodepletion is absolutely required for effective T cell therapies, particularly when the T cell product is optimally cultured and has adequate potency. Lymphodepletion has been established in trials of infusions of tumor-infiltrating T cells (TILs) that have been extensively cultured *in vitro* prior to infusion; TILs are likely much less potent T cells for several reasons: 1) their T cell receptors are generally of low-avidity, 2) they have had prolonged exposure to antigen both in the host prior to harvesting and in the laboratory, 3) the culture conditions in the laboratory have made them dependent on big concentrations of cytokines, and 4) they are exhausted and have minimal proliferative potential. In our studies of RNA electroporated biodegradable anti-mesothelin CAR in T cells (14 subjects), we have seen transient responses even in the absence of lymphodepleting chemotherapy, despite the lack of proliferative capacity of the active cell product.

Lymphodepleting chemotherapy has been used on nearly all CAR T cell clinical trials. While initial studies allowed investigators to choose different chemotherapy regimens for different patients based on their prior treatment histories, more recent studies have been more prescriptive with the recognition that the lymphodepletion regimen affects clinical activity and toxicity. For example, Turtle *et al.* compared results obtained in sequential cohorts of non-Hodgkin lymphoma patients treated with a CD28-based second-generation anti-CD19 CAR following cyclophosphamide with or without fludarabine (Cy vs Cy/Flu) [54].

Subjects receiving Cy/Flu were more likely to have a complete response (50% vs 8%) and exhibited more robust *in vivo* proliferation and more durable *in vivo* persistence. Cy/Flu was also associated with higher frequency of severe CRS and neurotoxicity, though this toxicity differential was only apparent in the highest cell-dose cohort. These data suggest that fludarabine contributes to *in vivo* CAR T cell expansion and persistence, leading to increased efficacy but also perhaps increased toxicity. However, fludarabine is likely just one of many factors (e.g., cell dose, CAR design specifications, target antigen expression, disease burden, pre-manufacturing T cell phenotype) contributing to efficacy and toxicity profile of CAR T cell treatment regimens. The optimal lymphodepletion regimen likely varies by CAR T cell product and clinical setting and will need to be determined empirically through clinical investigation.

Cyclophosphamide and fludarabine used in combination with adoptively transferred lymphocytes for the treatment of neoplasia induce modulation of several cytokines and homeostatic proliferation of the transferred lymphocytes, promotes homing of those lymphocytes to secondary lymphoid organs, and contributes to *in vivo* T cell persistence. This provides a rationale for combining adoptive immunotherapy with chemotherapy [55, 56]. The main goal of using both cyclophosphamide and fludarabine is to achieve lymphodepletion that may enhance engraftment of adoptive T cells, while minimizing complications from neutropenia/myelosuppression. Based on previous experience in our CAR T cell program, we plan to use the approved doses for both cyclophosphamide and fludarabine in this trial.

1.1.6 Local versus systemic administration of CAR T cells

The route of CART administration is an area of interest [57, 58] due to the finding that trafficking of CART cells to solid tumors is limited [59]. We previously showed that local intratumoral administration of anti-aFR CAR T cells in mice bearing subcutaneous ovarian cancer is superior to systemic intravenous administration [17]. Similarly, a paper published by Memorial Sloan Kettering Cancer Center indicates that intrapleural (IP) delivery of anti-mesothelin redirected CAR T cells in mice is superior to systemic delivery [57]. This publication was followed by opening of a clinical trial testing the safety of anti-mesothelin redirected CAR T cells (iCasp9M28z T cells) with or without cyclophosphamide preconditioning (1.5 g/m^2) in patients with malignant pleural disease from mesothelioma, lung cancer, or breast cancer by intrapleural administration (NCT02414269). Other studies are also testing the merits of local/intratumoral route of administration (NCT02498912, NCT01818323) of CAR T cells in solid tumors. As indicated above, in a clinical trial conducted by Canevari and colleagues in the 1990s, activated T cells armed with an aFR-specific bispecific antibody were safely delivered into the peritoneal cavity of patients with recurrent ovarian cancer with 27% of evaluable patients experiencing cancer regression [60]. In addition, in a preclinical ovarian cancer xenograft model, we have shown that local delivery of MOv19-BBz CAR T cells results in enhanced and more rapid antitumor activity (**Figure 8**, **Section 1.3.1**, below), compared to systemic administration [17]. Similarly, intraperitoneal injection of EpCAm specific CAR T cells was recently shown to be effective in mediating antigen-specific killing of human ovarian cancer cells in vivo in a preclinical xenograft model [61].

Thus, we propose to test the safety and efficacy of IP CAR T cell administration, test the CART escape and persistence into the blood, and directly compare to the same parameters in the presence or absence of lymphodepleting cyclophosphamide + fludarabine as a preconditioning regimen at the same T cell dose.

1.2 Pharmacology of modified T cells

1.2.1 Mechanism of action

Redirected T cells have been shown in experimental models to bind to cells that express the target antigen. Over the past decade, CARs directed against a wide variety of tumor antigens have been developed [62, 63]. In the case of MOv19-BBz CAR T cells, they specifically and efficiently lyse aFR-expressing tumor cells (**Figure 5 middle graph**). Furthermore, MOv19-BBz CAR T cells engraft and eradicate aggressive aFR-expressing tumor cells in immunodeficient mice (**Figure 7-8,** below**)**. There are however several potential limitations to the CAR T cells: 1) the tumor must express the target antigen on the cell surface; 2) large amounts of shed or soluble antigen may inhibit the CAR T cells; 3) the chimeric receptor may be immunogenic, resulting in the elimination of the redirected T cells by the host immune system, even though the CAR structure of completely human sequences minimizes its immunogenicity. Indeed, anti-aFR specific antibodies (MOv18) and CAR T cells using mouse derived scFvs have been shown to induce humoral immune responses that dampen their activity [60, 64].

It is possible that lymphodepletion as administered to subjects in Cohorts 2 and 3 will aid in T cell engraftment. Our hypothesis is that T cell engraftment and persistence of MOv19-BBz CAR T cells will correlate with anti-tumor efficacy.

1.2.2 Absorption, distribution and metabolism

Lymphocytes have complex trafficking and survival kinetics, and after adoptive transfer several fates have been demonstrated: 1) margination; 2) exit from the peripheral blood with trafficking to lymphoid tissues; and 3) death by apoptosis. Following an intravenous dose, retrovirally modified and adoptively transferred T cells have been shown to persist in the circulation for at least 10 years in immunodeficient SCID patients due to the replicative competence of T cells [65]. Human CD8 CTLs have an elimination half-life from the peripheral blood of about 8 days, and this increases to about 16 days when low doses of IL-2 are given [66]. In patients with HIV infection, it has been found that the mean half-life of lentivirally modified CD4 T cells in the circulation of 17 patients following a single infusion was 23.5 (± 7.7) days in patients [67]. Adoptively transferred human T cells have been shown to traffic to tumor and secondary lymphoid tissues [51, 66, 68, 69]. Only limited studies are available with CAR T cell infusions in humans with cancer, and the survival of intravenously infused cells has been disappointing with most of the cells disappearing in a few days in the reported studies [70], with the notable exception of the CART19 cells that we recently reported [9, 11, 18, 20]. Additionally, our current experience with a different CAR T cell product targeting EGFRvIII antigen in glioblastoma patients indicates that genetically redirected T cells are detectable in the brain of treated patients at more than 6 months post-infusion. Alternatively, our recent clinical experience with a murine scFv based anti-mesothelin CAR product in patients with mesothelin-expressing tumors showed that the mesothelin CAR T cells were detectable up to, but not more than, one month after infusion. Some patients developed human anti-mouse antibody responses, suggesting that an immune response against the CAR T cells might account in part for the lack of longer CAR T cell persistence. These data indicate that CAR T cells have the potential to be long lasting *in vivo* without safety concerns.

1.2.3 Drug interactions

Autologous aFR specific CAR T cells are expected to retain many of the properties of natural polyclonal T cells. As such, they will be expected to be inhibited by immunosuppressive agents such as corticosteroids, immunophilins such as cyclosporine and tacrolimus, methotrexate, mycophenolate mofetil, alemtuzumab, daclizumab, ontak, and mTOR inhibitors such as rapamycin. Corticosteroids were able to eliminate human engineered T cells in two different trials [71, 72], and to block effector function in our

CART19 trial [11]. Lymphocytes are especially susceptible to cytotoxic and chemotherapeutic agents that are commonly administered for hematologic malignancies such as cyclophosphamide and fludarabine.

1.2.4 Immune elimination

It is likely that MOv19-BBz CAR T cells will be immunogenic because of epitopes derived from the mouse scFv and new epitopes that are created at the fusion joint of human signaling domains that are not normally juxtaposed. Immunogenicity of the CAR could lead to the rejection of the adoptively transferred T cells. The basis for this supposition is that human retrovirally-modified CTLs expressing a fusion protein consisting of hygromycin:HSV thymidine kinase were eliminated by host CTLs in patients with advanced HIV infection[73]; importantly, this immune mediated elimination was not accompanied by adverse effects and required 6 to 8 weeks to occur. Multiple other studies report CAR T cells elimination possible by immune mechanisms, most of them testing CAR constructs based on mouse sequences [64, 71, 74]. Indeed, early first generation aFR CAR T cells that used the MO18 scFv was shown to be immunogenic and elicit CAR specific serum Ig responses [64].

At UPENN, we have treated more than 29 patients with CAR T cells targeting mesothelin. The construct used in these studies was based on a mouse derived scFv (SS1) and thus, CAR T cells were expected to be rejected by humoral and /or cellular immune mechanisms. Our data to date indicate that CART-meso cells (ss1 construct) were able to persist transiently, but did not persist more than 28 days post-infusion (for lentivirus transduced T cells). Lymphodepleting chemotherapy as a preconditioning regimen may increase the persistence of the infused CAR T cells that contain mouse sequences.

1.3 Main Investigational Agent

The investigational agent in this protocol is MOv19-BBz CAR T cells, which are autologous T cells transduced with chimeric antigen receptor (CAR) composed of the MOv19 anti-alpha folate receptor specific scFv fused to 4-1BB and TCRzeta signaling domains (**Figure 2**). MOv19-BBz CAR T cells will be manufactured using the lentiviral transduction platform, the same as multiple other investigational cellular products tested at UPENN. The same technology that is used to transduce CART19 cells will be used to transduce MOv19-BBz CAR T cells (lentiviral transduction). The MOv19 scFv with specificity for aFR is derived from the murine MOv19 antibody developed by our research collaborators, Drs. Silvana Canevari and Mariangela FIgini [75]. The scFv redirects specificity of the transduced T cells to aFR expressing cells [17]. The intracellular signaling domain of the CAR molecule is comprised of the TCRζ and 4-1BB signaling modules previously tested in clinical studies [18, 19, 76, 77], both entirely of the native human sequences. The CAR receptors are “universal” in that they bind antigen in an MHC-independent fashion, thus, one receptor construct can be used to treat a population of patients with aFR antigen-positive tumors.

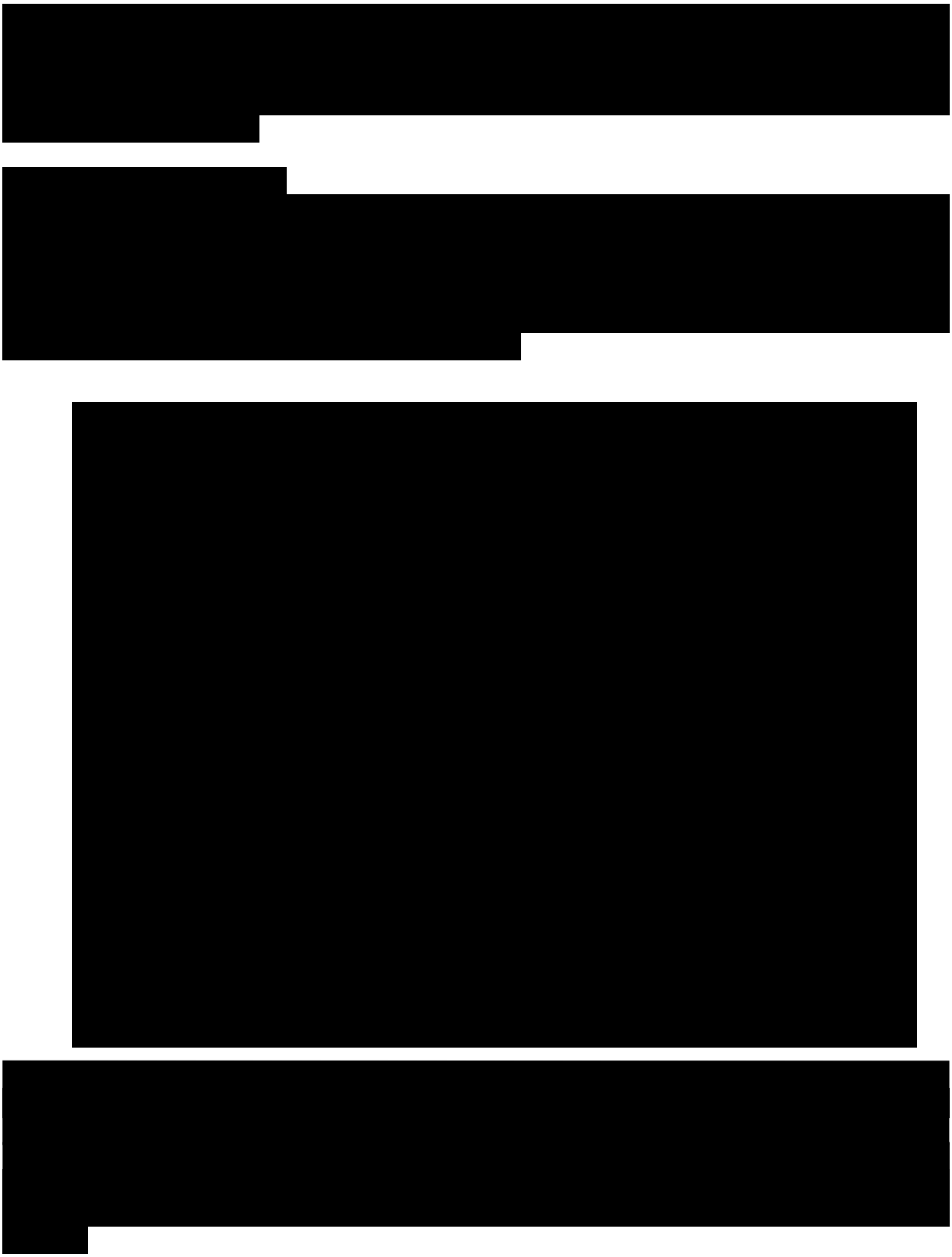
The engineered T cells will be manufactured at the UPENN Clinical Cell and Vaccine Production Facility (CVPF). At the end of cell cultures, the cells are cryopreserved.

1.3.1 Preclinical data

This section provides information regarding the design and scientific rationale for testing the MOv19-BBz CAR T cells in humans. The anti-alpha folate receptor CAR construct was generated in the Powell lab [17]. The MOv19 antibody was isolated from mice immunized with human cancer by Silvana Canevari and Mariangela Figini and shown to bind specifically to aFR [75]. The MOv19 scFv was subsequently cloned by the same group [78].

An extensive literature supports the use of engineered T cells for tumor immunotherapy in rodent tumor models [79-83]. Others have used soluble bispecific antibody comprised of an anti-CD3 antibody fused to the MOv19 antibody, which is functionally similar to the MOv19 scFv construct contained in the aFR CAR, to treat cancer patients with aFR-positive tumors, and found the compound to have adequate safety and some clinical activity [84]. Similarly, naked anti-aFR specific monoclonal antibody (Farletuzumab; MORAb-003) has been tested in Phase I, II and III studies with some clinical efficacy and a favorable toxicity profile [85, 86]. The incorporation of signaling modules such as CD28 and 4-1BB in T body constructs increases potency of the engineered T cells in pre-clinical studies [87-92]. Over the past decade improved T cell culture systems and T cell transduction conditions have been developed [93, 94]. The T-cell culture systems have been tested in phase I/II trials in patients with HIV infection and hematologic malignancies. The culture systems use anti-CD3 and CD28 costimulation and have proven to be efficient and feasible for large scale manufacturing, thereby overcoming a major barrier to adoptive immunotherapy. No significant safety concerns have emerged with well more than 1000 patients treated to date with CD4 and CD8 T cells, with and without genetic engineering with retroviral vectors [44, 52, 53, 95-100].

[redacted]



[redacted]

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1.3.2 Clinical data to date

1.3.2.1 CAR cells directed to alpha folate receptor

Early on in the development and testing of CAR T cell therapy, FRα emerged as an attractive target utilizing the chimeric antibody receptor (CAR)-T lymphocyte approach. In one of the first phase I studies of CAR T cells for cancer, patients with heavily pretreated ovarian cancer received adoptive transfer therapy using autologous or allogeneic MOv18-z aFR CAR T cells in combination with high dose Interleukin-2 (IL-2) [64]. This trial consisted of two arms, the first which received three cycles of escalating doses of CAR T cells expanded with aCD3 Ab and IL-2 for doses of 3 x 10^9, 1 x 10^{10} and 3-5 x 10^{10} respectively, combined with systemic IL-2. The second arm received 1-2 cycles (depending upon the number of cells available) of cells expanded with allogeneic PBMCs and IL-2, followed by allogeneic stimulation in vivo with live unirradiated PBMCs. Doses ranged from 4-169 x 10^9 cells, and two of six patients received 2 cycles. Cells were modified using a clinical retroviral vector provided by Cell Genesys containing the neomycin resistance gene, and were selected for using G418 after transduction. Grade 3 and 4 adverse events were observed in Arm 1, but were attributed to IL-2 administration. No serious adverse events were attributed to CAR T cell administration. Persistence of modified cells was poor, rapidly declined and did not exceed 3 weeks. No effect on tumor, as measured by imaging and CA-125 antigen was observed in all patients likely resulting from the poor CAR expression, poor in vivo persistence and poor function. In hindsight, the poor clinical results appeared to be explained by technical limitations in the study, such as low expression of the CAR construct due to the use of suboptimal gene transfer systems, and the short persistence of the transferred CAR T cells due to the absence of costimulatory domains in the CAR construct. Our preclinical results (**Section 1.4**) show that these limitations can now be overcome with the use of recombinant viruses for efficient gene transfer and the incorporation of a 4-1BB costimulatory domain into the intracellular tail of the aFR CAR construct [17].

1.3.2.2 Targeting aFR with antibodies, antibody-drug conjugates, and T cells

Various strategies used in the clinic for targeting the aFR protein in ovarian cancer has been reviewed [43]. A summary of the published results is provided in this section.

The safety of targeting αFR has been demonstrated by naked antibody therapy (farletuzumab) or radio-immunotherapy clinical studies, where toxicity has been generally low-grade and medically manageable [103]. Farletuzumab was also well-tolerated as single agent, without additive toxicity when administered with chemotherapy [104]. Similarly, combination farletuzumab/carboplatin/pegylated liposomal doxorubicin therapy was generally well tolerated, with no farletuzumab-related grades 3-4 adverse events [105]. In a Phase III randomized trial of farletuzumab at two doses versus placebo in 1100 women with ovarian cancer, the overall safety profile was comparable across all treatment groups, with no new safety signals identified in this study population [106].

In an antibody-guided radio-immunotherapy study, there was no on-target toxicity observed in 16 ovarian cancer patients treated with a single i.p. dose of ^{131}I-MOv18 but complete response (CR) was observed in five patients, no change (NC) in six patients, and progressive disease (PD) in five patients [107]. Unfortunately, these agents exhibited only modest single-agent activity and neither demonstrated

meaningful efficacy over chemotherapy alone when evaluated as part of combination regimens in Phase III trials.

The differential expression of aFR and its ability to internalize large molecules made the receptor well-suited for antibody-drug conjugate based therapeutic strategies. Antibody or folate conjugates targeting aFR have shown a similar safety profile in clinical trials. In phase I and phase I/Ib studies of folate immune (EC90 vaccine with GPI-0100 adjuvant followed by EC17, folate-fluorescein), folate immune was shown to be safe and well tolerated in patients with recurrent or metastatic RCC, but cancer responses were minimal [108, 109]. No dose-limiting toxicities were observed in the phase I/Ib study, and only 2 dose-limiting toxicities (DLTs) were observed in the Phase I trial: one hypersensitivity reaction (owing to an impurity in the batch of vaccine) and one case of acute pancreatitis, which are unrelated to the aFR target [108, 109].

More recently, dose-escalation in the first-in-human Phase I trial was completed [110]. This study included 44 individuals with aFR-positive solid tumors. Dose-limiting toxicities included grade 3 hypophosphatemia and grade 3 punctate keratitis. The principal treatment-related adverse effects included fatigue and diarrhea, with the majority of cases being mild (grade 1 or 2) and readily managed without requiring discontinuation of treatment. Grade 1 or 2 peripheral neuropathy was also seen, likely a consequence of the maytansinoid payload. Dosing was changed to utilize adjusted ideal body weight, after which the visual and corneal abnormalities were generally grade ≤2 and felt to be off-target and potentially associated with the payload. The strongest signals of clinical benefit were seen in patients with epithelial ovarian cancer, prompting an expansion cohort in this population. The phase I expansion study of the FRα-targeting antibody-drug conjugate mirvetuximab soravtansine (IMGN5=853; a humanized anti-FRα antibody linked to the maytansinoid DM4) in 27 women with heavily pre-treated ovarian cancer showed a confirmed objective response rate (ORR) of 22%, including two complete responses and four partial responses [111]. Adverse events were generally mild (≤grade 2) with keratopathy (48%), fatigue (44%), diarrhea, and blurred vision (each 37%) being the most common treatment-related toxicities. These toxicities were associated with action of the DM4 toxin, and were unrelated to aFR expression in those sites. One patient experienced grade 3 hypokalemia. Low-grade pneumonitis was observed in a small number of patients; grade I (n= 3; 11.1%) and grade II (n= 1, 3.7%), as was headache; grade I (n= 4; 14.8%) and grade II (n= 1, 3.7%). Of note, superior efficacy measures were observed in the subset of patients with the highest FRα levels in their tumor (ORR, 31%; progression-free survival, 5.4 months), which rationalizes the prescreening and selection of patients with tumors having baseline aFR expression prior to administration of aFR targeted therapies.

Patient T cells that target aFR have been administered in clinical trials of adoptive T cell transfer for ovarian cancer with promising results reported. A bispecific antibody approach for FRα-directed autologous T cells targeting FRα and CD3 in combination with IL-2 provided promising data for adoptive T cell transfer approaches [60, 84]. Patient T cells were activated outside of the body, and then armed with F(ab')2 fragments of the bispecific monoclonal antibody (MAb) OC/TR which is directed to the CD3 molecule on T lymphocytes and to the folate receptor on ovarian carcinoma cells. Intraperitoneal (IP) delivery resulted in significant clinical responses with a toxicity profile most related to IL-2 administration. Of the 19 patients evaluated by surgery and histology, three showed complete response, one showed complete intraperitoneal response with progressive disease in retroperitoneal lymph nodes, three showed partial response, seven had stable disease, and five had progressive disease. The overall intraperitoneal response rate was 27% (95% confidence interval [CI] = 10%-44%).

1.4 Toxicities associated with CART cells

1.4.1 Fatal SAEs with CARs

Two studies have reported fatal SAEs following CAR infusion in patients with malignancy. Brentjens et al designed a retrovirally-transduced CAR against the CD19 molecule for patients with B cell lymphoma [112]. The CD19 CAR was the second generation design containing CD28 and CD3ζ signaling domains. A total of 7 subjects have been treated on this protocol, 6 without SAE. However, subject four in this study was a 69 year old man with refractory CLL and who had a significant past medical history of myocardial infarction, coronary artery disease, hypertension, and chronic renal failure. This was the 4th patient in the study and the first one on the cohort undergoing lymphodepletion. This subject received pre-T cell conditioning with 1.5g/m^2 of cyclophosphamide followed 2 days later by infusion with genetically modified CD19 CAR T cells at 1.2-3x10^7 cells/kg. Twenty hours following T cell infusion, the patient developed persistent fever (transient fever was observed in the first 3 subjects on the study too) and hypotension that was rapidly followed by respiratory distress despite negative chest x-ray, hypoxemic respiratory failure, and acute renal failure. The family decided to remove further life sustaining therapies and the patient expired 44h post-T cell infusion. The post-mortem pathology report failed to support a diagnosis of tumor lysis syndrome as the primary source of renal failure. Analysis of serum cytokines revealed elevated levels of IL-2, IL-7, IL-15, and IL-12 following cyclophosphamide therapy which may have been secondary to a prior subacute infection exacerbated by the immune suppression associated with cyclophosphamide-mediated lymphodepletion. The authors concluded that concomitant sepsis was the most likely cause of death and attributed the etiology of the death as "possibly related" to CAR T cell infusion [112].

The second case of a fatal SAE related to CAR T cells was reported by the NCI group [113]. This study attempted to treat cancer patients with overexpressing ERBB2 tumors with an anti-**ERBB2 CAR** of 3rd generation (containing CD28, 41BB and CD3ζ signaling domains). The first subject in the study was a 39-year-old female with colon cancer metastatic to lungs and liver. The patient received lymphodepleting regimen (60mg/kg cyclophosphamide daily for 2 days followed by fludarabine 25mg/m^2 for the next 5 days) followed the next day by retrovirally-transduced 10^{10} ERBB2 CAR T cell (transduction efficiency 79%). At 15min post-infusion, the patient began to develop dyspnea and hypoxia with pulmonary infiltrates on chest x-ray. The patient progressed into hypoxemic respiratory failure requiring mechanical ventilatory support, vasopressor-dependent hypotension, and cardiopulmonary arrest. The patient was initially resuscitated and started on high dose steroids, but despite aggressive supportive care, the patient expired 5 days after infusion. Serum cytokine measurements demonstrated a dramatic rise in pro-inflammatory cytokines (IFN-γ, TNF-α, IL-6, GM-CSF) within 4 hours of infusion consistent with a cytokine storm initiating multi-system organ failure. Dr. Morgan postulates that upon first pulmonary circulation passage [113], the CAR ERBB2 T cells bound to native low level expression pulmonary epithelial cell ERBB2 proteins [114], leading to CAR activation and pulmonary microvascular injury.

Other fatal SAEs have been reported. Two events occurred in April 2014 at the Memorial Sloan Kettering Cancer Center using CD19 specific CAR redirected T cells [115]. Fatal events have occurred at the University of Pennsylvania using CART-19 T-cells (a CD19-specific CAR using a lentiviral vector) in patients with acute lymphoblastic leukemia (ALL). Three of the first six adult ALL subjects infused on UPCC21413 died as a result of refractory Cytokine Release Syndrome (CRS) in the setting of intercurrent infections. Thereafter, the single dose administered in UPCC21413 was reduced to 1-5x10^7 CART19 cells. In the next six adult ALL subjects treated at the de-escalated dose, two died from an intracranial bleed and sepsis, respectively.

In July 2017, the FDA initiated the clinical hold of Juno's Phase II clinical trial of their CD19 CAR product (JCAR015), known as ROCKET, in adult relapsed or refractory B cell acute lymphoblastic leukemia after two patient deaths from cerebral edema that appear to be treatment-related [116]. This followed an early death that was determined to be due to confounding factors. The fludarabine preconditioning regimen was proposed as the problem, since cerebral edema as a toxicity was not prevalent in JCAR015 with cyclophosphamide preconditioning only.

In December 2017, another fatal event occurred in a mesothelioma patient treated with investigational CART cells targeting mesothelin. At 2 days after infusion, the patient developed respiratory distress progressing to hypoxemic respiratory failure not responding to standard of care treatment, and expired 5 days after the infusion. The investigation on this event is ongoing.

1.4.2 Non-fatal SAEs

Our group at UPenn experienced one life-threatening SAE of anaphylaxis following intravenous (IV) infusions of autologous T cells expressing an anti-mesothelin CAR. In that case, the subject was administered repeated doses of the same product, and upon infusion of the 3rd dose following a rest period, he developed an allergic (anaphylaxis) response to the T cell product. The results of this investigation were published [117].

As of December 2021, we have administered 1.4 x 10^7- 1.1x10^9 autologous CART-19 cells into over 500 patients on multiple clinical studies conducted at Penn and the Children's Hospital of Philadelphia under the University of Pennsylvania [redacted] and [redacted] Subjects experienced manageable toxicities mostly related to tumor lysis syndrome, cytokine release syndrome (CRS), and macrophage activation syndrome (MAS), and the expected on target toxicity of B cell aplasia. Tumor lysis syndrome is related to the type and burden of disease and is more frequently encountered in hematologic malignancies than solid tumors. MAS appears to be a reaction to immune activation that occurs from the CRS, and therefore should be considered a manifestation of CRS.

A more detailed presentation of the CRS /MAS clinical manifestations and subject management is provided in **Sections 1.6** and **5.3.1.4**.

1.5 Trial Rationale

Immunotherapy is a novel and promising approach for the treatment of solid tumors; immunotherapy with CART cells in particular has the potential advantage of targeted therapies that can invoke a rapid tumor response, and the advantage of long-lived responses that are the hallmark of engagement of the adaptive immune system such as memory T cells.

This Phase I study poses the hypothesis that targeting the aFR antigen that is widely and frequently expressed in multiple tumor types, particularly epithelial ovarian cancer, will be safe, feasible, and result in anti-tumor responses. Furthermore, this study addresses the questions of whether lymphodepletion is necessary for engraftment and persistence of MOv19-BBz CAR T cells in patients with solid tumors, and whether intraperitoneal administration is safe and feasible.

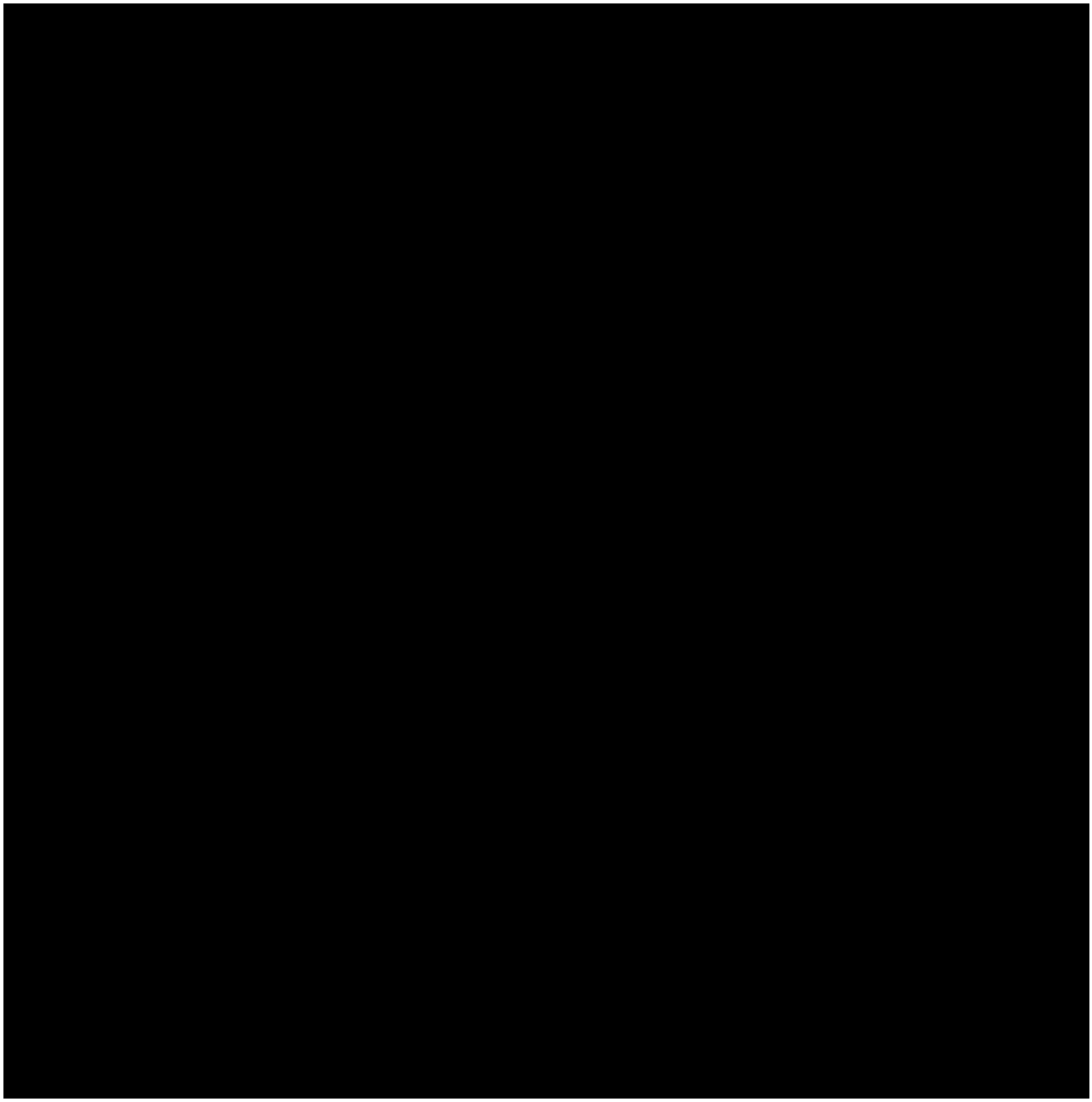
1.6 Potential risks and benefits

1.6.1 Risks of MOv19-BBz CAR T cells

This protocol is designed to determine the safety and feasibility of intraperitoneal administration of permanently modified CAR T cells that target alpha folate receptor. MOv19-BBz CAR T cells will be given as a single agent alone or in combination with a lymphodepleting dose of cyclophosphamide + fludarabine. Given that the patient populations recruited for this protocol have limited therapeutic options, we believe that the below risks are acceptable.

1.6.1.1 MOV19-BBz Expected Adverse Events

Our current safety experience with MOv19-BBz CAR T cells is included in **Table 1-1** below.



1.6.1.2 Off-tumor on-target toxicity

We expect minimal toxicity based on the restricted polarized expression of aFR which distributes in the luminal surface of tubular epithelium of the kidney, bronchial airway epithelium, choroid plexus, and placenta. This is further supported by previous clinical safety data specifically with aFR specific immunochemotherapy conjugates, antibody drug conjugates, radioimmunotherapy conjugates, with bispecific antibody redirecting T cells to alpha folate receptor and engineered T cells recognizing alpha folate receptor (reviewed in [43]). In spite of this luminal expression, the primary off-tumor on-target toxicity that may be anticipated is that engineered T cells will cause damage to sites of aFR expression including the bronchial epithelium, renal tubules, the choroid plexus, intestinal brush-border membranes, salivary glands, parathyroid and type 1 and type 2 pneumocytes of the lung.

The risk of pneumonitis resulting from involvement of the bronchial epithelium is anticipated to be lower than that of IV administration.

Evidence of on-target adverse events and immunopathology has not been reported in trials of various aFR targeted agents conducted over more than two decades. **Section 1.3.2.2** describes a recent phase I expansion study of a FRα-targeting antibody-drug conjugate, wherein adverse events were generally mild and unrelated to aFR targeting, however, low-grade pneumonitis was observed in a small number of patients; grade I (n= 3; 11.1%) and grade II (n= 1, 3.7%), as was headache; grade I (n= 4; 14.8%) and grade II (n= 1, 3.7%) [118]. While the mode of action resulting in these adverse events is not known, these are sites of aFR expression. As our CAR T cell approach is different in mode of action from the antibody drug conjugate, off-tumor toxicity may be expected.

There are two forms of “on-target” toxicity attributable to CAR T cells, one with rapid onset that results from synchronized activation of CAR T cells occurring during first pass through the vasculature, and another one that is dependent on biodistribution of CAR T cells trafficking to sites of antigen, a process that does not occur for at least 24 hours after infusion. The fatal case at the NCI was attributed to synchronous activation of 10^{10} CAR T cells encountering the specific ERBB2 antigen upon passing through the pulmonary capillary bed that resulted in rapid and profound systemic cytokine release following intravenous infusion [113]. We think that this scenario is not expected for MOV19-BBz CAR T cells, as aFR is expressed on the apical surface of vascular endothelial cells of the lungs and unavailable to aFR targeted

agents, and the biodistribution of CAR T cells administered into the peritoneal cavity will reduce lung accumulation and preferentially accumulation in tumor. The second type of toxicity reported with CAR T cells is consequent to cells trafficking following initial biodistribution and encountering cognate antigen on normal tissues. This kind of toxicity develops with delayed kinetics and in a non-synchronous fashion.

This type of toxicity developed 4-7 days after infusion of anti-CAIX CAR T cells upon activation by antigen present on bile ducts, and was easily managed with a short course of adrenal corticosteroids (Lamers et al., 2006, Lamers et al., 2011). aFR is reported to be expressed in the bronchial epithelium, renal tubules, the choroid plexus, intestinal brush-border membranes, salivary glands, thyroid and type 1 and type 2 pneumocytes of the lung, thus the encounter of the antigen requires MOV19-BBz CAR T cells to traffic to these sites. Given the known aFR distribution (i.e. not expressed within the vascular system) and safety of aFR targeted approaches to date, we do not anticipate immediate toxicity, but rather only the potential for delayed toxicity that may become evident several days post-infusion.

Of note, in our UPENN studies testing autologous T cells re-directed to mesothelin with an anti-mesothelin CAR (SS1 scFv), we have not observed any significant serosal toxicity (pleuritis, peritonitis, pericarditis).

Management. In the event of aFR reaction on normal tissue and inflammatory process leading to fluid accumulation, these cavities can be quickly and readily accessed in a minimally invasive fashion to remove the fluid as anti-lymphocyte therapy is initiated. T cell ablating therapies including corticosteroids, chemotherapy such as cyclophosphamide, or immunotherapy such as alemtuzumab may also be considered at the investigators' discretion.

1.6.1.3 Robust (but not leukemogenic) T cell proliferation

Participation in this study will expose the patient to genetically engineered autologous T cells. The signaling domains in the CARs could mediate uncontrolled T cell proliferation; however, we have not observed this toxicity in our pre-clinical models or other UPenn clinical trials. In the context of this protocol, it is possible that the T cells will proliferate in response to signals from the aFR expressing cancer and normal cells. This could be beneficial or harmful depending on the extent and the nature (local or generalized) of proliferation.

Management. In this case, corticosteroids and chemotherapy would be given to eradicate the CAR cells; this has worked in previous cases [71]. T cell ablating therapies including corticosteroids, chemotherapy such as cyclophosphamide, or immunotherapy such as alemtuzumab may also be considered at the investigators' discretion. Leukemogenic T cell proliferation which is uncontrolled, clonal, and potentially related to insertional mutagenesis from transduction is discussed under "Clonality and insertional oncogenesis" below. Robust T cell proliferation can be associated with cytokine release syndrome.

1.6.1.4 Cytokine release syndrome (CRS)/Macrophage Activation Syndrome (MAS)

An expected toxicity of cell therapies in general is CRS. Subjects treated with CART19 therapy at UPenn have often developed a CRS and MAS. The risk factors for development of these syndromes are still under investigation, but high baseline tumor burden was shown in ALL to be a risk factor [119]; it is not yet clear whether this toxicity will be manifested in subjects treated with CARs directed to other antigens such as aFR; it is unknown if the manifestations of the CRS in solid tumor subjects will be similar with that in CART19 treated subjects. This study will provide such new knowledge; due to the occurrence of severe

CRS in CART19 studies, it is therefore considered a possible risk in this protocol. The CRS characteristics, CRS grading, and management of CRS in CART19 studies is presented next and can be used to guide the PI if such toxicity is to occur in this protocol.

CRS overview: CRS is a potential risk in this study and may result from on-target toxicity, as has been observed in other CAR T cell studies. The experience gained from the CART19 studies at UPenn CCI indicates that CRS development likely correlates with efficacy, CRS grading directly correlates with tumor burden, and kinetics of onset are gradual within days following CART cells infusion. The CRS signature is elevation of cytokines, most prominently IL-6, IFN-γ, IL-8, solCD25, solIL6R, solgp130, and, to a lesser extent, IL-2, IL-10, and TNF [119]. It is still unknown whether CRS/MAS is beneficial or harmful to the anti-tumor response. Elevations in clinically available markers of inflammation including ferritin and CRP have also been observed to correlate with the clinical CRS syndrome.

CRS clinical manifestations: CRS diagnosis is based on clinical symptoms and events. The CRS typically starts with several days of fevers. In all cases, evaluations for infections are done. Fevers tend to be spiking and can be associated other clinical manifestations such as fatigue, anorexia, nausea, vomiting, diarrhea, myalgias, arthralgias, headache, rash, hypotension (occasionally requiring pressor support), tachypnea, hypoxia (occasionally requiring ventilator support), altered mental status including delirium confusion (in several patients) and word finding difficulties, evidence of disseminated intravascular coagulation, as well as MAS. Additional symptoms of CRS may also include rigors, sweating, dyspnea, and seizures. In some cases, CRS, TLS and hypotension have led to acute kidney injury and several patients have required at least transient dialysis. The CRS has been effectively abrogated with anti-cytokine directed therapy, including tocilizumab in most patients. Five patients on CART19 trials at UPENN have died of complications related to refractory CRS, in some cases this being associated with concomitant infections. In addition, it is unclear if treating the CRS with anti-cytokine directed therapy adversely impacts the anti-tumor response.

Features consistent with MAS or HLH have been observed in patients treated with CART19, coincident with clinical manifestations of the CRS. MAS appears to be a reaction to immune activation that occurs from the CRS, and therefore should be considered a manifestation of CRS. MAS is similar to Hemophagocytic lymphohistiocytosis (HLH); it is a reaction to immune stimulation by infection, autoimmune diseases or other precipitants, but is distinguished from familial or genetically mediated HLH. There are no definitive diagnostic criteria for MAS, but it is typically diagnosed by meeting HLH criteria. Some but not all features of MAS are typically observed. The clinical syndrome of MAS is characterized by high grade non-remitting fever, cytopenias affecting at least two of three lineages, and hepatosplenomegaly. It is associated with biochemical abnormalities, such as high circulating levels of serum ferritin, soluble interleukin-2 receptor (sCD25), and triglycerides, together with a decrease of circulating NK activity. Other findings include variable levels of transaminases up to signs of acute liver failure and coagulopathy with findings consistent with DIC. A pathologic feature of MAS is the presence of hemophagocytic CD163+ macrophages (HPC) in bone marrow or lymph-node aspirates.

MAS diagnosis is based on the fulfillment of criteria established in 2004 for HLH associated with autosomal recessive disorders (familial HLH, fHLH). A diagnosis of non-familial HLH/MAS is made by having 5/8 criteria:

- Fever
- Splenomegaly
- Cytopenias (affecting 2: 2 lineages in the peripheral blood; hemoglobin <9, plts <100k, ANC <1000)
- Fasting triglycerides 2: 265 mg/dL, Fibrinogen: = 1.5 g/L

- Hemophagocytosis in bone marrow or spleen or lymph nodes
- Low or absent NK-cell activity
- Ferritin > 500 g/L
- Soluble CD25R > 2400 U/L

Supportive clinical criteria include neurologic symptoms and cerebrospinal fluid pleocytosis, conjugated hyperbilirubinemia, and transaminitis, hypoalbuminemia and hyponatremia. Typically high fevers, cytopenias, and when performed hemophagocytosis in the bone marrow is observed (though marrow specimens at the time of the reaction are not often taken). Soluble CD25R and NK cell activity are not standard tests, though samples are taken for retrospective CD25R analysis. Therefore, patients may not meet strict definition of HLH/MAS, but given the constellation of findings, and the consistent dramatic elevation in Ferritin, this is indeed the reaction associated with the CRS.

In addition, some subjects have become confused and disoriented, have had seizures or have become unresponsive. These side effects may be caused by the CRS and MAS as in most instances, they resolved when the CRS was treated. However, one subject experienced a cognitive impairment which took over a month to resolve. While this might be a result of the chemotherapy that the individual received, we cannot exclude a role of T cells.

Grading of CRS: The Common Terminology Criteria for Adverse Events (CTCAE) grading system was originally developed to capture a cytokine syndrome occurring during infusional therapy; therefore, it is inadequate to capture the delayed CRS that occurs after CART cells infusions. The University of Pennsylvania has modified the CTC grading specifically to capture toxicity for protocols using CAR T cells. MAS/HLH observed signs and symptoms are a manifestation of CRS and will therefore not be graded separately (See **Table 9-1** in **Section 9.2**).

Management of CRS is described in **Section 5.3.1.4**.

1.6.1.5 Immunogenicity favoring rejection

Immunogenicity of this CAR construct is not known and thus, immunogenicity will be monitored as a secondary exploratory correlative endpoint. MOv19-BBz CAR T cells may be immunogenic due to the incorporation of the murine MOv19 scFv into the CAR construct and possible novel epitopes potentially created at the juxtaposition of various fragments within the CAR construct. A Mov18 based CAR was shown to induce a serum Ig response against the CAR [64]. In case of immune responses directed against the CAR constructs, it is expected that MOv19-BBz CAR T cells will be rejected. This rejection has not had clinical consequences in previous trials [71, 120].

Anaphylaxis. Anaphylaxis resulting from the infusion of a single dose of lentivirus transduced CAR T cells has not been reported to date. Our group at UPENN experienced one life-threatening and related serious adverse event of anaphylaxis following intravenous (IV) infusion of autologous T cells expressing the anti-mesothelin CAR under a separate clinical protocol (UPCC# 17510). This was the 24th infusion of RNA CART-meso out of a total of 101 infusions administered on three clinical protocols (UPCC#17510, 21211, 08212). We have not experienced any other serious adverse events of anaphylaxis. The cell product was prepared using RNA electroporation technology rather than vector transduction in order to acquire a transient CAR expression T cell phenotype. The SAE was triggered at several minutes after mesothelin-CAR T cell infusion and developed into a cytokine storm with high levels of serum IL-6. Of note is that the subject had been safely administered two other RNA CART-meso cells infusions 42 days before the one triggering the SAE.

The results of our investigations indicated that this was an anaphylaxis reaction mediated by anti-mouse antibodies developed following the first two infusions. Due to this incidence and to assure subjects safety, we modified our RNA CAR protocols infusion schedule to remove prolonged rest periods between infusions, reduce the therapy to one cycle of 2-3 weeks, and exclude subjects who had received products of murine origin. Consequently, no other reaction has been noted in a total of 101 infusions of RNA CART-meso cells. This risk of anaphylaxis is reduced in this protocol due to the administration of one MOv19-BBz CART cell infusion. If it occurs, anaphylaxis will be managed with epinephrine, volume resuscitation, corticosteroids, and other supportive care as needed (oxygen, ventilation, beta2 agonists for bronchoconstriction, etc.).

1.6.1.6 Tumor lysis syndrome (TLS)

The risk of TLS is dependent on the disease and burden of disease, but in most cases, this risk will be low. This generally does not occur in patients with solid tumors. TLS resulting in renal insufficiency, or rapidly rising uric acid, or evidence of organ dysfunction will be managed with fluids and rasburicase as clinically indicated and determined by the treating physicians; other supportive care as needed.

1.6.1.7 Neurologic toxicity

Neurologic toxicity has emerged as a risk of CAR T cell therapy. Neurotoxicity after CAR T cell therapy has been described as biphasic, with an initial period of susceptibility occurring amidst systemic CRS and a second period of susceptibility occurring days later, often after resolution of CRS [123]. Manifestations range from mild, subtle signs such as diminished attention and impaired handwriting to more severe abnormalities such as seizure, disorientation, and somnolence. In its most severe form, cerebral edema develops and is potentially fatal. Neurotoxicity in the form of encephalopathy along with various focal neurological deficits (including word finding) have been observed with CART19. The mechanism underlying the neurotoxicity of CAR T cells is uncertain, though the similarity in syndromes observed with CARs directed against different antigens argues against a target-specific effect. The link between biomarkers of endothelial activation and severe CRS/neurotoxicity suggest that neurotoxicity is mediated by cytokine-induced endothelial dysfunction. No mechanism for the neurotoxicity of CAR T cells has been definitively established, however, and it is uncertain whether the findings cited here from other CAR T cell products can be extrapolated to the CAR T cells employed in this study.

1.6.1.8 Intraperitoneal access administration of CAR T cells

Local administration of MOv19-BBz CAR T cells is thought to reduce the risk of CART cells binding to low aFR levels that might be present on bronchial epithelium, renal tubules, the choroid plexus, intestinal brush-border membranes, salivary glands, thyroid and type 1 and type 2 pneumocytes of the lung and thus, decreasing the risk of on-target toxicities.

Because the infusion criteria (**Section 6.6**) are evaluated immediately prior to cell infusion, one additional risk of IP catheter placement is that a subject who is deemed inappropriate for CAR T cell administration undergoes catheter placement.

Intraperitoneal Access. Some subjects with ovarian cancer may already have a catheter in place; however, in the event a catheter must be placed for Intraperitoneal (IP) administration, placement of the catheter will be performed by Interventional Radiology (IR) on the day of planned MOv19-BBz CAR T cell infusion. Percutaneous techniques will be utilized in this protocol. Percutaneous insertion with radiologic guidance has the advantage of minimally invasive and correct catheter positioning in the lower abdomen. Safely accessing the intra-abdominal space for an individual patient may or may not require administration of a small volume of saline or contrast.

Risks associated with the procedure include, but are not limited to, pain or discomfort at the needle insertion site, bleeding at the site, internal bleeding, injury to a blood vessel, organ puncture, and infection which may result in an infection of the blood stream. The development of any infection may result in the need for intravenous antibiotics. X-ray contrast material may be used at the time of catheter insertion. Risks associated with the X-ray contrast material include an allergic reaction. Moderate sedation Moderate sedation may be used during the catheter placement. The medications used for the moderate sedation are associated with the risks of aspiration (inhaling food or liquid into your lungs) or respiratory depression. In addition to these potential risks associated with the procedure, the X-ray contrast material, and the moderate sedation medications, there may be other unpredictable risks including death.

Subjects will be asked to sign a standard hospital consent form for this procedure. The subject will be closely monitored during the procedure by the anesthesia team and/or the primary proceduralist's team and subsequently by the research team as per protocol.

Intraperitoneal Administration of CAR T cells. The risk of peritoneal inflammation with IP administration is anticipated to be higher than that of IV administration given the direct administration into the peritoneal cavity.

1.6.1.9 Clonality and insertional oncogenesis

There is a risk that people who receive gene transfer may develop new tumors derived from their genetically modified cells. This risk is primarily associated with viral gene transfer vectors that integrate into the cellular DNA where they may dysregulate genes controlling proliferation. Transformation has not been observed following adoptive T cell transfer in hundreds of cancer and HIV patients receiving gamma-retroviral modified T cells treated on multiple protocols at many academic centers, and in the 21 HIV patients treated with lentiviral modified T cells treated at University of Pennsylvania [44, 45]. Additionally, no adverse events have been reported on 65 subjects infused with 263 T cell infusions of autologous T cells modified with LV, some of them being followed for over 8 years [46].

To date, we are not aware that clinically evident insertional mutagenesis of T cells has been reported following adoptive transfer of engineered T cells. Lentiviral vectors may have a lower risk than retroviral vectors based on several considerations. Monitoring for T cell clonal outgrowth will be performed by Q-PCR analysis for CAR-expressing cells and/or flow cytometric analysis (if feasible), and by CBC count. If during long-term follow-up ≥ 1% of the subject's sample is positive for vector sequences by qPCR, then the subject will be asked to return for a confirmatory blood test prior to the next study visit. If ≥ 1% of the subject's sample is positive upon the receipt of the confirmatory qPCR result, then the genomic vector integration sites will be determined. Identified vector integration sites will be evaluated using bioinformatics approaches to determine if the integration events are in regions with known relationships to human cancers (i.e. near oncogenes). A summary of any integration site analyses will be presented in the annual report to the FDA. If oligo- or monoclonality of vector integration site is observed, this data

will be reported as an informational amendment to the IND with best efforts to submit this amendment within 30 days of data confirmation.

1.6.1.10 Replication-competent lentivirus (RCL)

It is theoretically possible that RCL may be generated during the MOv19-BBz CAR manufacturing phase or subsequently after introduction of vector-transduced cells into the patient. However, our CAR T cell manufacturing platform utilizes a third-generation lentiviral vector system that has been designed to eliminate such risk, and all viral vectors used for clinical T manufacture are confirmed negative for RCR/L via sensitive detection assays as part of vector lot release testing. As such, RCL has not been detected in any of the T cell products or subjects samples tested under IND#14802 to date. This aligns with our extensive experience manufacturing lentiviral-transduced T cell products using similar or identical lentiviral vector design. As reported by Marcucci et al., 2018, RCR/L has not been detected in any products manufactured by UPenn Clinical Cell and Vaccine Production Facility (CVPF) using 17 different clinical vector lots under 8 INDs, either by qPCR detection assay or by the biological RCR assay. A total of 375 T cell products were included in this analysis, including 351 that were manufactured using third generation lentiviral vectors similar to that utilized in the above referenced IND. Since the publication of Marcucci et al. 2018, more than 170+ additional lentiviral-transduced CAR T cell products manufactured by UPenn CVPF have been tested by qPCR and met the release specification of < 50 average copies VSV-G per μg DNA. Five of these were also subjected to biological RCL testing, which confirmed the absence of RCL. These findings are confirmed by another publication reporting that 460 transduced T cell Products across 26 clinical trials were negative for RCR/L (Cornetta, Duffy, Turtle, et al. 2018).

The Marcucci et al. publication also included data from long-term monitoring for vector sequences in 305 infused subject samples from UPenn clinical trials. No evidence of RCR/L in any of the subject samples evaluated was found, with almost 195 years of cumulative post-infusion follow-up time (Marcucci et al. 2018). Similarly, Dr. Kenneth Cornetta's group was unable to detect RCL in 296 clinical trial subjects screened for RCL post-infusion (Cornetta, Duffy, Turtle, et al. 2018), along with other similar historical analyses (Scholler et al. 2012; Mohanlal et al. 2016). To date, there have been no reports of confirmed RCR/L-positive results reported in the literature for manufactured T cell products or post-treatment patient samples (Bear et al. 2012; Cornetta, Duffy, Feldman, et al. 2018; Cornetta, Duffy, Turtle, et al. 2018; Marcucci et al. 2018). These data support the overall safety of retroviral and third-generation lentiviral vectors in gene therapy clinical trials.

Based on the available clinical data, prospective testing on post-infusion patient samples will not be performed as of Protocol V3. Subject blood samples will be collected and banked at baseline (pre-infusion) and post-infusion at Months 3, 6, and 12. All archived samples will be stored in temperature monitored and alarmed freezers at -80°C. In the event RCL is suspected, these archived samples will be used to investigate and perform VSV-G DNA testing.

1.6.1.11 (False)-Positive HIV test

If a positive HIV DNA assay result is obtained, the PI will be informed and the subject rescheduled for a retest for the DNA test. If the second DNA test is positive, the patient will undergo a blood draw for isolation of HIV from his/her cells. The virus will be sequenced and compared to sequences of the transfer vector and packaging constructs, as well as to available HIV sequences to determine the origin of the virus. Determination of the origin of the virus can be easily performed by evaluation for HIV accessory genes such as vif, vpr and vpu which are not present in the packaging constructs. If the sequence is derived from wt-HIV then the patient will be referred to an infectious diseases specialist for further evaluation. If an

RCL is confirmed, or the virus cannot be isolated from the blood draw, the patient will be scheduled for apheresis and will undergo a full biological RCL testing for detection and/or characterization of the RCL.

1.6.1.12 Immune response to vector sequences

It is possible that the subjects may develop an immune response to vector sequences (e.g., VSV-G). This may result in rejection of the gene therapy product in the future or limit subjects' participation in future gene therapy studies.

1.6.1.13 Autoimmune disease

The use of genetically modified ex vivo expanded T cells could potentially result in the development of autoimmune disease(s).

[redacted]

1.6.1.15 Reproductive risks

The risks of MOv19-BBz CAR T cells on pregnancy are unknown. It is possible the cells could cause harm to a fetus or children who are breastfeeding. As such, it is recommended that all subjects of reproductive potential use at least one medical acceptable form of contraception for at least 1 year after their CAR T cell infusion. The Investigators are also advised to counsel subjects on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

Please refer to **Section 4.3** for additional information regarding pregnancy testing and medically acceptable birth control methods.

The cells could also affect the fertility of study participants. The Investigators should discuss options for fertility preservation, if not already discussed as part of the participants' routine cancer care.

1.6.2 Research Procedures

1.6.2.1 aFR Immunohistochemistry Test Failure

The risk of a failed aFR immunohistochemistry test (false-positive) resulting in MOv19-BBz infusion in a patient with no aFR expression on her tumor is the same as the risks listed above, with the exception of TLS and CRS which are not expected due to the lack of tumor antigen expression.

1.6.2.2 Apheresis

Potential risks of the apheresis procedure include nausea, vomiting, fainting or dizziness, seizures, skin rash, hives, flushing, blood loss, and infection. Tingling of the lips, muscle cramping and, very rarely, changes in heart rhythm can occur. These can be prevented or made milder by giving calcium supplements, either by mouth or in the vein, also called intravenous (IV).

Very rarely, (less than 1 in 1,000 procedures), clotting may occur in the apheresis machine or in a patient and is potentially life-threatening. To reduce the risk of clotting, a drug called ACD (acid-citrate-dextrose) will be used. This drug may increase the risk of bleeding and may cause temporary tingling of the lips and limbs, muscle cramping, seizures, or changes in the heart rhythm.

After the apheresis procedure the patient may experience temporary discomfort, including irritation, swelling or bruising at the place where the needle was inserted into the vein to collect the blood. Apheresis can also occasionally cause hives, numbness and tingling, or swelling of the feet and ankles.

1.6.2.3 Blood Draws

Risks associated with blood draws include bruising, swelling, black and blue marks, fainting and/or infection at the site. Rarely, patients may experience anemia from having blood drawn frequently.

1.6.2.4 Tumor Biopsy

Risks may differ depending on the type of biopsy performed; however, common side effects may include: pain, discomfort, soreness, bleeding, and bruising.

1.6.3 Risks of lymphodepleting chemotherapy

1.6.3.1 Fludarabine

When administered as part of routine care, fludarabine has been associated with myelosuppression (dose limiting toxicity), fever, nausea and/or vomiting, skin rashes, myalgia, fatigue, autoimmune hemolytic anemia (may be life-threatening), and pulmonary toxicity (both pneumonia and pulmonary hypersensitivity reactions have been reported; fatal pulmonary toxicity has been described, especially when fludarabine was used in combination with pentostatin). Severe or fatal CNS toxicity presenting with loss of vision and progressive deterioration of mental status has been described primarily after high doses of fludarabine monophosphate, or at usual doses (25-30 mg/m2) in elderly patients. Very rarely described complications include transfusion-associated graft versus host disease, thrombotic thrombocytopenic purpura, and liver failure. Tumor lysis syndrome has been observed, especially in patients with advanced bulky disease. Opportunistic infections (protozoan, viral, fungal, and bacterial) have been observed. Please refer to the package inserts for additional information. We expect similar side effects when administered as part of this study.

1.6.3.2 Cyclophosphamide

When administered as part of routine care, cyclophosphamide has been associated with myelosuppression, hemorrhagic cystitis, syndrome of inappropriate antidiuretic hormone (SIADH), fatigue, hyperuricemia, azoospermia, amenorrhea, cardiotoxicity (myocardial necrosis) with high doses. We expect similar side effects when administered as part of this study.

1.6.3.3 Fludarabine and Cyclophosphamide in Combination

- Common: Lowered neutrophils/granulocytes that may lead to infection. Lowered platelets may lead to an increase in bruising or bleeding, Lowered red blood cells. Lowered lymphocytes may lead to infection, Fatigue, Nausea, Vomiting, Time away from work, Hair loss, Herpes zoster infection of the skin.
- Less Likely: Allergic reaction, Severe allergic reaction that causes fever, aches and pains in the joints, skin rash, and swollen lymph glands, Stuffy or runny nose, sneezing, Sore throat, Abnormal fast heartbeat, Excessive sweating, Flushing, Itching, Rash, Swelling of the lips, eyes, tongue, and

throat which can be severe, Hives, Diarrhea, High blood sugar, Low blood potassium, Dizziness, Convulsion or seizure, Abdominal pain, Pain such as back, joint, and/or muscle pain, Headache, Wheezing, Cough, Shortness of breath, Inflammation of the lung which may cause difficulty breathing and difficulty getting oxygen, Infertility or sterility, Irregular menstrual periods. Some women may not resume their periods, SIADH, Increased production of tears associated with the administration of cyclophosphamide, Metallic taste, Cystitis and hematuria.

- Rare But Serious: hemolytic anemia. Changes in vision or changes in degree of alertness both of which can be severe or fatal, Rash which may become severe, Potentially life-threatening condition affecting less than 10% of the skin in which cell death causes the outer skin layer to separate from the middle layer, Life-threatening condition affecting greater than 30% of the skin in which cell death causes the outer layer of skin to separate from the middle layer, Severe lung dysfunction resulting in the ability to breathe which can be life-threatening, Allergic reactions to blood transfusions, Tumor lysis syndrome - a rapid decline in the number of tumor cells that can lead to kidney failure and/or chemical imbalances that may have a serious effect on other organs such as heart. If this were to occur, subjects will receive close monitoring and blood tests, as well as appropriate medical treatment. It is possible that secondary malignancies including myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) may also be experienced.

1.6.4 Potential Benefits

It is possible that the anti-aFR CAR T cells will exert an anti-tumor effect; in two published trials, objective response rates of 22% and 27% were reported in response to an aFR-specific antibody drug conjugate and IP infusion of T cells armed with an aFR-specific bispecific antibody, respectively [60, 118]. Additionally, the safety and efficacy of CAR T cells redirected against CD19 has established [19]. The safety and efficacy of CAR T cells specific for BCMA are tested in patients with multiple myeloma at UPENN and the preliminary results indicate that this cellular therapy is tolerable and induce durable responses (unpublished data).

1.7 Justification of route and dose regimen for Main Investigational Product

Route of Administration (ROA). For all cohorts, autologous MOv19-BBz CAR T cells will be administered as a single dose via intraperitoneal infusion (IP). In ovarian cancer, the tumor is often accessible in the peritoneal cavity and directed administration of therapeutic agents, such as CAR T cells, is possible. This route of administration is the most likely to result in distribution of MOv19-BBz CAR T cells to most sites of tumor. The method of localized instillation for targeted therapeutic delivery has been employed previously at the University of Pennsylvania in patients with malignant mesothelioma who had pleural administration of agent [124-126] and elsewhere in ovarian cancer patients [127]. In one patient with pancreatic adenocarcinoma with peritoneal carcinomatosis and no other treatment options available, anti-mesothelin CAR T cells were safely delivered by intraperitoneal administration on a compassionate use basis at UPenn with the expectation that delivery of T cells via an IP route of administration may provide significant clinical benefit (UPCC#21211; IRB#814373).

Dose Rationale for MOv19-BBz CART Product. We have chosen to use a single dose of MOv19-BBz CAR T cells for this protocol at a starting dose of 1-3x10^7/m^2. If this dose level is determined safe (both with and without lymphodepleting chemotherapy), the dose level will be increased to 1-3x10^8/m^2. If safety concerns are seen at this starting dose level, the dose will be reduced to 1-3x10^6/m^2.

Due to the unknown effects of targeting aFR with second generation MOv19-BBz CART cells, we chose a more conservative dosing regimen compared to that used in an ongoing Phase I dose-escalation study

evaluating PSMA-CAR T cells infused in mCRPC patients after lymphodepleting chemotherapy (NCT01140373). The dose regimen we have selected is also similar to that used by our group in a study evaluating the safety of anti-mesothelin CAR T cells in other solid tumors, such as mesothelioma, ovarian cancer and pancreatic cancer subjects with and without lymphodepleting chemotherapy (NCT02159716). This anti-mesothelin CAR T cell trial is still ongoing, thus only preliminary safety results are available. This includes one subject death at the 1-3x10^8/m^2 dose level due to respiratory failure in the setting of concurrent Grade 4 CRS. The proposed study will utilize intraperitoneal administration of the CAR T cells to reduce potential toxicity by reducing exposure to the bronchial tissue containing alpha-folate receptor.

2 STUDY OBJECTIVES

2.1 Primary objectives

Determine the safety and feasibility of intraperitoneal administration of lentivirally transduced MOv19-BBz CAR T cells in the target population. Intraperitoneal administration of MOv19-BBz CAR T cells is planned with and without cyclophosphamide + fludarabine as lymphodepleting chemotherapy.

2.2 Secondary objectives

Clinical objectives:

- Assess the clinical anti-tumor effect by standard criteria (RECIST 1.1 and irRECIST) for each tumor type.
- Assess overall response rate (ORR), progression-free survival (PFS) and overall survival (OS).

Correlative objectives:

- Evaluate MOv19-BBz CAR T cells engraftment and persistence in peripheral blood and peritoneal fluid.
- Determine the bioactivity of MOv19-BBz CAR T cells in peripheral blood and peritoneal fluid.
- Evaluate the development of anti-CART immune responses favoring rejection of MOv19-BBz CAR T cells.
- Evaluate the development of secondary anti-tumor immune responses as a consequence of epitope spreading.
- Evaluate the potential to follow tumor biomarker levels as a surrogate biomarker of anti-tumor activity.
- Where tumor material or body fluids can be obtained:
    a. Measure trafficking of MOv19-BBz CAR T cells
    b. Evaluate aFR expression on tumor cells to assess for antigen-escape
    c. Analyze tumor microenvironment and cell interactions (if feasible)

3 STUDY DESIGN

3.1 General Design

This protocol will test the safety of up to 3 dose levels of MOv19-BBz CAR T cells administered intraperitoneally alone or after lymphodepletion with a moderate dose of cyclophosphamide + fludarabine administered two-four days prior to MOv19-BBz CAR T cells. The dose escalation follows a 3+3 design. MOv19-BBz CAR T cells have been permanently modified to be directed to aFR protein with an anti-aFR scFv fused to the signaling domains of 4-1BB and TCRζ. Also, the safety of intraperitoneal

administration of CAR T cells will be evaluated. The study population includes women with aFR-expressing ovarian cancer.

As part of the informed consent process, subjects will be asked for permission to test their tumor for aFR expression as one of the eligibility criteria. Evaluation of aFR expression will occur on archived tumor tissue, if the patient has not had an anti-aFR directed therapy since the collection of the archived sample. However, if archived tumor tissue is not available, a fresh biopsy may be performed. Once aFR expression has been confirmed, subjects may be presented the informed consent for the main study.

Patients with confirmed tumor cells with aFR expression and who meet all other inclusion criteria will be eligible to participate. The minimum requirement of FRα positivity by immunohistochemistry (IHC) is ≥70% of tumor cells with ≥2+ aFR staining.

Once subjects are determined to be eligible by a physician-investigator and the monitoring visit for eligibility is completed, subjects will undergo apheresis to provide cells for MOv19-BBz CAR T cell manufacturing. If patients have an apheresis product collected prior to physician-investigator confirmation of eligibility for this study, this apheresis product may be used for CART cells manufacturing. In this instance, the subject will not need to undergo another apheresis, and CART manufacturing may be initiated immediately after the monitoring visit for eligibility has been completed.

All subjects will be assigned a cohort for the interventional portion of the protocol (see below) as per the 3+3 design. Subjects will be followed up for safety and research assessments as detailed in the Schedule of Events (**Appendix 1**).

Adverse events will be collected and evaluated during the protocol specified adverse event reporting period outlined in **Section 9.1**. While on study, subjects will be continually reassessed for evidence of acute and cumulative toxicity. At any time that a subject has progressed and/or initiates another anti-cancer therapy, the subject may be discontinued from Primary Follow-up and enter long-term follow-up under this same protocol. Long-term follow-up will continue for up to 15 years from their MOv19-BBz CAR T cell infusion. During long-term follow-up, subjects will be monitored for delayed adverse events that may be associated with the administration of the MOv19-BBz CAR T cells.

3.2 Cohort Assignment/Advancement

This is a Phase I study evaluating the safety and feasibility of intraperitoneal administered lentiviral transduced MOv19-BBz CAR T cells with or without cyclophosphamide + fludarabine in a 3+3 dose escalation design.

The trial will begin in Cohort 1 and progression from one cohort to another will occur chronologically and is dependent on dose limiting toxicity (per **Section 5.4**). The DLT observation period is 28 days post CAR T cell infusion. Infusions will be staggered to allow assessment of DLTs for cohort progression, expansion, or dose de-escalation. For example, the 2nd and 3rd subjects in each cohort may be infused and followed in parallel but only after the 1st subject in that cohort completes the day 28 visit without DLT. The formal DLT assessment/determination will be performed by the PI and Sponsor Medical Director prior to cohort advancement.

The Maximum Tolerated Dose (MTD) is defined as the dose at which 0 or 1 DLT occurs in 6 evaluable subjects tested within the dose range of this study. In order to gather additional data and establish the MTD dose level, the respective cohorts may be expanded to treat up to 6 evaluable subjects.

- Cohort 1: (n= 3 to 6 subjects): Single infusion of 1-3x10^7/m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 without lymphodepleting chemotherapy.
    - If 1 DLT/3 subjects occurs, the study will enroll an additional 3 subjects at this dose level.
    - If 0 DLT/3 subjects or 1 DLT/6 subjects occurs, the study will advance to Cohort 2.
    - If 2 DLT/3 subjects or 2 DLT/6 subjects occurs, then enrollment in this Cohort will be stopped and the dose will be de-escalated by 10-fold to 1-3 x 10^6 cells/m^2 (Cohort -1).
    - If the number of manufactured CAR T cells does not meet the protocol-specified minimum dose for Cohort 1 subjects of 1 x 10^7/m^2 cells, but does meet the protocol minimum dose requirement of at least 1 x 10^6/m^2 cells, then the subject may receive the cells, but will not be included in the DLT assessment for Cohort 1. Thus, the subject would be evaluable for safety, but would be replaced in this cohort for formal DLT assessment. If, however, the number of manufactured CAR T cells does not meet the minimum acceptable dose for infusion, then the cells will not be administered, and the subject will be replaced in the study.

- Cohort -1: (n= 3 to 6 subjects): Single Infusion of 1-3x10^6/m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 without lymphodepleting chemotherapy.
    - Dose de-escalated dose level, which will only enroll subjects in the event of 2 DLT/3 subjects or 2 DLT/6 subjects occurs in Cohort 1.
    - Up to 6 subjects will be infused in Cohort -1 with ≤ 1 DLT/6 subjects to establish the MTD.

- Cohort 2: (n= 3 to 6 subjects): Single infusion of 1-3x10^7/m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 beginning 3 days (+/- 1 day) after lymphodepleting chemotherapy with cyclophosphamide + fludarabine.
    - If 1 DLT/3 subjects occurs, the study will enroll an additional 3 subjects at this dose level.
    - If 0 DLT/3 subjects or 1 DLT/6 subjects occurs, the study will advance to Cohort 3.
    - If 2 DLT/3 subjects or 2 DLT/6 subjects occurs, further infusions within this cohort and subsequent dose escalation would be halted. If less than 6 subjects were infused in Cohort 1, up to 6 total subjects will be infused in Cohort 1 to establish the MTD.
    - If the number of manufactured CAR T cells does not meet the protocol-specified minimum dose for Cohort 2 subjects of 1 x 10^7/m^2 cells, but does meet the minimum dose requirement of at least 1 x 10^6/m^2 cells, then the subject may receive the cells but will not be included in the DLT assessment for Cohort 2. Thus, the subject would be evaluable for safety, but would be replaced in this cohort for formal DLT assessment. If, however, the number of manufactured CAR T cells does not meet the minimum acceptable dose for infusion, then the cells will not be administered, and the subject will be replaced in the study.

- Cohort 3: (n=3 to 6 subjects): Single infusion of 1-3x10^8/m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 beginning 3 days (+/- 1 day) after lymphodepleting chemotherapy with cyclophosphamide + fludarabine.
    - If 0 DLT/3 or 1 DLT/3 subjects occur, the study will enroll an additional 3 subjects to confirm tolerability and MTD.

- If 2 DLT/3 subjects or 2 DLT/6 subjects occurs, further infusions within this cohort will be halted. If less than 6 subjects were infused in Cohort 2, up to 6 total subjects will be infused in Cohort 2 to establish the MTD.
- If the number of manufactured CAR T cells does not meet the protocol-specified minimum dose for Cohort 2 subjects of 1 x $10^8/m^2$ cells, but does meet the minimum dose requirement of at least 1 x $10^6/m^2$ cells, then the subject may receive the cells but will not be included in the DLT assessment for Cohort 3. Thus, the subject would be evaluable for safety, but would be replaced in this cohort for formal DLT assessment. If, however, the number of manufactured CAR T cells does not meet the minimum acceptable dose for infusion, then the cells will not be administered, and the subject will be replaced in the study.

Subjects will be enrolled serially. Infusions will be staggered to allow assessment of DLTs for cohort progression, expansion, or dose de-escalation. The infusions for the first 2 subjects in each cohort will be staggered by 28 days; the second subject will not be infused until 28 days after the infusion of the first subject. However the 2nd and 3rd subjects in each cohort may be infused and followed in parallel but only after the 1st subject in that cohort completes the day 28 visit without DLT. DLT are defined as per **Section 5.4**.

Subjects will be followed up for safety assessments and research assessments post infusion as detailed in the Schedule of Events **(Appendix 1)**.

3.3 Collection of Research Samples

Peripheral blood samples will be obtained at defined time points to monitor for measures of safety and efficacy. Additional blood and tissue samples (e.g. fluids, tissue biopsy) that are obtained for clinical indications may also be sent for research analysis. At any time that tissue or body fluids are obtained (for example, drainage of peritoneal fluid or pleural/ascites fluid), fluid samples that would otherwise be discarded may be used instead for research purposes (see **Section 7.2**). These studies include, but are not limited to, MOv19-BBz CAR T cell persistence by Q-PCR and inflammation marker assessment with a Luminex™-based cytokine and chemokine panel. If clinically feasible/appropriate, subjects will be asked to undergo an image-guided minimally invasive biopsy pre-infusion and on day 14 (±7) for research purposes.

In case of unexpected AEs or SAEs, additional samples may be collected for research analysis, focused at evaluating the potential causality with the infused MOv19-BBz CAR T cells. Additional blood work for research evaluation may also be requested at any time at the investigators' discretion, and is especially encouraged whenever there is a clinical concern for a potential toxicity related to MOv19-BBz CAR T cells, but also for subjects with an unusual efficacy; additional studies may identify critical biomarkers of potency which may inform future trial designs. The additional samples collected for research will not exceed 3 tablespoons of blood twice in a week, and one procedure for collecting tissue/lymph node samples in a month.

3.4 Primary Study Endpoints

This phase I study is designed to test the safety and feasibility of intraperitoneal administration of MOv19-BBz CAR T cells in patients with aRF expressing ovarian cancer. Intraperitoneal administration of MOv19-BBz CAR T cells is planned with or without cyclophosphamide + fludarabine as lymphodepleting chemotherapy.

Safety of treatment will be defined by:

- The occurrence of study related adverse events, defined as NCI CTCAE v5.0 greater than or equal to (≥) grade 3 signs/symptoms, laboratory toxicities and clinical events that are possible, probably, or definitely related to study treatment.

Feasibility of treatment

- Clinical feasibility is defined as the proportion of subjects enrolled on this protocol who do not receive MOv19-BBz CAR T cells. Reasons for this occurrence include rapid clinical deterioration or death, and subject withdrawal.
- Manufacturing feasibility is determined based on the "manufacturing failures" products. The number of manufactured products that do not meet release criteria for vector transduction efficiency, CART+ cell number, T cell purity, viability, and sterility will be determined and defined as "manufacturing failures".

3.5 Secondary Study Endpoints

Secondary endpoints include clinical responses and research correlative studies.

3.5.1 Clinical Responses

Preliminary evidence of efficacy will be determined by monitoring tumor response rates in those subjects with measurable disease. Tumor response will be assessed using radiographic imaging (i.e. CT imaging) and serum biomarkers in accordance with the Schedule of Events in **Appendix 1**.

a. Radiographic responses will be measured according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Immune related response evaluation criteria in solid tumors Criteria (irRECIST) will be assessed when feasible.
b. Serum biomarker responses will be evaluated according to clinical standards. Serum biomarkers will not be used as the sole measurement of tumor response.
c. Data will be analyzed descriptively for overall response rates (ORR), progression-free survival (PFS), and overall survival (OS). ORR and PFS, up to 5 years post-infusion or until subjects initiate a cancer-related therapy, will be evaluated. OS up to 15 years post-infusion will be evaluated.

3.5.2 Research Correlative Studies

The following studies will measure the effect of CAR T cell infusion on systemic adaptive and innate immunity. Analyses will be performed on peripheral blood samples (peripheral blood mononuclear cells and serum) and body fluids (including peritoneal fluid) collected at time-points as detailed in the Schedule of Events (**Appendix 1**). Additional analysis may also be performed on additional sample collections (e.g. fluids, tissue biopsies). More specifically, in case of unexpected AEs or SAEs, additional samples may be collected for research analysis focused at evaluating the potential causality with the infused MOv19-BBz CAR T cells. Additional blood work for research evaluation may be requested at any time at the investigators' discretion, and is especially encouraged whenever there is a clinical concern for a potential toxicity related to MOv19-BBz CAR T cells, but also for subjects with an unusual efficacy; additional studies may identify critical biomarkers of potency which may inform future trial designs. The additional samples collected for research will not exceed 3 tablespoon of blood twice in a week and up to 1 procedure for collecting tissue/lymph nodes samples in a month. In addition, tissue samples (e.g. fluids, tissue biopsy) that are obtained as part of standard of care procedures for clinical indications may also be used for research analysis.

a. Evaluate leakage and persistence of MOv19-BBz CAR T cells in peripheral blood. This will be measured by Q-PCR for vector sequences. CAR T cell vector sequences will also be performed at time points according to the **Appendix 1**. This testing will occur until any 2 sequential tests are negative documenting "rejection" or loss of CAR T cells. Data will be displayed graphically. Flow cytometry will be used if feasible.
b. Determine the bioactivity of MOv19-BBz CAR T cells. This will be evaluated by measuring modulation of cytokines, chemokines and growth factors by Luminex technology. In addition, we may assess bioactivity of CAR T cells (product and post-infusion specimens) via stimulation with aFR expression target cells using flow cytometry-based functional assay.
c. Evaluate the development of immune responses favoring rejection of MOv19-BBz CAR T cells (including HACA, HAMA, and cellular immune responses directed to the MOv19-BBz CAR). Correlate the occurrence of such responses with loss of MOv19-BBz CAR T cells engraftment.
d. Evaluate the development of secondary anti-tumor immune responses as a consequence of epitope spreading. If tumor tissue is available at baseline and post-infusion, the analysis of breath and hierarchy of T cell receptor and immunoglobulin rearrangements via deep sequencing may be used to demonstrate antigen spreading.
e. Evaluate the potential to follow decreases in soluble tumor biomarker levels as a surrogate biomarker of anti-tumor activity. CA125 and SaFRP for all subjects will be measured before and after the infusion. This data will be correlated with radiographic information evaluating tumor status obtained at the same time-points and with clinical status.
f. Where tumor material or body fluids can be obtained, we may attempt to:
    - detect presence of MOv19-BBz CAR T cells
    - measure aFR expression
    - analyze tumor microenvironment using flow cytometric, IHC and transcriptomic analysis; the breadth and hierarchy of the T cell repertoire via deep sequencing and compare with baseline specimens.

For details on these assessments please see **Section 7** of the clinical protocol.

4 SUBJECT SELECTION AND WITHDRAWAL

4.1 Inclusion Criteria

1. Histologically confirmed persistent or recurrent stage II to IV high grade serous epithelial ovarian, fallopian tube or primary peritoneal carcinoma. Disease can be platinum-sensitive or platinum-resistant.
2. Failure of at least two prior chemotherapy regimens for advanced stage disease. Prior therapies against PD-1 or PDL-1 are permissible.
3. Confirmation of tumor aFR expression (≥70% of tumor cells with ≥2+ aFR staining).
4. Subjects must have measureable disease as defined by RECIST 1.1 criteria.
5. Patients with asymptomatic CNS metastases that have been treated and are off steroids are allowed. They must meet the following at the time of eligibility confirmation by physician-investigator:
    a. No concurrent treatment for the CNS disease
    b. No progression of CNS metastasis on brain MRI at screening
    c. No evidence of leptomeningeal disease or cord compression
6. Patients ≥ 18 years of age.

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Satisfactory organ and bone marrow function as defined by the following:
    i. Absolute neutrophil count ≥ 1,000/µl
    ii. Platelets ≥75,000/µl
    iii. Hemoglobin ≥ 9 g/dL
    iv. Total bilirubin ≤ 2.0x the institutional normal upper limit unless secondary to bile duct obstruction by tumor
    v. Creatinine ≤ 1.5x the institutional normal upper limit
    vi. Albumin ≥2
    vii. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 5x the institutional normal upper limit
    viii. Cardiac ejection fraction of ≥40%
9. Blood coagulation parameters: PT such that international normalized ratio (INR) is ≤ 1.5 and a PTT ≤ 1.2 time the upper limit of normal unless the patient is therapeutically anti-coagulated for history of cancer-related thrombosis and has stable coagulation parameters.
10. Provides written informed consent.
11. Subjects of reproductive potential must agree to use acceptable birth control methods, as described in protocol **Section 4.3**.

4.2 Exclusion Criteria

1. High grade serous ovarian, fallopian, or primary peritoneal cancer that is platinum refractory, defined as disease that has clinical or radiographic progression on platinum-based chemotherapy, as per the discretion of the treating physician.
2. Patients with symptomatic CNS metastases are excluded.
3. Participation in a therapeutic investigational study within 4 weeks prior to eligibility confirmation by physician-investigator, or anticipated treatment with another investigational product while on study. This refers to non-commercially approved investigational drugs different than those used in this protocol.
4. Active invasive cancer other than ovarian cancers. Patients with active non-invasive cancers (such as non-melanoma skin cancer, superficial cervical and bladder cancer) are not excluded.
5. HIV infection
6. Hepatitis B or hepatitis C infection
7. Active autoimmune disease requiring systemic immunosuppressive treatment equivalent to >/= 10 mg of prednisone. Patients with autoimmune neurologic diseases (such as multiple sclerosis) will be excluded.
8. Patients with active and uncontrolled infection.
9. Planned concurrent treatment with systemic high dose corticosteroids. Patients may be on a stable low dose of steroids (<10 mg daily equivalent of prednisone). Corticosteroids treatment as anti-emetic prophylaxis on the day of lymphodepleting chemotherapy administration is allowed per institutional guidance. The use of topical and/or inhaled steroids are not exclusionary.
10. Patients requiring supplemental oxygen therapy.
11. Prior therapy with lentiviral gene modified cells.
12. History of allergy or hypersensitivity to study product excipients (human serum albumin, DMSO, and Dextran 40)

13. Any ascites requiring therapeutic drainage within 4 weeks prior to eligibility confirmation by physician-investigator.
14. Pregnant or breastfeeding women.
15. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the physician-investigator, would make the patient inappropriate for entry into the study.

Please refer to the Concomitant Therapy Section 5.6 for windows related to apheresis and MOv19-BBz CAR T cell infusion.

4.3 Subject Recruitment

Subjects will be identified through the clinical practices of the clinical investigators in the Division of Gynecologic Oncology and Division of Hematology Oncology at the Hospital of the University of Pennsylvania and its affiliated hospitals and through referrals from outside hospitals and physicians. No direct-to-patient advertising will be performed. The trial will be publicized on the websites of Clinicaltrials.gov and the Abramson Cancer Center of the Hospital of the University of Pennsylvania.

4.4 Reproductive Status

Females and transgender men of reproductive potential (who have reached menarche or who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or have not undergone a sterilization procedure [hysterectomy or bilateral oophorectomy]) must have a negative urine pregnancy test performed at screening and a negative serum pregnancy test prior to study treatment as per the Schedule of Events in **Appendix 1**.

Due to the unknown risk of the MOv19-BBz CAR T cells with respect to pregnancy, as well as risks associated with lymphodepleting chemotherapy, it is recommended that all subjects of reproductive potential use at least one medically acceptable form of contraception during the study and for at least 1 year after their last infusion of MOv19-BBz CAR T cells. Investigators shall counsel subjects on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

Medically acceptable birth control includes the following methods:

- Abstinence
- Condoms (male or female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Hormonal/Non-hormonal Intrauterine device (IUD)
- Hormonal-based contraception

Subjects who are not of reproductive potential (females/transgender men who have been post menopausal for at least 24 consecutive months or have undergone hysterectomy, salpingotomy, and/or bilateral oophorectomy) do not require use of contraception. Acceptable documentation of sterilization or menopause is required and may take the form of written or oral attestation by clinician or clinician's staff of one of the following:

- Physician report/letter
- Operative report or other source documentation in the subject record
- Discharge summary

- Follicle stimulating hormone measurement elevated into the menopausal range

4.5 Subject Withdrawal/Discontinuation

4.5.1 Reasons for Subject Discontinuation

Subjects who enroll but do not receive MOv19-BBz CAR T cells will be prematurely discontinued from the study, will not be followed, and will be replaced in the study. Reasons for premature discontinuation prior to receipt of MOv19-BBz CAR T cells include, but are not limited to, the following:

1. The subject is lost to follow-up.
2. The principal investigator judges that the subject, prior to MOv19-BBz CAR T cell infusion, is too ill to continue.
3. Pregnancy- documented prior to MOv19-BBz CAR T cell infusion. If pregnancy occurs after the subject has received MOv19-BBz CAR T cells, they will be kept active in the study for safety follow-up and pregnancy outcome.
4. Voluntary withdrawal: a subject may remove himself/herself from the study at any time.
5. Significant and rapid progression of malignancy, requiring alternative medical, radiation or surgical intervention, prior to MOv19-BBz CAR T cell infusion.
6. A serious adverse event that requires the subject to be withdrawn from the trial prior to MOv19-BBz CAR T cell infusion.
7. Technical difficulties are encountered in the T cell genetic modification and expansion procedure that precludes the generation of clinical cell doses that meet all Quality Control release criteria.
8. Termination of the study.

Reasons for discontinuation of subjects from primary follow-up after receipt of MOv19-BBz CAR T cells may include, but are not limited to, the below. Subjects may not be discontinued from primary follow-up prior to the Day 28 safety follow-up visit for reasons other than subject withdrawal of consent or death.

1. The subject is lost to follow-up.
2. Voluntary withdrawal: a subject may remove himself/herself from the study at any time.
3. Disease progression of targeted malignancy
4. Receipt of alternative treatment for their targeted disease
5. Completion of protocol required follow-up
6. Termination of the study.

Subjects who are discontinued from primary follow-up, will go into the long-term follow-up phase. Reasons for discontinuation of subjects from long-term follow-up after receipt of MOv19-BBz CAR T cells may include, but are not limited to, the following:

1. The subject is lost to follow-up.
2. Voluntary withdrawal: a subject may remove himself/herself from the study at any time.
3. Completion of protocol required long-term follow-up.
4. Death
5. Termination of the study.

The reasons for discontinuation from both primary and long-term follow-up (for example, voluntary withdrawal, toxicity, death) must be recorded appropriately.

4.5.2 Data Collection and Follow-up

Follow-up data collection after receipt of gene-modified cell therapy clinical trials is specified by FDA. As long as subjects have detectable cells transduced with the lentiviral vector, they should be followed for toxicity, immune reactions, and any long-term adverse events.

In the event that a subject cannot return to the study site for follow-up visits because of subject preference or geographical concerns, the subject's primary care physician and/or local oncologist will be asked to provide information from the subject's medical record to the study team at protocol defined time points (including the results of any routine care examinations and/or laboratory assessments), and assist in the collection of protocol required blood samples (if applicable), which will be sent to the University of Pennsylvania for protocol-required analysis. The subject and local provider will also be contacted via telephone by a member of the study team to assess any potential toxicity.

In numerous previous cell therapy trials at the University of Pennsylvania, loss of follow-up is estimated to occur in less than 5% of cases. Every effort will be made to contact subjects who appear to be lost to follow-up in order to at least obtain survival data. In the event a subject fails to complete the follow-up requirements, documentation of all attempts to contact the subject includes at least 3 telephone contacts (on different days and at different times of the day), and a certified letter.

4.5.3 Replacement Subjects

All subjects who do not receive MOv19-BBz CAR T cells will be replaced. Subjects have the option to receive a lower than target dose per cohort assignment, if the MOv19-BBz CAR T cell product meets CVPF release criteria and minimum acceptable dose for infusion, and the subject cannot or is not willing to perform a second apheresis, or if the second manufacturing process fails. If a subject receives a lower than target dose per cohort assignment, they will be considered evaluable for safety, but will not be evaluable for response and will not be included in DLT evaluations (i.e. deemed Cohort non-evaluable and will be replaced in that cohort), but will follow all of the study visits as described in the Schedule of Events in **Appendix 1**. The minimum acceptable dose for infusion is $1x10^6$ MOv19-BBz CAR T cells/m^2.

5 INVESTIGATIONAL PRODUCTS

5.1 Description

5.1.1 MOv19-BBz CAR T cells

MOv19-BBz CAR T cells are autologous T cells that have been engineered to express an extracellular single chain variable fragment (scFv) with aFR specificity. The T cells express an intracellular signaling molecule comprised of the TCR ζ chain, and 4-1BB. The MOv19-BBz CAR T cells are cryopreserved in infusible cryomedia (**Section 5.3.1**). Each bag will contain a dose of CAR positive T cells corresponding to the subject's assigned cohort/dose level. The total cell dose is dependent on the transduction efficiency; the volume of cells is dependent on the total cell dose with a minimum of 10 mLs per bag. The minimum acceptable dose for infusion is $1x10^6$ MOv19-BBz CAR T cells/m^2.

5.1.2 Cyclophosphamide and Fludarabine

Cyclophosphamide and fludarabine are cytotoxic chemotherapy agents used for lymphodepletion prior to MOv19-BBz CAR T cell administration in Cohorts 2 and 3. The main goal of using cyclophosphamide and fludarabine is to achieve lymphodepletion that may enhance engraftment of adoptive T cells, while

minimizing complications from neutropenia. The proposed regimen has been used widely in other studies and has been tolerated well. Although both cyclophosphamide and fludarabine are FDA-approved agents and will be prepared and infused in accordance with their FDA-approved labels and standard institutional practice, their use in this trial will be considered investigational. This is due to the use of these drugs in combination as well as their use in this patient population. Also, to our knowledge, cyclophosphamide and fludarabine have not been used for lymphodepletion prior to IP CAR T-cells.

Cyclophosphamide and fludarabine will be administered as a regimen of cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2 daily over three days. Fludarabine doses will be rounded down to the nearest 50 mg vial size, if the rounded dose does not differ by > 10% of the original dose prescribed. This lymphodepleting chemotherapy regimen must be scheduled so that the last day of therapy falls 3 days (+/- 1 day) prior to CAR T cell infusion.

5.2 Treatment Regimen

A single dose of MOv19-BBz CAR T cells will be administered by rapid intraperitoneal (IP) infusion (all Cohorts) via intraperitoneal catheter as follows.

- Cohort 1: (n= 3 to 6 subjects): Single infusion of 1-3x10^7/m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 without lymphodepleting chemotherapy.
- Cohort -1: (n= 3 to 6 subjects): Single Infusion of 1-3x10^6/m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 without lymphodepleting chemotherapy. Dose de-escalated dose level, which will only enroll subjects in the event of 2 DLT/3 subjects or 2 DLT/6 subjects occurs in Cohort 1.
- Cohort 2: (n= 3 to 6 subjects): Single infusion of 1-3x10^7/m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0 beginning 3 days (+/- 1 day) after lymphodepleting chemotherapy with cyclophosphamide + fludarabine.
- Cohort 3: (n=3 to 6 subjects): Single infusion of 1-3x10^8/m^2 lentivirally transduced MOv19-BBz CAR T cells on day 0, beginning 3 days (+/- 1 day) after lymphodepleting chemotherapy with cyclophosphamide + fludarabine.

MOv19-BBz CAR T cells will be routinely administered on an outpatient basis, however inpatient administration may occur at treating investigator's discretion. Clinic visits, hematology, and other safety laboratory tests will be performed according to the Schedule of Events (**Appendix 1**). Additional sample collection and assessments may be performed as clinically necessary to evaluate specific adverse events per Investigator discretion.

5.3 Preparation and Administration of Study Drug(s)

5.3.1 MOv19-BBz CAR T cells

5.3.1.1 Manufacturing of MOv19-BBz CAR T cells

The manufacture and release testing of MOv19-BBz CAR T cells will be performed by the Clinical Cell and Vaccine Production (CVPF) at the University of Pennsylvania. The MOv19-BBz CAR T cell product will be manufactured from the patients' apheresis product.

MOv19-BBz CART products are not released from the CVPF until release criteria for the infused cells (e.g., cell purity, sterility, identity) are met. At the end of cell cultures, the cells are cryopreserved in infusible

cryomedia in bags. Weight used for dosing will be the weight obtained prior to the apheresis procedure. Dosing will not be changed for changes in subject weight.

Bags containing autologous modified CAR T cell products will be stored in a controlled and monitored freezer at the CVPF at the Hospital of the University of Pennsylvania until the subject is ready for infusion. Each dose will be packed and cryopreserved in infusion bag(s) in a volume dependent on the total cell number which is a function of the transduction efficiency. Each bag will contain an aliquot (volume dependent upon total cell dose) of cryomedia containing the following infusible grade reagents (% v/v):

- [redacted]

A qualified alternative cryopreservation media contains the following infusible grade reagents (% v/v):

- [redacted]

5.3.1.2 Release and Preparation of MOv19-BBz CAR T cells

The CVPF will release MOv19-BBz CAR T cells to the bedside for administration per CVPF SOPs. The MOv19-BBz CAR T cells will not be released from the CVPF until release criteria for the infused cells are met.

Packaging and Labeling

The investigational product will have affixed to it a label containing the following statements: "FOR AUTOLOGOUS USE ONLY" and "Caution: New Drug – Limited by Federal Law to Investigational Use". In addition, the label will have at least two unique identifiers, among other information required by law.

Cell Thawing/Receipt of MOv19-BBz CAR T cells

The frozen MOv19-BBz CAR T cells will be transported to the subject's bedside in dry ice on the day of infusion. The cells will be thawed by trained personnel using a water bath maintained between 36°C to 38°C. The bag will be gently massaged until the cells have just thawed. There should be no frozen clumps left in the container at the time of infusion.

If the MOv19-BBz CART product appears to be damaged or leaking, or otherwise appears to be compromised, it should not be infused and should be returned to the CVPF as specified below.

Return or Destruction of Study Drug

MOv19-BBz CAR T cells may need to be returned to the CVPF for a variety of reasons, including but not limited to: 1) Mislabeled product; 2) Condition of patient prohibits infusion/injection, and 3) Subject refuses infusion. Any unused product will be returned to CVPF. Final disposition of the investigational product is to be documented.

5.3.1.3 Administration of MOv19-BBz CAR T cells

Intraperitoneal Catheter Placement

The subject will have an intraperitoneal catheter placed by Interventional Radiology according to standard hospital procedure, on the day of planned MOv19-BBz CAR T cell infusion, at a location determined by Interventional Radiology. At this time the peritoneal cavity may be maximally drained.

Evaluation Prior to MOv19-BBz CAR T cell Administration

Following catheter placement, the subject will be transported to the outpatient clinical facility for continued care and receipt of cells. Prior to CAR T cell administration, the subject will be evaluated by the treating physician for criteria specified in **Section 6.6**.

Premedication for MOv19-BBz CAR T cells

Premedication for CAR T cell infusions is given due to the possibility of side effects including transient fever, chills, rigors, myalgias/arthralgias, headache, fatigue, and/or nausea. Subjects will be pre-medicated with acetaminophen 650 mg by mouth and diphenhydramine hydrochloride by mouth or IV prior to MOv19-BBz CAR T cell infusion. If Benadryl is contraindicated, an H2-blocker, such as ranitidine, will be administered. These medications may be repeated every six hours or as needed. A course of non-steroidal anti-inflammatory medication may be prescribed if the patient continues to have fever not relieved by acetaminophen. It is recommended that patients do not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol), or dexamethasone (Decadron). If corticosteroids are required for an acute infusional reaction, an initial dose of hydrocortisone 100 mg is recommended.

MOv19-BBz CAR T cell Administration

The MOv19-BBz CAR T cell infusion will take place on an outpatient basis at the Hospital of the University of Pennsylvania. T-cell infusions will be performed by a licensed Registered Nurse at the Hospital of the University of Pennsylvania.

Prior to the infusion, two trained study team members will independently verify the information on the label of the product bag in the presence of the subject and confirm that the information correctly matches the participant.

The transduced T cells will be instilled through the indwelling peritoneal catheter into the affected peritoneal space.

Vital signs (temperature, respiration rate, pulse, blood pressure, and oxygen saturation by pulse oximetry) will be measured within 10 minutes prior and within 15 minutes after the infusion. Thereafter, vital signs will be measured at 30 (+/- 5) minutes, 45 (+/- 5) minutes, and 60 (+/- 5) minutes after the infusion, and then every hour (+/- 10 minutes) for the next two hours until these signs are satisfactory and stable. If vital signs are not satisfactory and stable 3 hours after the MOv19-BBz CAR T cell infusion, vital signs will continue to be monitored as clinically indicated until stable. The subject will be discharged when medically stable and in accordance with hospital policy. Subjects will be instructed to return to the University of Pennsylvania within 24 hours after the first infusion for blood tests and follow-up examination according to the Schedule of Events (**Appendix 1**).

Following the infusion, the subject should lie in the lateral decubitus position on the opposite side of the catheter for 15 minutes, if applicable. The IP catheter will be removed prior to the subject being discharged.

5.3.1.4 Additional Safety Monitoring

Emergency medical equipment (i.e. a crash cart) must be available for an emergency situation during the infusion in the event that the subject has an allergic response, or severe hypotensive crisis, or any other reaction to the infusion.

5.3.1.5 Toxicity Management Considerations

Please refer to **Section 1.6**/Potential risks and benefits for additional information.

Febrile reaction

In the unlikely event that the subject develops sepsis or systemic bacteremia following MOv19-BBz CAR T cell infusion, appropriate cultures and medical management will be initiated. If a contaminated MOv19-BBz CART product is suspected, the product can be retested for sterility using archived samples that are stored in the CVPF.

Infusion Reactions

Several reactions may develop during and immediately after T cell infusions. A summary description of these reactions and the medical management is provided below:

Flu-like symptoms

- Fever/arthralgia/myalgia: The onset of these symptoms usually occurs 2 to 4 hours after the cell product administration. Management: Administration of acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) is effective in controlling and preventing symptoms.
- Rigors/chills: These symptoms may occur during and/or after cell infusion administration. Management: The agent of choice to improve severe chills or rigors is an opioid such as dilaudid. If subjects develop rigors consistently after cell product administration, prophylactic administration of NSAIDS (e.g. ibuprofen) may prevent these reactions.

Hemodynamic Effects

- Edema: Adequate hydration is necessary to ensure renal perfusion, but over-hydration should be avoided. Subjects should be encouraged to drink electrolyte-containing fluids such as sport drinks and soups. Management: If diuretics are to be used to manage edema, they should be used with caution to avoid decreasing intravascular volume. If participants develop hypotension, IV fluids should be administered and appropriate evaluation with observation in an acute hospital bed is advisable.
- Hypotension: Organ dysfunction, oliguria, and increases in BUN and creatinine are usually reversible upon discontinuation of cell product and 24 to 48 hours of supportive treatment. Management: On rare occasions, low doses of dopamine and fluid support may be warranted. Educating the subject to slowly rise from a supine to a sitting position and then to a standing position can prevent orthostatic hypotension. Evaluation in the Emergency Department if symptoms occur is advisable.

Dermatologic Reactions

Skin reaction: Dry skin, pruritis, erythema, and sloughing may occur following cell infusions. No interruption of therapy is usually needed. Skin rashes have been observed in approximately 20 to 25% of subjects treated with T cells to date. The rashes have generally been transient maculopapular rashes that appear about a week after T cell administration. The rashes may

resemble those described in autologous graft versus host disease (GVHD), but to date, the pathogenesis has not been clarified. Management: Anti-histamines and topical corticosteroids, water or oil-based lotions, and oatmeal baths may help control the symptoms.

Other potential short-term and long-term toxicities and their management include:

Cytokine release syndrome (CRS) Cytokine release syndrome is caused by a release of inflammatory cytokines such as IL-6, IL-2R, IFN-γ, and IL6 receptor [128]. This type of reaction is common in cancer immunotherapy where antibodies bind T cells that release large amounts of cytokines, or cause rapid destruction of tumor/target cells. This causes a systemic inflammatory response similar to sepsis and includes fever, nausea, chills, rash, flushing, rigors, hypotension, tachycardia, headache, throat tightness, and dyspnea. Capillary leak with fluid retention is worsened by hydration commonly given to treat hypotension. The syndrome can be associated with pulmonary infiltrates, pulmonary edema, arrhythmias, and cardiac arrest. The syndrome is also associated with an elevation in LFTs, D-dimers, LDH, CR, uric acid and phosphorus from immune-mediated cytolysis of targeted cells, with release of intracellular contents as well as possible bystander effect (on neighboring, non-targeted cells).

Most UPENN patients who have responded to CART19 cells experienced CRS. The CRS was initially defined to describe an infusion reaction or reaction to antibodies. It is manifested by high fevers, anorexia, nausea, headache, rash, and, in some patients, hypotension, shortness of breath, hypoxia, delirium and biochemical evidence of disseminated intravascular coagulation (DIC) and macrophage activation syndrome (MAS). The clinical syndrome of MAS is characterized by high grade non-remitting fever, cytopenias affecting at least two of three lineages, and hepatosplenomegaly. It is associated with biochemical abnormalities, such as high circulating levels of serum ferritin, soluble interleukin-2 receptor (sCD25), and triglycerides, together with a decrease of circulating NK activity. Other findings include variable levels of transaminases up to signs of acute liver failure and coagulopathy with findings consistent with DIC. A pathologic feature of MAS is the presence of hemophagocytic CD163+ macrophages (HPC) in bone marrow or lymph node aspirates. MAS appears to be a reaction to immune activation that occurs from the CRS, and therefore should be considered a manifestation of CRS. Macrophage activation syndrome (MAS) is similar to Hemophagocytic lymphohistiocytosis (HLH); it is reactive to immune stimulation, infection, autoimmune diseases or other precipitants but is distinguished from familial or genetically-mediated HLH.

Management: Upon developing the prodrome of high-persistent fevers following CAR infusion, patients should then be followed closely. Infection and tumor lysis syndrome work up should be immediately undertaken. Additional blood will be collected as soon as possible and sent to TCSL for real time cytokine analysis. CRS management decisions should be based upon clinical signs and symptoms and response to interventions, not on laboratory values *per se*. Ferritin, CRP and serum cytokine levels should NOT be used for clinical management decisions. Additional blood collection is warranted and will be performed as needed to manage the CRS toxicity. This includes but it is not limited to analysis of D-dimers, ferritin, LDH, triglycerides, CRP, and haptoglobin.

Mild CRS such as fever alone in the absence of organ dysfunction or hypotension can be managed with acetaminophen. For higher grades CRS, all standard of care will be offered to assure subject wellbeing including treatment with steroids to prevent further cytokine activation and release, anti-histamines, and supportive care (fluids, pressors, intubation if needed). Because steroids are thought to interfere with CAR function and efficacy, if used, they should be rapidly tapered. In addition, the investigator or treating

physicians may choose to administer anti-cytokine therapy such as tocilizumab, siltuximab or other (such as anakinra).

In addition to supportive care, tocilizumab may be administered in cases of moderate to severe CRS, especially if the patient exhibits any of the following:

- Hemodynamic instability despite intravenous fluid challenges and moderate stable vasopressor support
- Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow O2, and/or need for mechanical ventilation.
- Any other signs or symptoms of rapid deterioration despite medical management

Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1k subclass. It binds both the membrane bound and soluble forms for the IL-6 receptor, and thus blocks IL-6 mediated pro-inflammatory effects. Tocilizumab has been approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) inhibitor therapies (i.e., infliximab). In 2011, it received approval for children with systemic juvenile idiopathic arthritis. Most recently in 2017, the FDA approved tocilizumab for the management of CAR T cell-induced cytokine release syndrome.

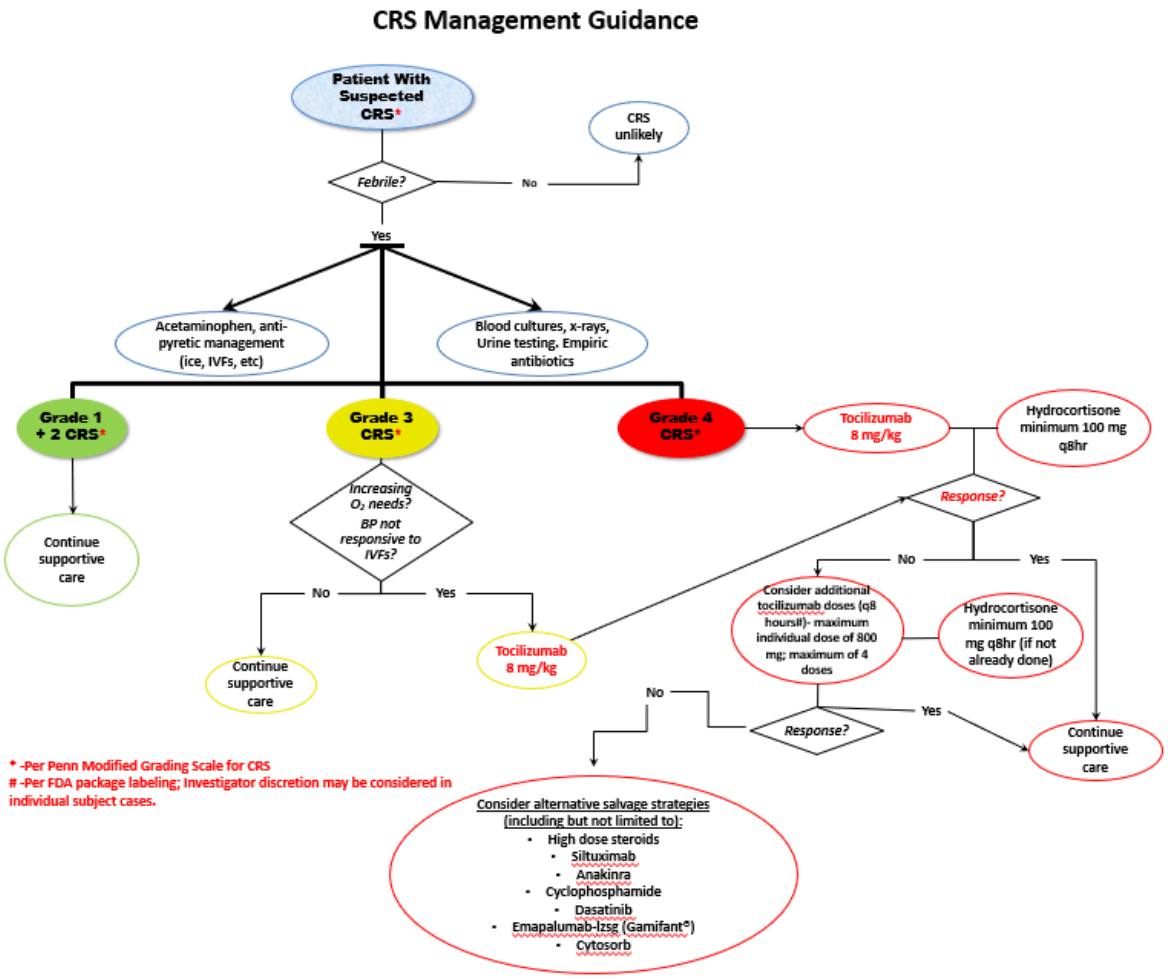
The moderate to severe cases of CRS observed required intervention with tocilizumab, with or without high dose corticosteroids, between 2 and 9 days after T cell infusion. This resulted in rapid reversal of the high persistent fevers and hemodynamic instability associated with CRS in most but not all patients. Patients with a suboptimal response to the first dose of tocilizumab have received a second dose of tocilizumab with CRS resolution. Given the dramatic clinical improvement of patients after treatment with anti-cytokine therapy, patients with moderate to severe cytokine toxicities should be managed with administration of tocilizumab. Steroids have not always been effective in this setting and may not be necessary given the rapid response to tocilizumab. Not all Grade 4 CRS reactions following CART-19 have been immediately treated with tocilizumab and decisions are, in part, based upon the rapidity of the syndrome onset and underlying patient reserve.

Tocilizumab should be used as a single, weight-based dose of 8 mg/kg at the time of hemodynamic instability. This management approach is designed to avoid life-threatening toxicities, while attempting to allow the CAR cells to establish a proliferative phase that appears to correlate with anti-tumor efficacy. Thus, the timing of the tocilizumab should be individualized, in close consultation with the Principal Investigator and/or expert consultants.

Other anti-cytokine therapies, such as repeat administration of tocilizumab or use of siltuximab or etanercept, may also be considered if the patient does not respond to the initial dose of tocilizumab. If the patient experiences ongoing CRS despite administration of anti-cytokine directed therapies, anti T-cell therapies such as cytoxan, ATG, campath may be considered.

A detailed treatment algorithm has been established for with clear criteria for CRS management following CART-19 administration and guidance on when to administer tocilizumab (**Figure 5.3.1.4**). This approach was designed to avoid life-threatening toxicities, while attempting to allow the CART-19 transduced cells to establish a proliferative phase which appears to correlate with tumor response. The management of CRS is based solely upon clinical parameters. This algorithm may be used to guide CRS management related to MOv19-BBz CAR T cell treatment; however, changes specific to the MOv19-BBz CAR T cells should be considered and based on clinical judgment. Specific CRFs have been developed for the capture of CRS elements, severity, management and response to intervention.

Figure 5.3.1.4 CRS Management Algorithm



Neurologic Toxicity.

Guidelines for management of neurologic toxicity are described in **Table 5-1**. The mechanism underlying neurotoxicity after CAR T cell administration is poorly understood. Anecdotal evidence suggests that anti-IL6 therapies, which are effective for CRS, do not reverse neurotoxicity. Neurotoxicity can be asynchronous with cytokine release syndrome, often reaching its maximum intensity later than CRS or even arising after resolution of CRS. This has led to the appearance in some cases that treatment of CRS with anti-IL6 agents worsens or precipitates neurotoxicity; a causative relationship between anti-IL6 therapy and neurotoxicity has not been conclusively established, however, and severe neurotoxicity has been observed in the absence of CRS and in cases where no anti-IL6 therapy has been used. The following principles guide the recommended management of neurotoxicity:

- Most instances of neurologic toxicity are self-limited, but life-threatening complications such as cerebral edema develop in some cases. Corticosteroid therapy aimed at dampening CAR T cell proliferation and activity is therefore recommended for moderate (grade 2-3) neurotoxicity with the objective of preventing development of life-threatening, grade 4 manifestations. The efficacy of corticosteroids is unproven, however, and corticosteroids may adversely affect CAR T cell efficacy. The recommended dose of corticosteroids is therefore stratified based on perceived risk of developing life-threatening complications; low/moderate doses are recommended for grade 2, moderate doses for grade 3, and high-doses for grade 4. In addition, it is recommended that cytotoxic chemotherapy be considered in grade 4 cases based on a report that cerebral edema improved promptly after cyclophosphamide chemotherapy in one case [129].
- Consultation with a neurologist is helpful for properly documenting and tracking neurologic abnormalities, evaluating for other potential etiologies of neurologic abnormalities, and managing neurologic emergencies such as seizure or elevated intracranial pressure.
- Coagulopathy and thrombocytopenia should be aggressively managed. Both coagulopathy and thrombocytopenia often develop with CRS. Intracranial hemorrhage has been observed in conjunction with severe neurotoxicity. Intracranial hemorrhage may provide a portal of entry for CAR T cells and systemic cytokines to affect the CNS or may simply confound interpretation of neurologic abnormalities. In addition, a recent report suggests that thrombocytopenia is an independent risk factor for CAR-related neurotoxicity, and platelets may serve as a source of mediators that stabilize the endothelium and counteract destabilizing effects of cytokines elaborated during CAR T cell proliferation[130].
- CRS should be managed concurrently with neurotoxicity according to guidelines enumerated above. It is difficult to distinguish delirium secondary to CRS from mild/early CAR-related neurotoxicity (and these phenomena may not be distinct pathophysiologically). In general, for subjects with grade ≥2 neurologic toxicity in conjunction with CRS requiring tocilizumab, it is recommended that corticosteroids be administered together with or before tocilizumab to dampen a potentially exacerbating effect of tocilizumab on neurotoxicity.

Table 5-1: Neurotoxicity management

Neurologic Event Grade	Toxicity Management Guidelines - **If subject experiencing concurrent CRS, follow CRS management guidelines in parallel.**
Grade 1	• Consider non-sedating antiseizure medicines (eg levetiracetam) for seizure prophylaxis.
Grade 2	• Consider neurology consultation • Perform head imaging, preferably MRI; consider lumbar puncture and/or funduscopic exam. • Consider dexamethasone 8-40 mg/day in divided doses • Consider non-sedating antiseizure medicines (eg.levetiracetam) for seizure prophylaxis • Administer platelet transfusion if platelet count <30000/µl; monitor for coagulopathy- if fibrinogen < 150 mg/dl give cryoprecipitate
Grade 3	• Consider neurology consultation • Perform head imaging, preferably MRI; consider lumbar puncture and/or funduscopic exam. • Administer dexamethasone 10mg every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days • Consider non-sedating antiseizure medicines (eg.levetiracetam) for seizure prophylaxis • Administer platelet transfusion if platelet count <30000/µl; monitor for coagulopathy- if fibrinogen < 150 mg/dl give cryoprecipitate
Grade 4	• Consider neurology consultation • Perform head imaging, preferably MRI; consider lumbar puncture and/or funduscopic exam. • Administer methylprednisone 1000 mg intravenous per day for a total of 3 days then taper as indicated. Consider a 50% decrease every 3 days. • Consider non-sedating antiseizure medicines (eg.levetiracetam) for seizure prophylaxis • Administer platelet transfusion if platelet count <30000/µl; monitor for coagulopathy- if fibrinogen < 150 mg/dl give cryoprecipitate • Consider cytotoxic chemotherapy (e.g., cyclophosphamide 1.5 g/m2)

Anaphylaxis

According to our experience treating 14 subjects with anti-mesothelin SS1 CAR mRNA T cells (7 mesothelioma subjects under UPCC# 17510, 6 pancreatic cancer subjects under UPCC# 08212, and one pancreatic cancer subject under UPCC# 21211), anaphylaxis is a rare but possible toxicity created by repeated CAR T cells infusions with long periods of time between infusions (See **Section 1.6**). Management of anaphylaxis includes epinephrine, volume resuscitation, and corticosteroids, and other supportive care as needed (oxygen, ventilation, beta2 agonists for bronchoconstriction, etc.). Management is generally similar to that described for cytokine release syndrome (as above), but with the use of epinephrine as the principal therapeutic medication. The dose of epinephrine used depends on the degree of systemic involvement (low dose for hypotension, high dose -1 mg iv repeated every minute as necessary) for PEA arrest, according to ACLS guidelines.

Off-Tumor On-Target Toxicities
In the event of aFR reaction on normal tissue and inflammatory process leading to fluid accumulation, these cavities can be quickly and readily accessed in a minimally invasive fashion to remove the fluid as anti-lymphocyte therapy is initiated. T cell ablating therapies including corticosteroids, chemotherapy such as cyclophosphamide, or immunotherapy such as alemtuzumab may also be considered at the investigators' discretion. These toxicities should also be further managed per treating investigator discretion and standard clinical practice.

For additional potential risks of therapy, please refer to **Section 1.6**.

5.3.2 Cyclophosphamide

Receipt of Cyclophosphamide
Cyclophosphamide will be ordered through the site-designated research pharmacy for research purposes.

Storage
Cyclophosphamide will be a stored according to the manufacturing instructions in the approved package insert.

Premedication for Cyclophosphamide
It is anticipated that patients receiving cyclophosphamide may experience nausea and vomiting as a side effect of the treatment. Anti-emetic prophylaxis premedication for nausea (including corticosteroids) can be administered prior to infusion of chemotherapy according to the institutional standards. Choice of specific agent will be left to the discretion of the investigator, and may include corticosteroids as appropriate. For more details, see **Sections 5.6** and **6.5**.

Cyclophosphamide Administration
Cyclophosphamide will be administered at a dose of 300 mg/m^2/day x 3 days by IV infusion either in the Hematology-Oncology infusion suite at the Perelman Center for Advanced Medicine or elsewhere at the Hospital of the University of Pennsylvania. Infusions will be scheduled so that the last day of chemotherapy falls 3 days (±1 day) prior to CAR T cell infusion (Day 0) (**Section 6.6**). Appropriate institutional procedures for proper handling and disposal of antineoplastic drugs will be followed.

5.3.3 Fludarabine

Receipt of Fludarabine
Fludarabine will be ordered through the site-designated research pharmacy for research purposes.

Storage
Fludarabine will be a stored according to the manufacturing instructions in the approved package insert.

Premedication for Fludarabine
It is anticipated that patients receiving fludarabine may experience nausea and vomiting as a side effect of the treatment. Anti-emetic prophylaxis premedication for nausea (including corticosteroids) can be administered prior to infusion of chemotherapy according to the institutional standards. Choice of specific agent will be left to the discretion of the investigator, and may include corticosteroids as appropriate. For more details, see **Sections 5.6** and **6.5**.

Fludarabine Administration

Fludarabine will be administered at a dose of 30 mg/m^2/day x 3 days by intravenous infusion either in the Hematology-Oncology infusion suite at the Perelman Center for Advanced Medicine or elsewhere at the Hospital of the University of Pennsylvania. Fludarabine doses will be rounded down to the nearest 50 mg vial size, if the rounded dose does not differ by > 10% of the original dose prescribed. Infusions will be scheduled so that the last day of chemotherapy falls 3 days (±1 day) prior to CAR T cell infusion (Day 0) (**Section 6.6**). Appropriate institutional procedures for proper handling and disposal of antineoplastic drugs will be followed.

5.3.3.1 Possible Reactions after Cyclophosphamide Infusion

Potential risks of cyclophosphamide administration and their management are described in **Section 1.6** and **6.5**.

5.4 Dose-Limiting Toxicity (DLT) and Cohort Progression

A dose limiting toxicity is defined as grade ≥3 hematologic or non-hematologic toxicity [NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0)] which develops following dosing and through the Day 28 safety follow-up visit, is new (not existent before infusion), at least possibly related to T cells, and does not improve to Grade ≤ 2 within 7 days of optimal medical management. Component events that are captured as adverse events of particular interest (such as hypoxia and hypotension in the setting of CRS) may not be evaluated separately against the DLT definition.

Events excluded from the above DLT definition are:

- Alopecia
- Grade 3 electrolyte abnormalities
- Hyperglycemia
- Diarrhea
- Nausea and vomiting that can be managed with supportive care
- Grade 4 neutropenia/leukopenia or thrombocytopenia that improves to ≤ Grade 2 by Day 28

5.5 Subject Compliance Monitoring

Adherence to scheduled follow-up visits is important in order to assess the primary safety endpoint associated with this study. During the process of informed consent, each patient will be clearly informed of the study schedule, associated procedures, and the requirement for follow-up. Patients that are not able to commit to the study schedule will not be enrolled in the study.

5.6 Prior and Concomitant Therapy

All prescription and nonprescription medication, vitamins, herbal and nutritional supplements, or devices taken/used by the subject as well as any prior surgeries beginning within 30 days prior to consent will be recorded. At every visit following the MOv19-BBz CAR T cell infusion, concomitant medications will be recorded in the medical record and on the appropriate CRF. Any additions, deletions, or changes of these medications will be documented. All prior oncology therapies for their targeted disease will also be collected in the appropriate eCRF.

Concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed. Subjects may also continue to receive standard therapies and/or undergo routine care procedures for the management of their disease prior to receipt of study treatment and while their

product is being manufactured. However, the following concomitant therapy guidelines must be adhered to during the study:

- The addition of any other concurrent cancer treatment (including cytotoxic, hormonal, homeopathic, or immunologic therapy) will confound the assessment of safety and efficacy of the investigational product. Thus, cancer treatment is not allowed within the 2 weeks before apheresis and 2 weeks before T cell infusion. Medication intended solely for supportive care (e.g. analgesics, antiemetics, antidiarrheals, antidepressants or bisphosphonates, etc.) may be used at the investigator's discretion. Palliative radiation therapy for symptom management is allowed.
- PD-1 or PD-L1 targeted therapies are not allowed while the subject is in primary follow-up.
- Prior aFR targeted therapies are permissible if received > 4 weeks from study treatment.
- Prophylactic use of granulocyte colony-stimulating factor (G-CSF, filgrastim) may be used if medically indicated, particularly in a patient who is experiencing recurrent difficulties with neutropenia, however the effects of G-CSF on product manufacturing are unknown.
- GM-CSF should be avoided due to potential to worsen CRS symptoms. Therapeutic use in patients with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, etc. may be considered at the investigator's discretion, consistent with American Society of Clinical Oncology guidelines. The use of erythropoietin is also permitted at the discretion of the treating physician.
- Use of systemic high dose (e.g. > 100 mg of prednisone daily or >40 mg dexamethasone daily or equivalent) corticosteroids or other immunosuppressant drugs should NOT be used as pre-medication for MOv19-BBz CAR T cell infusion or following the infusion, unless under life threatening circumstances or to manage toxicity. Patients may be on a stable low dose of steroids (≤10mg daily equivalent of prednisone) if determined clinically appropriate, except if used for the treatment of CNS disease. Corticosteroids treatment as anti-emetic prophylaxis on the day of lymphodepleting chemotherapy administration is allowed per institutional guidance. Topical and inhaled steroids are permitted at any time as per clinical discretion.
- The use of systemic cyclosporine or other immunosuppressive drugs while on study is not permitted unless deemed medically necessary by the investigator for treatment of adverse events.
- Paracentesis: Therapeutic paracentesis may be performed at the time of CAR T cell infusion per clinical discretion. Paracentesis should be avoided within 1 week after CAR T cell infusion.
- Therapeutic anticoagulation is allowed while on study and may be held around the time of catheter placement as per standard clinical procedure.
- Prophylaxis will be initiated post lymphodepleting chemotherapy. To align with standard hospital practice in CAR T cell therapies using fludarabine and cyclophosphamide for lymphodepletion, the following prophylaxis is recommended. Alterations to these recommendations may be implemented as per physician-investigator clinical discretion.
    - Levofloxacin and fluconazole until count recovery (ANC ≥ 500), AND
    - Acyclovir and Bactrim for 100 days or until absolute CD4 ≥ 200

6 STUDY PROCEDURES

Overview

The study consists of 1) pre-screening 2) a screening/enrollment phase, 3) apheresis and T cell manufacturing, 4) pre-infusion safety check, 5) an intervention phase consisting of MOv19-BBz CAR T cell administration alone or following study-mandated chemotherapy, 6) primary follow-up visits, and 7) long-term follow-up. The Schedule of Events is included in **Appendix 1**.

6.1 Screening

Pre-Screening

Patients will first be pre-screened for alpha folate receptor expression. The test for alpha folate receptor expression is a laboratory developed test, developed and conducted by the Hospital of the University of Pennsylvania Pathology and Laboratory Medicine lab to determine subject eligibility. This test is not an approved FDA device and its use is investigational.

Subjects will be asked to sign a separate pre-screening informed consent requesting permission to test their tumor for aFR expression. Evaluation of aFR expression will occur on archived tumor tissue, if the patient has not had an anti-aFR directed therapy since the collection of the archived sample. However, if archived tumor tissue is not available, a fresh biopsy may be performed. Once aFR expression has been confirmed, subjects may be presented the informed consent for the main study. If the aFR expression of their tumor is known prior to signing the tissue testing consent for this study, the results of this testing will need to be confirmed as part of the subjects' participation on this protocol. Once aFR expression has been confirmed, subjects may proceed to the next step and be presented the informed consent for the main study.

Screening

Informed consent must be obtained before the subject can undergo any research-related procedures. Results obtained in routine clinical care prior to informed consent may also be used for screening purposes as long as they are obtained within the protocol required windows.

Screening procedures include:

- ECOG performance status
- Complete medical history
- Physical examination including vital sign assessments, height and weight
- Review of concomitant medications
- Leukapheresis screening- Subjects can be given the opportunity to undergo temporary central venous access for apheresis if peripheral access cannot be obtained.
- Complete blood count and differential
- Chemistry panel- including sodium, potassium, chloride, CO2, blood urea nitrogen, creatinine, glucose, magnesium, phosphate, total protein, albumin, calcium, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
- Coagulation Factors- PT, PTT, fibrinogen, INR
- Viral serologies: HIV, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody, Hepatitis B core antibody, and Hepatitis C antibody. If the HCV antibody is positive, a screening HCV RNA by any RT-PCR or bDNA assay must be performed. Eligibility will be determined based on the screening value. The test is not required if documentation of a negative result of a HCV RNA test performed within 60 days prior to screening is provided.
- Autoantibody panel: ANA
- Urinalysis
- 12 lead Electrocardiogram (EKG)
- Resting echocardiogram (ECHO) or MUGA- must be performed within 8 weeks prior to the CAR T cell infusion.
- Urine β HCG pregnancy (women of childbearing potential)
- CT chest/abdomen/pelvis-with or without contrast within 8 weeks of physician-investigator confirmation of eligibility. CT scans are the preferred modality; however, other methodologies

may be utilized at the physician-investigator's discretion, if performed in accordance with RECIST 1.1 criteria.
- MRI brain- required only if the subject has known CNS metastases

In the event that the time between the above screening tests and the infusion of MOv19-BBz CAR T cells exceeds the 8-week Screening/Enrollment Window the following will be repeated: Physical Examination, Performance Status Assessment, Complete Blood Count with differential and Platelet Count, Chemistry Panel, Pregnancy test, HIV and Hepatitis B/C tests, echocardiogram/MUGA, and CT chest/abdomen/pelvis.

6.2 Monitoring Visit for Eligibility

Assignment of subject numbers will occur at the time of pre-screening consent, will be in ascending order, and no numbers will be omitted. Subject numbers will be used on all study documentation. Once assigned, the subject number must not be reused for any other subject and it must not be changed, even if the subject is rescreened.

A Consent Notification Form should be completed at the time of Pre-Screening Consent and Main Informed Consent. Once required screening tests have been completed and the subject has been determined eligible by the Physician-Investigator, provide the documents listed below to:

Sponsor Protocol Monitor and Sponsor Project Manager
Center for Cellular Immunotherapies (CCI)

Documents required:
- Completed Eligibility Form
- Redacted copy of signed subject informed consent and HIPAA Authorization
- Redacted source documentation to confirm enrollment/eligibility (including patient past medical history, laboratory, radiological reports, physical exam, concomitant medications and any other source documentation to support that the patient meets eligibility criteria and has completed all required screening assessments).

Upon receipt of screening and eligibility documentation, the Sponsor Protocol Monitor will review and provide documentation that the monitoring visit for eligibility has been completed. This documentation must be received prior to apheresis and/or cell product manufacturing.

6.3 Leukapheresis

A large volume apheresis procedure will be carried out at the University of Pennsylvania Apheresis Center according to standard clinical procedures (~4-6 weeks prior to infusion of the MOv19-BBz CAR T cells). PBMC are obtained for CAR T cells during this procedure. From a single leukapheresis, the intention is to harvest at least 5 x 10^9 white blood cells to manufacture MOv19-BBz CAR T cells. The MOv19-BBz CAR T cell product is expected to be ready for release approximately 4 weeks later. If the harvest of cells or the T cells manufacture is unsuccessful, subjects will have the option to undergo a second leukapheresis for a second manufacturing process. Subjects have the option to receive a lower than target dose if the MOv19-BBz CART product meets CVPF release criteria, and the subject cannot or is not willing to perform a second apheresis, or if the second manufacturing process fails. If a subject has previously had an adequate apheresis collection banked according to current Good Manufacturing Practices at the Clinical Cell and

Vaccine Production Facility, these cells may be used as the source of cells for MOv19-BBz CAR T cells manufacturing.

Recommended criteria for apheresis product acceptance to initiate processing for clinical manufacturing to meet the dosing requirements includes the following specifications: It is recommended that the patient have an absolute lymphocyte count (ALC) ≥500/µl, prior to undergoing apheresis. If the patient's ALC is <500/µl, it is recommended that a lymphocyte subset analysis (CD3, CD4, CD8 counts) be performed to confirm that the patient has an absolute CD3 count of ≥150/µl. If the absolute CD3 count is <150/µl, it is recommended that the leukapheresis procedure be delayed until their ALC is ≥500/µl or absolute CD3 count is ≥150/µl.

The apheresis product is transported to the CVPF for processing. A portion of the peripheral blood leukocytes will be saved for the TCSL laboratory at the University of Pennsylvania and used for baseline immunoassessment research assays, a portion will be sent to PDCS for biobanking, and the other portion used for The MOv19-BBz CAR T cell manufacturing in CVPF. Baseline blood leukocytes for FDA look-back requirements will also be obtained and cryopreserved.

Historical Apheresis Sample

Cryopreserved historical apheresis products collected from the patient as part of routine care or under a separate research protocol may be usable for the MOv19-BBz CAR T manufacturing if the sample was collected at an appropriately certified apheresis center and if the product meets adequate mononuclear cell yields.

6.4 Pre-infusion safety visit (Week -2 to -1)

1-2 weeks prior to the scheduled T cell infusion, subjects will be tested for baseline evaluations according to the Schedule of Events in **Appendix 1**.

If the subject has an accessible tumor and it is determined clinically feasible, a baseline tumor biopsy will be performed prior to MOv19-BBz CAR T cell infusion. This may include a CT-guided needle biopsy or needle aspiration of malignant effusion. The baseline biopsy may occur any time prior to infusion between Day -14 and initiation of study treatment (i.e. lymphodepleting chemotherapy in applicable cohorts or MOv19-BBz CAR T cells). This baseline biopsy sample will be used to evaluate the level of aFR expression and if feasible, other immune markers at baseline. If the subject had a fresh biopsy at pre-screening in order to evaluate aFR expression, a repeat biopsy at the pre-infusion timepoint is not required.

6.5 Lymphodepleting chemotherapy administration (Cohorts 2 and 3 only)

Subjects in Cohorts 2 and 3 will receive lymphodepleting chemotherapy as a regimen of cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2 daily over three days. Note: Fludarabine doses will be rounded down to the nearest 50 mg vial size, if the rounded dose does not differ by > 10% of the original dose prescribed. This lymphodepleting chemotherapy regimen must be scheduled so that the last day of therapy falls 3 days (+/- 1 day) prior to CAR T cell infusion. Although both cyclophosphamide and fludarabine are FDA-approved agents and will be prepared and infused in accordance with their FDA-approved labels and standard institutional practice, their use in this trial will be considered investigational.

Lymphodepleting chemotherapy is **NOT** required if the subjects WBC ≤ 1,000 /µL or if the subject received bridging chemotherapy with cyclophosphamide or fludarabine as per routine care within 28 days of the 1st day of the planned lymphodepleting chemotherapy regimen. Subjects who receive lymphodepleting

chemotherapy but in whom their CAR T cell infusion is subsequently delayed >2 weeks after the first day of lymphodepleting chemotherapy may receive a second cycle of lymphodepleting chemotherapy prior to CAR T cell infusion at the discretion of the physician-investigator.

Subjects will undergo assessments per the Schedule of Events in **Appendix 1** prior to their first day of lymphodepleting chemotherapy. If >48 hours have passed since subject's last blood work, a complete blood count with differential, and full chemistry panel will be repeated prior to initiating chemotherapy.

The following criteria must be met in order to proceed with lymphodepleting chemotherapy administration:

1) Patients should not have received systemic chemotherapy within 2 weeks prior to the scheduled MOv19-BBz CAR T cell infusion. If chemotherapy was administered, then this procedure will be re-scheduled.
2) Patients must have recovered from toxicities, including myelosuppression, resulting from routine care chemotherapy or other immunotherapies administered after physician-investigator confirmation of eligibility as per the discretion of the treating physician.
3) Patients should not experience a significant change in performance status compared to initial eligibility criteria that would, in the opinion of the treating physician-investigator or PI, increase the risk of experimental cell infusion.
4) Patients must not have laboratory abnormalities after physician-investigator confirmation of eligibility that, in the opinion of the treating physician-investigator or PI, may impact subject safety or the subjects' ability to receive lymphodepleting chemotherapy or the MOv19-BBz CAR T cells. If this occurs, patients may have their treatment delayed until both the treating investigator and PI determine it is clinically appropriate to proceed.
5) All subjects must undergo a Respiratory Virus Panel (RVP) within 10 days prior to MOv19-BBz CAR T cell infusion. If the patient is positive for influenza, Tamiflu® or equivalent should be administered per package insert. The patient must complete treatment **prior** to receiving lymphodepleting chemotherapy and MOv19-BBz cells. The test does not need to be repeated prior to the MOv19-BBz cell infusion; however if influenza signs and symptoms are present, the infusion should be delayed until the patient is asymptomatic. If the patient is positive for another virus on the RVP, the MOv19-BBz cell infusion will be delayed for at least 7 days to be sure clinical symptoms of a viral infection do not develop. If clinical symptoms develop, the lymphodepleting chemotherapy and CAR T cell infusion will be delayed until resolution of these symptoms.
6) Patients should not experience any of the following specific toxicities:
    a. Pulmonary: New requirement for supplemental oxygen or presence of progressive radiographic abnormalities on chest x-ray (chest x-ray is not required at this juncture but should be evaluated if performed for clinical purposes)
    b. Cardiac: New cardiac arrhythmia not controlled with medical management.
    c. Hypotension requiring pressor support.
    d. Active Infection: Positive blood cultures for bacteria, fungus, or virus within 48-hours of T cell infusion.

Anti-emetic prophylaxis:
It is anticipated that patients receiving cyclophosphamide may experience nausea and vomiting as a side effect of the treatment. Premedication for nausea can be administered prior to infusion of chemotherapy. Choice of specific agent will be left to the discretion of the investigator. Corticosteroids treatment as anti-emetic prophylaxis on the day of cyclophosphamide administration is allowed per institutional guidance per **Section 5.6**.

Prophylactic antibiotics will be administered post lymphodepleting chemotherapy per institutional standards and practices for cellular therapies as described in **Section 5.6**.

Potential Side Effects
See **Section 1.6**/ Risks of fludarabine and cyclophosphamide for more information.

6.6 MOv19-BBz CART Product Administration (Day 0)

CAR T cell infusion will begin 3 days (±1 day) after completion of chemotherapy (Cohorts 2 and 3).

Prior to the administration of MOv19-BBz CAR T cells, all subjects will undergo tests/procedures in accordance with the Schedule of Events in **Appendix 1**. Subjects will also have an intraperitoneal catheter placed by Interventional Radiology according to standard hospital procedure.

The following criteria must be met in order to proceed with the MOv19-BBz CAR T cell infusion:

a. Subjects in Cohorts 2 and 3 should not have received systemic chemotherapy other than lymphodepleting chemotherapy per protocol within 2 weeks prior to the MOv19-BBz CAR T cell infusion. If chemotherapy was administered, then this infusion will need to be re-scheduled.
b. Subjects should not experience a significant change in performance status compared to initial eligibility criteria that would, in the opinion of the treating physician-investigator or PI, increase the risk of experimental cell infusion.
c. Subjects must not have laboratory abnormalities after physician-investigator confirmation of eligibility that, in the opinion of the treating physician-investigator or PI, may impact subject safety or the subjects' ability to receive MOv19-BBz CAR T cells. If this occurs, subjects may have their treatment delayed until both the treating investigator and PI determine it is clinically appropriate to proceed.
d. All subjects must undergo a Respiratory Virus Panel (RVP) within 10 days prior to MOv19-BBz CAR T cell infusion. If the subject is positive for influenza, Tamiflu® or equivalent should be administered per package insert. The subject must complete treatment **prior** to receiving lymphodepleting chemotherapy and MOv19-BBz cells. The test does not need to be repeated prior to the MOv19-BBz cell infusion; however if influenza signs and symptoms are present, the infusion should be delayed until the subject is asymptomatic. If the subject is positive for another virus on the RVP, the MOv19-BBz cell infusion will be delayed for at least 7 days to be sure clinical symptoms of a viral infection do not develop. If clinical symptoms develop, the lymphodepleting chemotherapy and CAR T cell infusion will be delayed until resolution of these symptoms.
e. Subjects should not experience any of the following specific toxicities:
    a. Pulmonary: New requirement for supplemental oxygen or presence of progressive radiographic abnormalities on chest x-ray (chest x-ray is not required at this juncture but should be evaluated if performed for clinical purposes)
    b. Cardiac: New cardiac arrhythmia not controlled with medical management.
    c. Hypotension requiring pressor support.
    d. Active Infection: Positive blood cultures for bacteria, fungus, or virus within 48-hours of T cell infusion.

Please refer to **Section 5.3** (Preparation and Administration of Study Drug) for complete details. Potential reactions after infusion are presented in **Section 5.3.1.4**.

6.7 Post-infusion visits and tumor biopsy

Subjects will return to the center (outpatient clinic of the study investigators or treating physician) at days +1, +2(+1), +7 (±1), +10 (±1), +14 (±1), and +21 (±1) for safety follow-up and to have blood drawn for evaluation of the safety endpoints and secondary (research) endpoints per the Schedule of Events in **Appendix 1**.

If the subject's tumor is measurable by CT and accessible by image-guided biopsy, subjects will undergo a tumor biopsy under image guidance at day 14(±7) to evaluate the impact of therapy on the tumor microenvironment and to assess for the presence of CAR T cells and aFR expression. These will be compared to baseline values from fresh biopsies if available, or stored surgical tumor specimens as applicable. Thus, the same tumor site biopsied at baseline should be preferentially biopsied at this timepoint.

In case of unexpected AEs or SAEs, additional samples may be collected for research analysis, focused on evaluating the potential causality with the infused MOv19-BBz CAR T cells see **Section 3.3**/Collection of Research Samples.

6.8 Day 28 (+/- 5 days): Safety and Tumor staging

At this study visit, subjects will undergo tests and procedures in accordance with the Schedule of Events in **Appendix 1**. Tumor response will be assessed as described in **Section 7.1**. A mini-apheresis procedure (~5 L) will also be performed at this visit for research purposes. A 60 ml blood draw may be substituted for the mini-apheresis procedure at the discretion of the treating investigator.

6.9 Month 2 (+/- 5 days): Safety

Subjects will return to the center at Month 2 following MOv19-BBz CAR T cell infusion. At this study visit, subjects will undergo tests and procedures in accordance with the Schedule of Events in **Appendix 1**.

6.10 Month 3 (+/- 5 days): Safety and Tumor staging

Subjects will return to the center at Month 3 following MOv19-BBz CAR T cell infusion. At this study visit, subjects will undergo tests and procedures in accordance with the Schedule of Events in **Appendix 1**. In addition, tumor staging (CT chest/abdomen/pelvis) will be performed. A CT scan within 4 weeks of this visit is acceptable. Tumor response will be assessed as described in **Section 7.1**.

6.11 Month 6 (+/- 5 days): Safety and Tumor staging

Subjects will return to the center at Month 6 following MOv19-BBz CAR T cell infusion. At this study visit, subjects will undergo tests and procedures in accordance with the Schedule of Events in **Appendix 1**. In addition, tumor staging (CT chest/abdomen/pelvis) will be performed. A CT scan within 4 weeks of this visit is acceptable. Tumor response will be assessed as described in **Section 7.1**.

6.12 Quarterly evaluations for up to 2 years post-infusion

After month 6, subjects will be evaluated on a quarterly basis for up to 2 years post infusion or until the subjects' disease progresses and/or they initiate another cancer-related therapy. At these study visits, subjects will undergo tests and procedures in accordance with the Schedule of Events in **Appendix 1**.

6.13 Long-term Follow-up Phase

Subjects who complete or prematurely discontinue from primary study follow-up will enter into the long-term follow-up phase of this study and will be followed for up to 15 years after the MOv19-BBz CAR T cell infusion. The visit schedule during long-term follow-up is calculated from the time of the subject's MOv19-BBz CAR T cell infusion (Day 0) and the time of discontinuation from primary follow-up. **Table 6-1** indicates the **1st** LTFU study visit that would need to be completed based on Day 0.

Table 6-1: 1st LTFU study visit to be completed

Last study visit in primary follow-up	1st LTFU study visit
<3 months	3 mo
≥3 months and <6 months	6 mo
≥6 months and <9 months	9 mo
≥9 months and <1 year	1 yr
>1 year and <1.5 years	1.5 yr
>1.5 years and <2 years	2 yr
= 2 year	2.5 yr

During long-term follow-up, subjects will undergo tests and assessments in accordance with the Schedule of Events in **Appendix 1**. Subjects who enter long-term follow-up prior to disease progression will be followed for response per routine clinical care, until the subject's disease progresses post MOv19-BBz CAR T cell infusion or they begin a new cancer therapy.

In the event that a subject cannot return to the University of Pennsylvania for follow-up visits, the subject's local provider will also be asked to provide information from the patient's medical record to the study team at protocol-defined time points (i.e. the results of routine care physical examinations and/or laboratory assessments), and assist in the collection of protocol-required blood samples for persistence testing, which will be sent to the University of Pennsylvania Translational and Correlative Studies Laboratory (TCSL). The patient's local provider will also be asked to assist in the monitoring and reporting of protocol defined adverse events, and provide copies of documentation pertaining to the absence or presence of delayed adverse events, along with the relevant reports of tests and procedures. After the Month 60 (5 year) follow-up visit, subjects will only be asked to return for study visits if there is evidence of ongoing persistence of CAR T-cells in the previous year. If there is no evidence of CAR T-cell persistence in the previous year, follow-up will be conducted via phone/email/mail. The Follow-up Survey in **Appendix 2** may be used to facilitate contact with the subject as required. The template Physician Letter in **Appendix 3** may be used to contact the patient's local provider and facilitate their assistance in identifying any protocol defined adverse events.

Additional research blood may also be collected during the primary or long-term follow-up phases of the study. The total amount of extra blood that may be collected will not exceed 3 tablespoons of blood twice in one week. In addition, tumor tissue from tumor biopsies that are performed during long-term follow-up as part of routine care may be provided to TCSL for correlative studies.

7 ASSESSMENTS

7.1 Tumor assessments

All subjects who receive the target dose of MOv19-BBz CAR T cell infusion will be considered evaluable for response. Baseline scans should be obtained within 28 days prior to infusion of MOv19-BBz CAR T cells and after any cancer therapy administered between collection and MOv19-BBz CAR T cell infusion. In Cohorts 2 and 3, baseline scans should be obtained prior to lymphodepleting chemotherapy administration and MOv19-BBz CAR T cell infusion.

Radiographic imaging (CT) assessment

Radiographic responses will be measured using two imaging assessment approaches: 1) Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and 2) immune related response evaluation criteria in solid tumors (irRECIST) when feasible. For RECIST 1.1 evaluation, the determination of antitumor efficacy will be based on objective tumor assessments made according to the system of unidimensional evaluation. The same method and technique should be used to characterize each identified and reported lesion at baseline, during the study treatment period, and during follow-up. Imaging-based evaluation rather than clinical examination is the required technique when either could be used to assess the antitumor effect of the treatment. Computed Tomography (CT) scan is the preferred method for the tumor assessment. While CT scans are the preferred modality, other methodologies (MRI, etc.) may be utilized at the physician-investigator's discretion, if performed in accordance with RECIST 1.1 criteria. Scans may be administered with or without contrast at the investigator's discretion.

Because immune therapy can cause an initial tumor volume increase due to inflammation prior to subsequent tumor shrinkage, an exploratory analysis of response status will also be conducted using the recently developed immune related response evaluation criteria in solid tumors (irRECIST) [131-133]. Novel to the irRECIST is the measurement of overall tumor burden as a metric of disease progression, compared to the limitation of using only baseline lesion measurements according to RECIST 1.1. According the irRECIST, new lesions do not constitute disease progression if net tumor burden including new lesions is stable or decreases. The irRECIST also permit disease progression at a subsequent time point after first detection. This accounts for the period required for activated T-cells to infiltrate the tumor, which may cause initial tumor volume increase due to inflammation but can subsequently translate into tumor shrinkage. The irRECIST also classifies durable stable disease as clinical activity. Thus, this protocol will explore two distinct imaging criteria for determination of disease outcome in response to treatment with MOv19-BBz CAR T cells.

For details, please see the Schedule of Events **(Appendix 1)**, which summarizes information on the timing of study assessments.

Tumor biomarkers

Tumor biomarkers as appropriate for ovarian cancer patients, such as CA125, will be measured according to the Schedule of Events (**Appendix 1**).

7.2 Research Correlative Studies Assessment

The planned correlative studies are as follows:

1. Determine the persistence of MOv19-BBz CAR T cells in peripheral blood.
   Peripheral blood mononuclear cells' DNA will be evaluated by Q-PCR using a validated assay that detects a fragment unique to the CAR sequence. PBMC may also be used for a flow cytometry

based assay for determination of MOv19-BBz CAR T cells. These analyses will be performed in bulk on each patient on peripheral blood, tumor derived material where available, or other tissues/fluids (ascites, peritoneal fluid, etc.). The primary engraftment endpoint is the # DNA CAR vector copies at Day 28 after infusion. CAR T cell vector sequences will be performed at pre- and all post-infusion study visits as outlined in the Schedule of Events (**Appendix 1**). Additional testing may also be performed at unscheduled timepoints at the discretion of the Sponsor. This analysis will continue until any 2 sequential tests are negative documenting loss of CAR T cells. Additionally, flow cytometry may be used to detect cells expressing the MOv19-BBz CAR construct, if feasible.

2. Determine the bioactivity of MOv19-BBz CAR T cells in peripheral blood.
   Serum or fluid (e.g. ascites) will be analyzed using Luminex to determine the presence of a panel of cytokines/chemokines/immune factors. Measurements will be performed in batches to maximize utilization of immune assay kits. In addition, bioactivity of the manufactured and infused MOv19-BBz CAR T cells may be assessed by functional flow cytometry via detection of cytokine production and cytotoxic activity of the cells stimulated with an aFR-expressing cell line.

3. Evaluate the development of immune responses favoring rejection of MOv19-BBz CAR T cells.
   Development of HAMA and HACA antibody responses are expected to result in elimination of MOv19-BBz CAR T cells. Cellular immune responses directed to the modified T cells may also develop and be measured. Correlate the occurrence of such responses with loss of engraftment of CAR T cells.

4. Evaluate the development of secondary anti-tumor responses as a consequence of MOv19-BBz CAR T cells. Tumor cell death mediated by MOv19-BBz CAR T cells may expose the immune system to new antigens, leading to new immune responses directed to the tumor. The development of new immune responses that develop to established tumor cell lines may be assessed and displayed as appropriate to each assay. This may be determined using next-generation sequencing of T cell receptor and immunoglobulin rearrangements in the tumor at baseline and post-infusion.

5. Evaluate the potential to follow tumor biomarker levels as a surrogate of anti-tumor activity. These data will be correlated with changes in imaging and clinical progression. MOv19-BBz CAR T cells may lower serum aFR levels in ovarian cancer patients. This could occur directly by MOv19-BBz CAR T cells eliminating aFR-expressing cells or through binding to soluble aFR protein.

6. Where tumor material or body fluids can be obtained:
   a. Measure trafficking of MOv19-BBz CAR T cells.
   b. Evaluate aFR expression on tumor cells to assess for antigen-escape.
   c. Analyze tumor microenvironment and cell interactions (if feasible)- Immune correlates such as local immune activation (using qRT-PCR); the breath and hierarchy of the B and T cell repertoire via deep sequencing and compare with baseline specimens.

8 STATISTICAL PLAN

8.1 General Design Issues

This is a single-center pilot study in cancer patients to evaluate the safety and feasibility of autologous T cells engineered to express a CAR that targets aFR. The standard 3+3 dose escalation scheme will be

implemented to explore 3 dose cohorts (Cohort 1: 1-3x10^7 cells/m^2 without lymphodepleting chemotherapy; Cohort 2: 1-3x10^7 cells/m^2 after lymphodepleting chemotherapy with cyclophosphamide + fludarabine; Cohort 3: 1-3x10^8 cells/m^2 after lymphodepleting chemotherapy with cyclophosphamide + fludarabine). Dose may be de-escalated to dose cohort -1 (1-3x10^6 cells/m^2 without lymphodepleting chemotherapy) if 2 DLT/3 subjects or 2 DLT/6 subjects occurs in Cohort 1. The Maximum Tolerated Dose (MTD) is defined as the dose at which ≤1 DLT occurs in 6 evaluable subjects tested within the dose range of this study. In order to gather additional data and establish the MTD dose level, the respective cohorts may be expanded to treat up to 6 total evaluable subjects.

8.2 Sample Size Determination

This study will enroll approximately 9 to 18 subjects depending on the occurrence of DLT and the number of dose cohorts examined. With 9 or 18 evaluable subjects, the half-width of the exact 90% confidence interval (CI) will be no more than 27% or 21%, respectively.

8.3 Endpoints for Primary Objectives

The primary objective is to evaluate safety and feasibility. Safety will be evaluated by determining the frequency of adverse events. Clinical feasibility is defined as the frequency of subjects enrolled on this protocol who do not receive MOv19-BBz CAR T cells. Reasons for this occurrence include rapid clinical deterioration or death, and subject withdrawal. Manufacturing feasibility is determined based on the "manufacturing failures" products. The number of manufactured products that do not meet release criteria for vector transduction efficiency, CAR T cell number, T cell purity, viability, and sterility will be determined and defined as "manufacturing failures".

8.4 Endpoints for Secondary Objectives

The secondary objective is to evaluate clinical endpoints of tumor response (e.g., overall response rate, ORR), progression-free survival (PFS) and overall survival (OS). Disease response will be evaluated using RECIST 1.1 criteria. Immune related response evaluation criteria in solid tumors (irRECIST) will also be evaluated when feasible. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment. Additional correlative endpoints include MOv19-BBz CAR T cells engraftment and persistence in peripheral blood and body fluids (including peritoneal fluid), bioactivity of MOv19-BBz CAR T cells in peripheral blood and body fluids (including peritoneal fluid) and other secondary anti-tumor responses as a consequence of epitope spreading.

8.5 Subject Population(s) for Analysis

- The **Screen Set** comprises all patients who are screened for the study.
- The **Enrolled Set** comprises all patients who sign an informed consent form and are determined eligible to participate in the study (excluding screen failures).
- **Screening Failure Set** comprised all patients of who fail to meet the inclusion/exclusion criteria specified by the protocol. This set will be used to evaluate clinical and manufacturing feasibility endpoints.
- The **Safety Evaluable Set** comprises all subjects who received minimum acceptable dose of the MOv19-BBz CAR T cells and will be used for the primary safety endpoints.
- The **Efficacy Evaluable Set** comprises all patients who receive the MOv19-BBz CAR T cells at the intended dose range. Efficacy evaluable patients also include those with disease

progression or death prior to completion of study safety visits. The Efficacy Evaluable Set will be used for the secondary efficacy endpoints.

- The **Efficacy Non-Evaluable Set** comprises patients who receive MOv19-BBz CAR T cells at lower than intended dose. These subjects will be evaluable for safety, but will not be evaluable for response. These subjects will also not be included in DLT evaluations, thus will be replaced in that cohort.
- The **Full Analysis Set (FAS)** comprises all patients who received the MOv19-BBz CAR T cells. This set includes both safety and efficacy evaluable sets and will be used for feasibility, and secondary correlative endpoints or other exploratory analyses.

8.6 Statistical Analysis of Primary and Secondary Endpoints

This is a phase I to study safety and feasibility of MOv19-BBz CAR T cells. The statistical analysis will be primarily descriptive. Summary tables of patient depositions, baseline demographic and clinical characteristics of the patients will be presented. For the primary objective of safety, adverse events will be collected and evaluated for all patients during the protocol specified adverse event reporting period outlined in **Section 9.1**. AEs will be graded for severity using the National Cancer Institute (NCI) – Common Terminology Criteria (v5.0). Frequency and severity of all adverse events will be listed and tabulated by organ system for both overall and within major categories and by grade. Descriptive and exact 90% confidence intervals will be produced for adverse event rates. Feasibility endpoints will be analyzed using proportions and exact 90% confidence intervals. For the secondary clinical endpoints, rates of clinical responses (e.g., overall response rate) will be summarized using proportions and with exact 90% confidence intervals. Distributions of progression-free (PFS) and overall survival (OS) will be presented graphically using Kaplan-Meier curves. **Overall survival** is defined as the time from the date of the infusion to the date of death due to any reason. In case a subject is alive at the date of last contact on or before the date of data cutoff, OS is censored at the date of last contact. Cause of death will be described when applicable. Progression-free survival is defined as the time from the date of the infusion to the date of first documented disease progression or death whenever comes first. Patients will be censored at the date of last documented disease evaluation. Median survival times, PFS and OS probabilities at specific time point (e.g., 6 month, 12 month) will also be presented. Descriptive statistics will be applied to correlative endpoints such numbers of modified CAR T cells in peripheral blood, HACA, measures of host immunity to aFR and measures of adaptive immune function. Relative persistence and trafficking to blood (and optionally tumor) of the MOv19-BBz CAR T cells will be examined by plotting the number of CAR T cells in blood, and the tracking of soluble biomarker levels over time. Correlations between two continuous measures will be determined with non-parametric Spearman rank correlations. We will compute exact 90% confidence intervals for proportions and means when appropriate. Statistical tests if performed will be limited. Efficacy or correlative analyses will be mainly exploratory and used to generate hypothesis for future studies. No adjustment of multiple testing will be made. Possible statistical evaluations may include examining the within-subject change in biomarker values between specific time points via a Wilcoxon signed-rank test (or its parametric test analog if the normally assumption is satisfied) and to compare a continuous (e.g., biomarker) variables between two independent groups of subjects (e.g., responder vs. non-responder) via a Wilcoxon rank sum or two sample t-test.

9 SAFETY AND ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event

An ***adverse event*** (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Intercurrent illnesses or injuries should be regarded as adverse events.

9.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** (SAE) is any AE or protocol-defined AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- leads to a persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- a congenital anomaly or birth defect
- an important medical event

Hospitalizations that meet the following criteria should not be reported as serious adverse events:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, such as preplanned study visits and preplanned hospitalizations for study procedures or treatment administration
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the subject's general condition

Note: Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event.

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-subject hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

9.1.3 Unexpected adverse events

An adverse event is considered unexpected if the event and/or severity (grade) of the event, is not consistent with the risk information described in the investigator brochure or protocol. An investigator brochure is not currently available for this investigational product. Please refer to the Expected Adverse Event Table (**Table 1-1**) for determinations of expectedness. The package insert may be referenced for expected toxicities of fludarabine and cyclophosphamide.

9.1.4 Related adverse events

An adverse event is considered related to participation in the research if there is a reasonable possibility that an event was caused by an investigational product, intervention, or research-required procedures. For the purposes of this study, "reasonable possibility" means there is evidence to suggest a causal relationship. Related adverse events will be classified as possibly related, probably related, and definitely related.

- **Possibly Related**: There is some evidence to suggest a causal relationship, however other factors may have contributed to the event.
- **Probably Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- **Definitely Related:** There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.

9.1.5 Unanticipated Adverse Device Effect (UADE)

(Note: Device refers to the aFR Immunohistochemistry Test) Is any serious adverse effect on health or safety, or any life threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.1.6 Protocol-defined Adverse Events (PDAEs)

During long-term follow-up, only protocol-defined adverse events (PDAEs) will be collected and reported. Protocol-defined adverse events that are also determined to be serious as defined above will be considered protocol-defined serious adverse events (PDSAEs) and require expedited reporting to the sponsor per **Section 9.3**.

The PDAEs are as follows:

1. New incidence or exacerbation of a pre-existing neurologic disorder
2. New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
3. New incidence of hematologic disorder
4. New malignancy (T cell & non T cell)
5. Any serious adverse event or condition the investigator believes may have a reasonable relationship to CAR T cell therapy (including unexpected illnesses or hospitalizations in this patient population)

The following correlative laboratory results will also constitute a protocol-defined adverse event, however these events will be identified by the Sponsor and subsequently reported to the PI/site and FDA:

1. Positive RCL test result
2. Vector insertion site sequencing result with a mono- or oligoclonal vector integration pattern or in a location near a known human oncogene

9.1.7 Adverse Event Reporting Period

For this study, collection of adverse events will begin at the time of apheresis and will continue until the subject is off-study. For subjects who do not undergo apheresis on this study (i.e. historical apheresis product available), adverse event reporting period will begin at the time of CAR T cell infusion (Cohorts 1 and -1) or at the start of lymphodepleting chemotherapy (Cohorts 2 and 3). Collection of adverse events will continue until the subject is off-study.

All adverse events will be collected during Primary Follow-up. After transitioning to long-term follow-up (LTFU), subjects will only be followed for PDAEs. Subjects may not be transitioned to LTFU prior to the Day 28 safety follow-up visit.

9.1.8 Preexisting Condition/General Physical Examination Findings

A preexisting condition is one that is present prior to the start of the Adverse Event Reporting Period. All clinically significant abnormalities should be recorded as a preexisting condition on the medical history eCRF. During the course of the study, a preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens. Preexisting conditions that improve should also be recorded appropriately.

9.1.9 Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if determined to be clinically significant by the physician-investigator. Repeat testing to confirm the abnormality may be performed as per clinical discretion.

Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event. Laboratory abnormalities that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious defined above and/or as per investigator's discretion. Whenever possible, a diagnosis, rather than a symptom should be provided (i.e. anemia instead of low hemoglobin).

9.2 Recording of Adverse Events

Safety will be assessed by monitoring and recording potential adverse effects of the treatment using the Common Terminology Criteria for Adverse Events version 5.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible. Specialized grading systems have also been developed to more appropriately capture events of Cytokine Release Syndrome and CAR Neurotoxicity as described in **Section 9.2.1** and **Section 9.2.2** below.

Subjects will be monitored through interval medical history evaluations, physical examinations, and clinical laboratory assessments as per the Schedule of Events in **Appendix 1**. Adverse events will be collected on an ongoing basis throughout the subject's participation; using testing/examinations, non-directive questioning (e.g. review of systems), subject self-reporting, etc. Information on all adverse events should be recorded in the source documentation. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis. To the extent possible, adverse events should be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event. Do not list symptoms separately if a diagnosis can be assigned. The safety team may require events be reported separately if they occur as SAEs (or in the context of a SAE) even if they can also be considered a constituent of another AE such as CRS.

All adverse events occurring during the adverse event reporting period (defined in **Section 9.1** above) must be recorded. If there are no adverse events identified during a study visit occurring after the AE

reporting period commences, physician-investigator confirmation of the absence of adverse should be documented.

Adverse events that begin in Primary Follow-up and are ongoing at the time the subject enters the LTFU phase of the study will continue to be followed in LTFU until: a) the adverse event resolves; b) the subject discontinues participation (i.e. End of Study); or c) there is a change in the adverse event that would normally require the event be captured as a new event (i.e. change in attribution). Please refer to the CRF Completion Guidelines (CCG) for specific instructions on data entry.

As much as possible, each adverse event should be evaluated to determine the following information:

1. The severity grade (CTCAE Grade 1-5)
2. Duration
3. Its relationship to the study treatment (as defined in **Section 9.1**)
4. Expectedness to study treatment (as defined in **Section 9.1**)
5. Action taken with respect to study or investigational treatment
6. Whether medication or therapy was administered
7. Whether it is serious (as defined as in **Section 9.1**)

Physician-investigator assessment of whether an adverse event is serious (as defined by **Section 9.1.2**) must occur within 24 hours from the date the adverse event is first identified, in order to meet SAE reporting requirements described in **Section 9.3**. Additional assessment of non-serious adverse events, including grade and relationship to study treatment, should occur within 7 days from the date of knowledge of the adverse event or from the date of the study visit where the absence of adverse events was confirmed. Accelerated timelines for adverse event assessments and reporting may be requested in the event of emergent safety concerns and/or to address time-sensitive requests from the DSMB/FDA

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and evaluated for any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy, documented appropriately in the medical records, should not be reported as a serious adverse event. Adverse events that occur concurrently with the progression of malignancy but that are not related to disease progression (i.e. deep vein thrombosis or hemoptysis) will be reported as an adverse event as described above. Progression of malignancy resulting in death that occurs during Primary Follow-up should be reported as a serious adverse event. During long-term follow-up, any death determined to be related to disease progression would not qualify as a protocol-defined adverse event.

Serious adverse events that are still ongoing at the end of the adverse event reporting period must be followed to determine the final outcome. Any serious adverse event that occurs after the adverse event reporting period and is considered to be possibly related to the study treatment or study participation should be recorded and reported.

9.2.1 Cytokine Release Syndrome Grading System

A protocol specific grading system (**Table 9-1**) has been developed to capture cytokine release syndrome (CRS) in CAR T-cell protocols. Please refer to **Section 1.6** for additional detail on CRS in CAR T-cell therapy.

The start date of CRS is a retrospective assessment of the date of onset of persistent fevers and/or myalgia consistent with CRS and not explained by other events (i.e. sepsis). The stop date of CRS is defined as the date when the patient has been afebrile for 24 hours and off vasopressors for 24 hours. For the purposes of defining the CRS start date, a fever is defined as a temperature of 100.4°F/38°C.

CRS will be considered ongoing until all signs and symptoms leading to the diagnosis of CRS have resolved, or there are alternative causes for these events (i.e., sepsis, etc). Therefore, the CRS stop date is defined as the date when the subject meets all of the following criteria. The stop date would be considered the date the last criteria was successfully met.

- The subject is afebrile for 24 hours; or an alternative cause of fever has been identified.
- The subject is durably off vasopressors (defined as the time pressors are off, but must be off for a minimum of 24 hours); or the use of vasopressors is attributable to another cause.
- The subject is no longer requiring oxygen (defined as the time oxygen and mechanical ventilation have been discontinued, but must be off for a minimum of 24 hours); or the use of oxygen and/or mechanical ventilation is attributable to another cause.

Table 9-1: CRS grading criteria

CRS Toxicity Grade (Modified)				
1	**2**	**3**	**4**	**5**
Mild reaction: Treated with supportive care such as anti-pyretics, anti-emetics	Moderate reaction requiring IV fluids or parenteral nutrition; some signs of organ dysfunction (i.e. grade 2 creatinine or grade 3 liver function tests [LFTs] related to CRS and not attributable to any other condition). Hospitalization for management of CRS related symptoms including fevers with associated neutropenia.	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction including grade 4 LFTs or grade 3 creatinine related to CRS and not attributable to any other conditions. This excludes management of fever or myalgias. Includes hypotension treated with IVFs* or low-dose pressors, coagulopathy requiring fresh frozen plasma (FFP) or cryoprecipitate, and hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, Continuous Positive Airway Pressure [CPAP] or Bilateral Positive Airway Pressure [BiPAP]. Patients admitted for management of suspected infection due to fevers and/or neutropenia may have grade 2 CRS.	Life-threatening complications such as hypotension requiring high dose pressors (see **Table 9-2**), or hypoxia requiring mechanical ventilation	Death

* CRS Grade 3 language clarification: "hypotension treated with intravenous fluids" is further defined as hypotension requiring multiple fluid boluses for blood pressure support.

Table 9-2: High Dose Vasopressor Use

Definition of "High-Dose" Vasopressors	
Vasopressor	Dose for ≥ 3 hours
Norepinephrine monotherapy	≥ 0.2 mcg/kg/min or ≥ 20 mcg/min (if institutional practice is to use flat dosing)
Dopamine monotherapy	≥ 10 mcg/kg/min or ≥ 1000 mcg/min (if institutional practice is to use flat dosing)
Phenylephrine monotherapy	≥ 2 mcg/kg/min or ≥ 200 mcg/min (if institutional practice is to use flat dosing)
Epinephrine monotherapy	≥ 0.1 mcg/kg/min or ≥ 10 mcg/min (if institutional practice is to use flat dosing)
If on vasopressin	High-dose if vaso + Norepinephrine Equivalent (NE) of >0.1 mcg/kg/min (or 10mcg/min) (using Vasopressin and Septic Shock Trial (VASST) formula)
If on combination vasopressors (not vasopressin)	Norepinephrine equivalent of ≥ 0.2 mcg/kg/min (or ≥ 20 mcg/min) (using VASST formula)

Vasopressin and Septic Shock Trial (VASST) Equivalent Equation:
Norepinephrine equivalent dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷10]
Criteria previously published [134].

9.2.2 Grading System for CAR Neurotoxicity

As described above (**Section 1.6**), neurotoxicity has been observed with CAR T cell products. Since the myriad manifestations of CAR-related neurotoxicity may not fall cleanly under a single CTCAE category, this study will utilize the grading system in **Table 9-3** to categorize adverse events that are: a) judged by the investigator to constitute neurotoxicity related to CAR T cells; and b) which can be evaluated using the event descriptions included in **Table 9-3** below. To align with CTCAE V5.0 reporting criteria, for qualifying events, the CTCAE Term "Nervous System Disorders – Other, Specify" will be utilized in accordance with the corresponding grades below, with additional toxicity detail reported as "CAR Neurotoxicity".

Constituent adverse events of neurotoxicity will contribute to an evaluation of the overall neurotoxicity grade as described in **Table 9-3**. All other events, including specific component neurotoxicity adverse events, will also be reported separately and will be graded in accordance with CTCAE 5.0 (e.g. seizures, cerebral edema, headache, tremors, etc).

If a non-qualifying event becomes a qualifying event, it would be followed by both the original CTCAE term, as well as the new CAR Neurotoxicity event term, as these events are evaluated differently and may have different start/stop dates.

Table 9-3: Neurotoxicity grading system

Neurologic Event Grade	Event Descriptions
Grade 1	• Mild impairment or confusion • No objective evidence of increased intracranial pressure
Grade 2	• Moderate impairment or confusion • No objective evidence of increased intracranial pressure (or not assessed) • Symptoms limiting instrumental ADLs • Aphasia- receptive or expressive characteristics; ability to read, write or communicate intelligibly is not impaired or only mildly impaired

Grade 3	• Severe Impairment
	  ○ Grade 3 confusion (severe disorientation)
	  ○ Grade 3 somnolence (obtundation or stupor)
	  ○ Grade 3 encephalopathy (severe symptoms)
	• Stage 1-2[#] Papilledema (if assessed); CSF opening pressure <20 mmHg (if assessed)
	• Seizure
	• Symptoms limiting self-care ADLs
	• Aphasia- Severe receptive or expressive characteristics, impairing ability to read, write or communicate intelligibly

Grade 4	• Life-threatening consequences
	  ○ Grade 4 confusion (life-threatening consequences; urgent intervention indicated)
	  ○ Grade 4 somnolence (obtundation or stupor)
	  ○ Grade 4 encephalopathy (life-threatening consequences)
	• Stage 3-5 papilledema[#] (if assessed); CSF opening pressure ≥20 mmHg (if assessed); evidence of cerebral edema on brain imaging.
	• Status epilepticus
	• New, focal and sustained motor weakness
	• Requirement for mechanical ventilation due to neurologic symptoms

[#]Papilledema is staged according to the modified Frisen scale.

9.3 Reporting of Serious Adverse Events

Every SAE, UADE and PDSAE (during LTFU), **regardless of suspected causality**, occurring during the adverse event reporting period defined in **Section 9.1** must be reported to the sponsor within 24 hours of learning of its occurrence. The original SAE notification may take place by email to meet the 24-hour reporting window.

Within 3 business days of initial knowledge of the event, the investigator must submit a complete SAE form to the Sponsor along with any other diagnostic information that will assist the understanding of the event. The Investigator will keep a copy of this SAE Form on file at the study site.

New or follow-up information on SAEs/PDSAEs/UADEs should be promptly reported as updates become available.

At a minimum follow-up SAE Forms should be submitted:

- Within 1 week of ICU admission or any life-threatening event
- Within 2 weeks of hospital discharge

Follow-up information should be submitted as an amendment to the initial SAE form, and should include both the follow-up number and report date. The follow-up information should describe whether the event has resolved or continues, if there are any changes in assessment, if and how it was treated, and whether the patient continued or withdrew from study participation.

Report serious adverse events by email to:

Attention: Clinical Safety Manager or designee
Center for Cellular Immunotherapies (CCI)
University of Pennsylvania

At the time of the initial report, the following information should be provided:

- Study identifier
- Subject number
- A description of the event
- Date of onset
- Current Subject status
- Whether study treatment was discontinued
- The reason the event is classified as serious
- Investigator assessment of the association between the event and study treatment
- Expectedness relative to investigational product(s)

9.3.1 Investigator Reporting: Local Regulatory Review Committees

Report events to local regulatory review committees per institutional requirements.

9.3.2 Pregnancies

The majority, if not all subjects enrolled on this trial are likely to have undergone surgical removal of the ovaries and thus, not be of childbearing potential. However, to ensure subject safety, each pregnancy occurring while the subject is on study treatment must be reported to protocol sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. If a pregnancy occurs on study, this will be reported as an SAE using the SAE Report Form.

9.4 Toxicity Management, Stopping Rules and Study Termination

It is expected that AEs may occur frequently in this population based on the underlying advanced cancer and that these can be SAEs. Therefore, there is no specific occurrence of SAEs that define a stopping rule, but the review of SAEs will form the basis for potential early stopping of the study. Only unexpected SAEs that are related to the MOv19-BBz CAR T cells would define a stopping rule. The review of these adverse events, and any decision to prematurely stop subject enrollment, will be determined by the Sponsor.

In addition to the above, premature termination of the clinical trial may also occur because of a regulatory authority decision, determination that there are problems in the cell product generation, or as a result of safety concern. Additionally, recruitment may be stopped for reasons of particularly low recruitment, protocol violations, or inadequate data recording.

9.4.1 Criteria for stopping or pausing the study

The study will be reviewed for potential termination if:

- Any subject develops uncontrolled T cell proliferation that does not respond to management.
- The study meets the DLT safety signal for grade 3 AEs described in **Section 5.4**. If 2 DLTs occur in Cohort 1, we will dose de-escalate by 10-fold to Cohort -1. If 2 DLTs occur in the de-escalated cohort, Cohort -1, the study will be stopped.
- Premature study termination may occur if the Investigator, Sponsor, Study Funder, DSMC, Medical Director, DSMB, or any independent review board or regulatory body decides for any reason that subject safety may be compromised by continuing the study.
- Premature study termination may occur if the Sponsor decides to discontinue the development of the intervention to be used in this study.

Subject accrual will be paused if death occurs within 30 days of study treatment. Accrual will be held until an investigation is performed and the safety data is evaluated by the DSMB and applicable changes are implemented (as appropriate). The outcome of the DSMB review will be shared with the Sponsor. This information will then be provided to the FDA and site (for local regulatory submission) in the form of an outcome letter. If all parties are in agreement as to the event resolution, then the pause will be lifted.

The protocol will be paused and subject accrual suspended to review the manufacturing process should there be ≥33% failed manufacturing products (i.e. failure to release the product and/or failure to reach the target dose).

9.4.2 General toxicity considerations

Infusion related toxicities and their management are described in **Section 5.3.1.4**.
Other potential toxicities and their management are described in **Section 1.6**.

9.5 Protocol Exceptions and Deviations

Exception

A one-time, **intentional** action or process that departs from the approved study protocol, intended for **one** occurrence. If the action disrupts the study progress, such that the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, **advance** documented approval from the Regulatory Sponsor and local regulatory review committees per institutional guidelines is required. Approval from the Regulatory Sponsor must be received prior to submission to local regulatory review committees for approval.

Deviation

A one-time, **unintentional** action or process that departs from the approved study protocol, involving one incident and **identified retrospectively**, after the event occurred. If the event has any potential impact on the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the Regulatory Sponsor within 10 business days of PI knowledge, and to local regulatory review committees per institutional guidelines. Acknowledgement from the Regulatory Sponsor must be received prior to submission to local regulatory review committees.

Other deviations should be appropriately documented (such as a subject missing a visit is not an issue unless a critical/important treatment or procedure was missed and must have been done at that specific time) per site policies/procedures.

Include the following information on the Sponsor supplied exception/deviation form: protocol number, subject study number, comprehensive description of the exception/deviation from the protocol, rationale and corrective and preventative action plan (deviations only). Ensure all completed exception/deviation forms are signed by the Principal Investigator (or Physician Sub-investigator) and submitted to the Sponsor Project Manager for review.

Attention: Sponsor Project Manager
Center for Cellular Immunotherapies (CCI)
University of Pennsylvania

Once approval of the exception request or acknowledgement of the deviation has been granted by the Regulatory Sponsor, the exception or deviation will be submitted to all applicable committees for review and approval/acknowledgement as per institutional guidelines.

9.6 Data and Safety Monitoring Board

An Independent Data and Safety Monitoring Board (DSMB) comprised of at least four individuals including physicians with experience in oncology and/or gene transfer therapy will be assembled, and will work under a charter specifically developed for safety oversight of this study. The DSMB will provide guidance/advice to the Sponsor. The DSMB will evaluate patient-subject safety as specified in the DSMB Charter.

The DSMB will review safety data at the following timepoints:

- Approximately every 6 months.
- If necessary, additional meetings of the DSMB may be held if safety issues arise in between scheduled meetings.

It is envisioned that the DSMB may make four types of recommendations, namely:

- No safety or efficacy issues, ethical to continue the study as planned
- Serious safety concerns precluding further study treatment, regardless of efficacy
- Overwhelming evidence for futility, recommend stopping the study.
- Recommendation to continue the study but proposing an amendment to the protocol (e.g., incorporate an additional safety assessments)

A sponsor representative will share the outcome of the DSMB meeting with the PI via email, for submission to local regulatory review committees as required per institutional policy.

10 DATA HANDLING AND RECORDKEEPING

10.1 Confidentiality

Information about study subjects obtained as part of this study will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research subject to revoke their authorization for use of their PHI

In the event that the subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinical medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information recorded on the eCRFs must be traceable to source documents in the subject's file. The investigator must also keep the original signed informed consent form, and a signed copy must be given to the subject.

Paper based records will be kept in a secure location and only be accessible to personnel involved in the study. Computer-based records or files will only be made available to personnel involved in the study through the use of access privileges and passwords. Whenever feasible, subject identifiers will be redacted from study related records and replaced with study assigned identification numbers.

10.3 Data Management

Data management responsibilities will be governed by CCI Clinical Operations policies/procedures including current Clinical Operations Standard Operating Procedures (SOPs), Guide to Daily Operations (GDOs) and Work Instructions (WI).

A part 11 compliant electronic data capture (EDC) system will be used as the primary data collection tool for the purposes of this study. All data requested on the study-specific eCRF must be recorded. Data entry will be performed by clinical site team members who have been delegated this responsibility by the Principal Investigator and who have completed all required protocol and database training. The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

10.4 Sharing of Study Data

Participants will have access to research related information within their medical record through Penn Medicine's patient portal – called MyPennMedicine (MPM). This includes information from all clinical tests/procedures required as part of their study participation. Results of research testing conducted in non-CLIA certified laboratories will not be included in the participant's medical record or made available to the patient.

10.5 Future Use of Research Data/Specimens

Blood or other samples obtained from the participant will be stored indefinitely and used for future research. Study data and samples may also be shared with other researchers within Penn, or other research institutions, as well as with for-profit pharmaceutical or biotechnology companies. This future research may include genetic testing and/or whole genome sequencing. Data/specimens used for future research will be coded using the unique subject identifier. There are no plans to tell participants about future testing on their specimens, or share the results of this analysis.

10.6 Records Retention

Essential study essential documents must be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by local regulations or per sponsor agreement. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. No records will be destroyed without the written consent of the sponsor.

11 STUDY MONITORING, AUDITING, AND INSPECTING

11.1 Study Monitoring Plan

This study will be monitored according to the Sponsor Data and Safety Monitoring Plan.

Interim Monitoring Visits will be conducted during the course of the study. The Monitors will assure that submitted data are accurate and in agreement with source documentation; verify that investigational products are properly stored and accounted for, verify that subjects' consent for study participation has been properly obtained and documented, confirm that research subjects entered into the study meet inclusion and exclusion criteria, and assure that all essential documentation required by Good Clinical Practices (GCP) guidelines are appropriately filed.

At the end of the study, Monitors will conduct a close-out visit and will advise on storage of study records and disposition of unused investigational products.

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

11.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, government regulatory bodies, and University compliance groups. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance offices.

The Principal Investigator must notify the Sponsor in real-time if an audit/inspection notification is received.

12 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, the revised Common Rule, and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. All consent forms will be submitted with the protocol for review and approval by the University of Pennsylvania IRB. The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, will facilitate the informed consent discussion with the participant, in language and terms they are able to understand. All subjects must have the cognitive ability to provide consent as determined by the treating physician-investigator. Written informed consent will be signed/dated by the participant and the person conducting the informed consent discussion. A copy of the signed/dated informed consent will be provided to the participant, and the original consent should be retained for the investigator's research records. Participant consent, using the IRB-approved consent form, must be obtained before that subject undergoes any study-specific procedures.

The protocol is listed under clinicaltrials.gov.

13 STUDY FINANCES

13.1 Funding Source

This study will be funded through awards from Ovacure, the Alliance for Cancer Gene Therapy, Ovarian Cancer Alliance of Greater Cincinnati, the NIH, and Penn Internal Funds.

13.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research. This requires that any individuals who have a role in the design, conduct, or analysis of this clinical trial disclose all potential conflict of interest as part of their participation in this clinical trial, including changes in their conflict of interest as they occur. Persons who have a perceived

conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

13.3 Subject Stipends or Payments

There is no subject stipend/payment for participation in this protocol.

14 PUBLICATION PLAN

Publication of the results of this trial will be governed by University of Pennsylvania policies, the Center for Cellular Immunotherapies (CCI) Authorship Guidance, and any applicable contractual agreements. Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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16 APPENDIX 1 - SCHEDULE OF EVENTS

Trial Period	**~Week -8**	**~Week -6 to -4**	**~Week -2 to -1**	**Between Pre-Infusion Visit and Day 0**	**Day 0[24]**	**Day 1**	**Day 2 (+1), 7, 10, 14, 21 (±1 day)**	**Day 28(±5)**	**Month 2, 3, 6 (±5 days)**	**Month 9, 12, 15, 18, 21, 24 (±2 weeks)**	**Long-term Follow-up[22]**			
Visits	**Screening**	**Apheresis**	**Pre-Infusion Safety**	**LD Chemo-Therapy[31]**	**Infusion**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**M3, M6, M9 (+/- 1 month)**	**M12, M18, and q6 months up to M60 (+/- 2 months)**	**Annual Visits Years 6 to 15 (if evidence of vector-modified cells)[32]**	**Annual Visits Years 6 to 15 (if no evidence of vector-modified cells)[32]**
CLINICAL ASSESSMENTS														
Consent	X													
Recent Med History and Physical Exam	X		X	X	X	X	X	X	X	X	X	X		
Vital Sign Assessments[1]	X		X	X	X[14]	X	X	X	X	X				
Concomitant Meds	X		X----------	----------	----------	----------	----------	----------	----------	----------X	X[25]----------	----------	----------	----------X[25]
ECOG Performance Status	X		X	X	X	X	X	X	X	X				
Adverse Events[15]		X----------	----------	----------	----------	----------	----------	----------	----------	----------X	X[23]----------	----------	----------	----------X[23]
EKG	X													
Echocardiogram/ MUGA	X[30]													
Leukapheresis screening[2]	X													
Survival Follow-up											X	X	X	X[33]
CLINICAL LABORATORY TESTS														
CBC with differential (4 ml-lavender top)	X		X	X	X[24]	X	X	X	X	X	X	X	X	

Trial Period	~Week -8	~Week -6 to -4	~Week -2 to -1	Between Pre-Infusion Visit and Day 0	Day 0[24]	Day 1	Day 2 (+1), 7, 10, 14, 21 (±1 day)	Day 28(±5)	Month 2, 3, 6 (±5 days)	Month 9, 12, 15, 18, 21, 24 (±2 weeks)	Long-term Follow-up[22]			
Visits	**Screening**	**Apheresis**	**Pre-Infusion Safety**	**LD Chemo-Therapy[31]**	**Infusion**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**M3, M6, M9 (+/- 1 month)**	**M12, M18, and q6 months up to M60 (+/- 2 months)**	**Annual Visits Years 6 to 15 (if evidence of vector-modified cells)[32]**	**Annual Visits Years 6 to 15 (if no evidence of vector-modified cells)[32]**
Comprehensive Metabolic Panel (5 ml-gold top)[16]	X		X	X	X[24]	X	X	X	X	X	X	X	X	
PT, aPTT, fibrinogen (7.5 ml-blue top)	X		X											
Autoantibodies, ANA (1 ml-gold top)	X													
Viral screens: HIV, HCV, HBV, (20ml – gold top)[17]	X													
Urinalysis	X		X	X	X[24]				X					
Urine pregnancy test[9]	X													
Serum pregnancy test[9]			X											
Ferritin, haptoglobin, CRP (4ml-gold top)[19]			X		X[24]									
Triglycerides (1 ml-gold top)			X											
Tumor Biomarker CA125 (5ml- gold top)			X		X		X[35]	X	X	X				

Trial Period	**~Week -8**	**~Week -6 to -4**	**~Week -2 to -1**	**Between Pre-Infusion Visit and Day 0**	**Day 0[24]**	**Day 1**	**Day 2 (+1), 7, 10, 14, 21 (±1 day)**	**Day 28(±5)**	**Month 2, 3, 6 (±5 days)**	**Month 9, 12, 15, 18, 21, 24 (±2 weeks)**	**Long-term Follow-up[22]**			
Visits	**Screening**	**Apheresis**	**Pre-Infusion Safety**	**LD Chemo-Therapy[31]**	**Infusion**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**M3, M6, M9 (+/- 1 month)**	**M12, M18, and q6 months up to M60 (+/- 2 months)**	**Annual Visits Years 6 to 15 (if evidence of vector-modified cells)[32]**	**Annual Visits Years 6 to 15 (if no evidence of vector-modified cells)[32]**
aFR Expression Testing[34]	X		X				X							
Respiratory Virus Panel (RVP)			X[20]											
Radiographic imaging														
Tumor imaging[3]	X[26]		X[26]					X	X[10]					
Brain MRI	X[27]													
Interventions														
Apheresis		X[2,5]						X[21]						
Lymphodepleting Chemotherapy (Cohorts 2 + 3 only)				X[6]										
T cell infusion					X[28]									
Tumor biopsy	X[18]		X[13]				X[8]							
Research specimens[4]														
Serum (~6ml- red top tube)[11]			X		X[7]	X	X	X	X	X				
PBMC (~25ml-Purple Top EDTA)[12]			X		X[7]	X	X	X	X	X	X	X	X	
DNA (qPCR persistence)[29]					X[7]	X	X	X	X	X	X	X	X	

Trial Period	~Week -8	~Week -6 to -4	~Week -2 to -1	Between Pre-Infusion Visit and Day 0	Day 0[24]	Day 1	Day 2 (+1), 7, 10, 14, 21 (±1 day)	Day 28(±5)	Month 2, 3, 6 (±5 days)	Month 9, 12, 15, 18, 21, 24 (±2 weeks)	Long-term Follow-up[22]			
Visits	**Screening**	**Apheresis**	**Pre-Infusion Safety**	**LD Chemo-Therapy[31]**	**Infusion**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**Follow-up**	**M3, M6, M9 (+/- 1 month)**	**M12, M18, and q6 months up to M60 (+/- 2 months)**	**Annual Visits Years 6 to 15 (if evidence of vector-modified cells)[32]**	**Annual Visits Years 6 to 15 (if no evidence of vector-modified cells)[32]**
TOTAL BLOOD DRAWS														
Total clinical blood draw (~mL)	9	0	22.5	9	14	9	Up to 14	14	14	14	9	9	9	
Total research blood draw (~mL)	28.5	0	36	0	62	31	31	31-91	31	31	25	25	25	
Total blood draw (~mL)	**37.5**	**0**	**58.5**	**9**	**76**	**40**	**Up to 45**	**45-91**	**45**	**45**	**34**	**34**	**34**	
Total blood draw (Tbsp., approximate)	**2.5**	**0**	**4**	**0.6**	**5.1**	**2.7**	**Up to 3**	**3-6**	**3**	**3**	**2.3**	**2.3**	**2.3**	

1. Includes weight/height at screening/enrollment only. Vital signs include blood pressure, body temperature, heart rate and oxygen saturation via pulse oximetry.
2. If a subject's veins are not adequate for apheresis procedure, the subject may have a central venous apheresis catheter line placed by interventional radiology. It is recommended that the patient have an absolute lymphocyte count (ALC) ≥500/µl, prior to undergoing apheresis. If the patient's ALC is <500/µl, it is recommended that a lymphocyte subset analysis (CD3, CD4, CD8 counts) be performed to confirm that the patient has an absolute CD3 count of ≥150/µl. If the absolute CD3 count is <150/µl, it is recommended that the leukapheresis procedure be delayed until their ALC is ≥500/µl or absolute CD3 count is ≥150/µl. Up to a 4 week delay may occur; following this, further discussion is needed with the study PI and the CVPF prior to proceeding.
3. CT is the preferred method for tumor assessment, however other methodologies (MRI, etc.) may be utilized at the physician-investigator's discretion, if performed in accordance with RECIST 1.1 criteria. Scans may be administered with or without contrast at the investigator's discretion. Please refer to **Section 7.1** for additional details.

4. Additional blood draws may be performed at the discretion of the investigator (for example, to evaluate clinical events). Moreover, additional tissue and fluid collections from the standard of care procedures may be used for research studies.
5. Subjects have the option for a second apheresis in case the T cell product is not successfully manufactured from the first apheresis. Please refer to **Section 6.3** for additional information.
6. Cyclophosphamide + fludarabine for subjects participating in Cohorts 2 + 3 only. Please refer to **Section 6.5** for additional information
7. Blood draw before infusion and ~1 hour after T cell infusion.
8. If the subject's tumor is measurable by CT and accessible by image-guided biopsy, subjects will undergo a tumor biopsy under image guidance at day 14(±7) to evaluate the impact of therapy on the tumor microenvironment and to assess for the presence of CAR T cells and aFR expression. These will be compared to baseline values from fresh biopsies or stored surgical tumor specimens, if available.
9. Participants of childbearing potential only. The serum pregnancy test performed at the Pre-Infusion Visit must occur prior to the first day of lymphodepleting chemotherapy.
10. Months 3 and 6 only; thereafter to be performed per clinical discretion. Imaging performed within 4 weeks of the M3 and M6 visits will be accepted.
11. Correlative testing/analysis includes multiplex cytokine analysis, immunogenicity (HAMA/HACA), and serum aFR protein expression (SaFRP) and will be performed as indicated. All serum samples to be delivered to the TCSL for processing, storage and analysis (as applicable).
12. A portion of these samples will be archived at the TCSL. In the event RCL is suspected, these archived samples will be used to further investigate and perform VSV-G DNA testing.
13. If the subject has an accessible tumor and it is determined clinically feasible, a baseline tumor biopsy will be performed prior to MOv19-BBz CAR T cell infusion. The baseline biopsy may occur any time prior to infusion between Day -14 and initiation of study treatment (i.e. lymphodepleting chemotherapy in applicable cohorts or MOv19-BBz CAR T cells). This baseline biopsy sample will be used to evaluate the level of aFR expression and if feasible, other immune markers at baseline. If the subject had a fresh biopsy at pre-screening in order to evaluate aFR expression, a repeat biopsy at the pre-infusion timepoint is not required.
14. On Day 0, vital signs (temperature, respiration rate, pulse, blood pressure, and oxygen saturation by pulse oximetry) will be measured within 10 minutes prior and within 15 minutes after the infusion. Thereafter, vital signs will be measured at 30 (+/- 5) minutes, 45 (+/- 5) minutes, and 60 (+/- 5) minutes after the infusion, and then every hour (+/- 10 minutes) for the next two hours until these signs are satisfactory and stable. If vital signs are not satisfactory and stable 3 hours after the infusion, vital signs will continue to be monitored as clinically indicated until stable.
15. Collection of adverse events will begin at time of apheresis and will continue until the subject is off-study. Please see **Section 9.1** for additional information.
16. Chemistry panel including sodium, potassium, chloride, CO2, blood urea nitrogen, creatinine, glucose, magnesium, phosphate, total protein, albumin, calcium, alkaline phosphatase, total bilirubin, ALT, AST, uric acid, LDH
17. HIV, Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody, Hepatitis B core antibody, and Hepatitis C antibody. If the HCV antibody is positive, a screening HCV RNA by any RT-PCR or bDNA assay must be performed. Eligibility will be determined based on the screening value. The test is not required if documentation of a negative result of a HCV RNA test performed within 60 days prior to screening is provided.

18. Evaluation of aFR expression will occur on archived tumor tissue, if the subject has not had an anti-aFR directed therapy since the collection of the archived sample. However, if archived tumor tissue is not available, a fresh biopsy may be performed. Once aFR expression has been confirmed, subjects may be presented the informed consent for the main study. If the aFR expression of their tumor is known prior to signing the tissue testing consent for this study, the results of this testing will need to be confirmed as part of the subjects' participation on this protocol. Once aFR expression has been confirmed, subjects may proceed to the next step and be presented the informed consent for the main study.
19. Repeated as clinically indicated or if HLH/MAS or CRS is suspected.
20. All subjects must undergo a Respiratory Virus Panel (RVP) within 10 days prior to MOv19-BBz CAR T cell infusion. If the patient is positive for influenza, Tamiflu® or equivalent should be administered per package insert. The subject must complete treatment **prior** to receiving lymphodepleting chemotherapy and MOv19-BBz cells. The test does not need to be repeated prior to the MOv19-BBz cell infusion; however if influenza signs and symptoms are present, the infusion should be delayed until the subject is asymptomatic. If the subject is positive for another virus on the RVP, the MOv19-BBz cell infusion will be delayed for at least 7 days to be sure clinical symptoms of a viral infection do not develop. If clinical symptoms develop, the lymphodepleting chemotherapy and CAR T cell infusion will be delayed until resolution of these symptoms.
21. A mini-apheresis procedure (~5 L) will be performed at this visit for research purposes. A 60 ml blood draw may be substituted for the mini-apheresis procedure at the discretion of the treating investigator.
22. Please refer to **Section 6.13** for long-term follow-up requirements.
23. Please refer to **Section 9.1** for protocol-defined adverse event (PDAE) reporting requirements in long-term follow-up.
24. All tests/procedures will be performed pre-infusion on Day 0 unless otherwise specified. The results of the CBC with differential and comprehensive metabolic panel must be reviewed by a physician-investigator prior to the infusion.
25. During long-term follow-up, only medications used to treat the subject's cancer will be collected.
26. Imaging performed within 8 weeks of subject signing main consent will be accepted. Baseline imaging should be obtained within 28 days prior to infusion of MOv19-BBz CAR T cells and after any cancer therapy administered between collection and MOv19-BBz CAR T cell infusion. In cohorts 2 and 3, baseline scans should be obtained prior to lymphodepleting chemotherapy administration and MOv19-BBz CAR T cell infusion.
27. Required at screening for subjects with known CNS metastases.
28. Please refer to **Section 5.3.1.3**, **5.6**, and **6.6** for additional information.
29. Testing for persistence by Q-PCR will continue until any 2 sequential tests are negative documenting loss of CAR T cells. Thereafter samples will continue to be collected and archived.
30. ECHO/MUGA must be performed within 8 weeks prior to the CAR T cell infusion.
31. Lymphodepleting chemotherapy will be scheduled so that the last day of chemotherapy falls 3 days +/- 1 day prior to CAR T cell infusion. Please refer to **Section 6.5** for additional information on protocol required lymphodepleting chemotherapy.
32. Visit window ±60 days
33. Survival follow-up may be conducted via the Penn Patient Portal, phone or email/mail. The Follow-up Survey in **Appendix 2** may be used to facilitate contact with the subject as required.

34. aFR expression testing will be performed on archived/fresh tumor tissue specimens collected at protocol defined timepoints- Screening, Pre-Infusion Safety and Day 14 (+/- 7 days). Please refer to the Tissue Handling Manual for additional instructions.
35. Day 14 only

17 APPENDIX 2 - LONG-TERM FOLLOW-UP SURVEY

This follow-up survey is for:

- Subjects who cannot return for an onsite visit at any time point.
- Subjects to be contacted annually because they had no sign of gene therapy product at the 5-year follow-up visit or later and are, therefore, not required to return for any remaining future onsite visits.

Follow-Up Survey
Name of Participant: _____ **Method of Contact.** Document method of contact ☐ Mail: _____ ☐ Email: _____ ☐ Phone: _____ Above information to be filled out by Coordinator
1) Today's Date:_____/_____/_____ MM DD YYYY
2) Update contact information. Document any changes below since your last study visit or last contact with the study team. ☐ **Phone:** _____ ☐ **Email:** _____ ☐ **Address:** _____ **Preferred method of contact:** _____
3) Have you been diagnosed with any type of cancer since your last study visit or last contact with the study team? ☐ No, I have not been diagnosed with Cancer. ☐ Yes, I have been diagnosed with Cancer. [*Please complete the fields below*.] • Cancer Diagnosis: _____ • Type of Cancer: _____

Follow-Up Survey
• Date of Diagnosis: _____
4) Have you developed any of the following symptoms since your last study visit or last contact with the study team? ☐ Experienced a worsening or new loss of feeling in any part of your body, especially hands and feet ☐ Experienced a worsening or new loss of control of any body part (arms, legs…) ☐ Experienced a worsening or had a seizure ☐ Experienced a worsening or new experience memory loss **Please explain if necessary:**
5) Have you developed a worsening or arthritis or been recently diagnosed with arthritis by a doctor since your last study visit or last contact with the study team? ☐ **Yes** ☐ **No** **Arthritis:** Most kinds of arthritis cause pain and swelling in your joints.
6) Have you developed a worsening of your autoimmune disease or been recently diagnosed with an autoimmune disease by a doctor since your last study visit or last contact with the study team? ☐ **Yes** ☐ **No** **Autoimmune Disease:** The body's immune system protects you from disease and infection. Autoimmune diseases are when your immune system attacks healthy cells in your body by mistake. Autoimmune diseases can affect many parts of the body.
7) Have you had any new or unexpected illnesses or been hospitalized unexpectedly? ☐ **Yes** ☐ **No** **If yes, please explain:**

Completed By:

_____

Name **Signature** **Date**

18 APPENDIX 3 - EXAMPLE PHYSICIAN LETTER

EXAMPLE LETTER TO PHYSICIANS

[*date*]

[*name and address*]

Dear [*physician name*],

Your patient [*patient name*] is participating in a clinical research study that requires 15 year monitoring for adverse events. To aid in reporting of adverse events that are possibly related to the clinical research study, we are asking the patients on our research study to designate a primary care physician or local oncologist that may help in the monitoring and reporting of adverse events. Your patient has designated you. **If upon any of your visits with your patient, any of the following events are reported or discovered, please contact the study coordinator as soon as possible**:

1. New malignancies
2. New incidence or exacerbation of a pre-existing neurologic disorder
3. New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
4. New incidence of a hematologic disorder.
5. Events that may be unexpected in this patient population and thus potentially related to the investigational product they received.

If your patient experiences any of these events, please contact the study coordinator below as soon as you can so that we can record the event and then monitor your patient's health if necessary. When you call, remember to mention the protocol number of the study which is UPCC 03818, Subject ID (*XXX*) and the brief study title which is "MOv19-BBz CAR T cells in aFR expressing recurrent high grade serous ovarian, fallopian tube, or primary peritoneal cancer".

Study Coordinator
Name
Address
Phone
Email

In addition, if your patient cannot return to the University of Pennsylvania for some of their follow-up visits, we will contact you to provide information from their medical record, including the results of any routine care physical examinations and/or laboratory assessments performed. We may also ask for your assistance in the collection of protocol required blood samples, which will need to be sent to the University of Pennsylvania for required analysis.

If you have any questions about this letter or the study itself, please do not hesitate to contact the above study nurse or physician.

Thank you for your support in helping us to monitor for delayed adverse events.

Best regards,
[*Principal Investigator*]