SARC Protocol #: SARC045

TITLE: SARC045: A Phase II Trial of Tebentafusp in HLA-A*02:01 Positive Patients with Advanced Clear Cell Sarcoma

Sponsor: SARC

Supporter: Immunocore (Study #: IMCgp100-0008)

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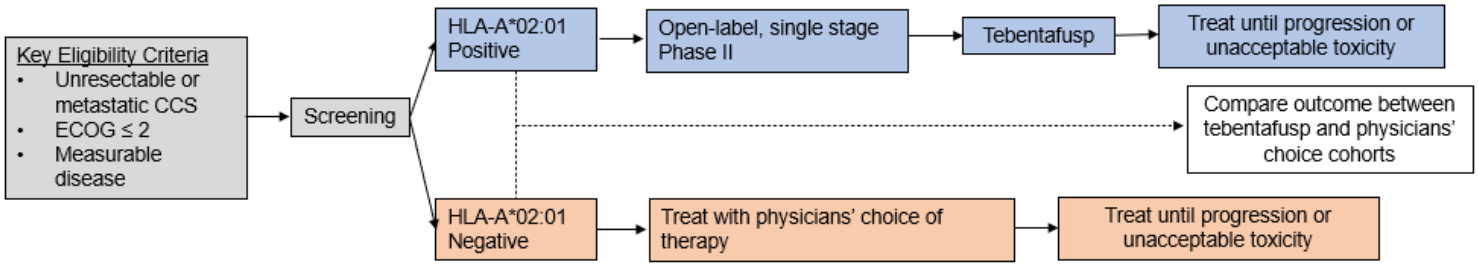
GLOSSARY OF ABBREVIATIONS

ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate aminotransferase
CCS	Clear cell sarcoma
CI	Confidence interval
CR	Complete Response
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
EMR	Electronic medical record
EOT	End of treatment
FISH	Fluorescence in situ hybridization
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
IHC	Immunohistochemistry
LLN	lower limit of normal

GLOSSARY OF ABBREVIATIONS

LVEF	Left Ventricular Ejection Fraction
MUGA	Multiple Gated Acquisition scan
NCI	National Cancer Institute
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease or Pharmacodynamic
PFS	Progression free survival
PS	Performance Status
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable Disease
SF	Shortening Fraction
TNM	primary tumor/regional lymph nodes/distant metastasis
TTP	Time to Tumor Progression

SCHEMA



Synopsis

Primary Objective

1. To estimate the proportion of HLA-A*02:01-positive patients with metastatic or unresectable clear cell sarcoma and treated with tebentafusp who are progression free at 24 weeks by RECIST 1.1

Secondary Objectives

1. To estimate the best overall ORR by RECIST v1.1[1] and by Choi criteria[2]
2. To estimate the median duration of response (DoR) among responders
3. To estimate the clinical benefit of rate (CBR), defined as the proportion of patients who achieve a best response of SD, PR, or CR by RECIST 1.1 for ≥ 6 months
4. To estimate the disease control rate (DCR), defined as the proportion of patients who achieve a best response of SD, PR, or CR by RECIST 1.1
5. To estimate the median PFS
6. To estimate the median OS
7. To describe the safety of study treatment, as assessed by CTCAE version 5.0
8. To estimate the progression-free survival of HLA-A*02:01-negative patients with unresectable or metastatic CCS treated with physician's choice compared to HLA-A*02:01-positive patients treated with tebentafusp

Hypothesis and Rationale

CCS expresses melanocytic antigens and has few efficacious treatment options. To date, cytotoxic chemotherapies are relatively ineffective in this disease and the efficacy of alternative treatment options is marginal. We hypothesize that treatment with tebentafusp will generate a T cell-mediated immune response and lead to anti-tumor activity in patients with unresectable or metastatic CCS.

Trial Design

This will be a multi-center, open label, phase II study of tebentafusp in patients with unresectable or metastatic CCS. Patients who screen positive for HLA-A*02:01 and meet the eligibility requirements will be treated with weekly tebentafusp. Radiographic assessment via CT or MR (where CT is not feasible or per the investigator's discretion) will occur at baseline and every subsequent 6 weeks through 48 weeks, and then every 9 weeks thereafter. Patients will be treated until progression of disease or unacceptable toxicity. All patients treated with tebentafusp will undergo mandatory research biopsies at baseline and on-treatment (week 6), if it is safe and feasible to do so. Serial peripheral blood samples for correlative analysis will be collected at baseline and at various time points on treatment.

Patients who are HLA-A*02:01-negative and ineligible to receive tebentafusp will be prospectively enrolled onto a separate study arm and treated with physicians' choice of treatment. They will also be radiographically assessed at the same schedule as patients treated with tebentafusp, if feasible, and kept on this treatment arm until progression of disease or unacceptable toxicity on the physicians' choice regimen.

Maximum Total Number of Subjects

23 patients will be on treatment arm. 24 patients will be on a physician's choice arm. This equals 47 total.

Target Population

Unresectable or metastatic clear cell sarcoma patients who are HLA-A*02:01 positive.

Anticipated Length of Study (patient enrollment period, overall length including follow-up)

5 years total: 3 years of enrollment, 1 year on treatment, 1 year follow-up

Study Drug (s)

Tebentafusp

Dosing and Administration

Tebentafusp will be administered via IV infusion on Days 1, 8, and 15 of a 21-day cycle. Treatment on C1D1 will be 20mcg, treatment on C1D8 will be 30 mcg. After this initial dosing period, beginning at C1D15 and beyond, patients are eligible to receive the full dose of 68 mcg. This escalated dose administered at C1D15 will be the dose used for the remainder of the treatment period unless dose reduction is implemented for toxicity.

Efficacy Evaluations

Radiographic assessment via CT or MR (where CT is not feasible or per the investigator's discretion) will occur at baseline and every subsequent 6 weeks through 48 weeks, and then every 9 weeks thereafter (+/- 7 days on scan date).

Tumor evaluations for the purposes of the primary endpoint are made based on RECIST v1.1. The efficacy assessments and definitions of best response and PD for the purposes of the primary endpoint of ORR described in this study are based on the RECIST v1.1 (section 11.1.4).

Safety Evaluations/ Concerns

Tebentafusp is FDA-approved for HLA-A*02:01-positve adult patients with unresectable or metastatic uveal melanoma. Patients will be monitored for AEs and toxicities will be reported per CTCAEv5.

Special warnings and precautions listed in the investigator's brochure include:

1) Cytokine release syndrome
2) Rash
3) Elevated liver enzymes

Other clinically relevant AEs include:

1) Tumor flare/pain
2) Elevated pancreatic enzymes
3) Lymphopenia

Correlative Studies

Blood for research will be collected at baseline, C2D1, C3D1, C5D1, C9D1, and EOT. Blood evaluations will be used to evaluate biomarkers for biomarkers of response and resistance.

Tumor biopsies for research purposes will be done at baseline and week 6, where feasible. Biopsy at the time of progression for analysis of tumor microenvironment and for potential mechanisms of immune escape will be optional.

Please refer to section 9 for more details.

Brief Statistical Design

Simon's two-stage minimax design will be used. The null hypothesis that the true PFS rate at 24 weeks is 10% will be tested against a one-sided alternative that it is 30%. In the first stage, 13 patients will be accrued. If ≤ 1 of the first 13 patients enrolled is progression-free at 24 weeks, the protocol will stop enrolling patients due to futility. Otherwise, 10 additional patients will be accrued for a total of 23 patients treated. The study will be claimed positive if 5 or more of 23 patients are progression-free at 24 weeks. This design yields a one-sided type I error rate of 0.1 and power of 0.84.

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1. OBJECTIVES

1.1 Primary Objective

- To estimate the proportion of patients' progression free at 24 weeks by RECIST 1.1 of HLA-A*02:01-postiive patients treated with tebentafusp in patients with unresectable or metastatic clear cell sarcoma.

1.2. Secondary Objectives

- To estimate the best overall ORR by RECIST v1.1[1] and by Choi criteria[2]
- To estimate the median duration of response (DoR) among responders
- To estimate the clinical benefit of rate (CBR), defined as a best response of SD, PR, or CR by RECIST 1.1, and the CBR at 12 and 24 weeks.
- To estimate the median PFS
- To estimate the median OS
- To describe the safety of study treatment, as assessed by CTCAE version 5.0
- To estimate the progression-free survival of HLA-A*02:01-negative patients with unresectable or metastatic CCS treated with physician's choice compared to HLA-A*02:01-positive patients treated with tebentafusp

1.3. Exploratory Objectives

- To assess the effect of tebentafusp on selected biomarkers (CD4+ and CD8+ T cells, gp100, PD-L1, and other immune markers) measured in tumor tissue at baseline and on-treatment and the association between these biomarkers (baseline level of expression and the change in biomarker level of expression following treatment) and clinical outcome.

- To evaluate associations between biomarkers measured in serial peripheral blood samples (e.g. ctDNA) with clinical efficacy, including immunophenotyping and functional analyses, evaluation of serum levels of chemokines, cytokines, or other immune mediator

2. BACKGROUND

2.1 Study Disease

Clear Cell Sarcoma

An Ultra-rare Soft Tissue Malignancy with No Clearly Effective Treatments

In 1965, Franz Enzinger, a pathologist at the Armed Forces Institute of Pathology (AFIP), described a new subtype of sarcoma based on a histologic review of 21 cases of soft tissue tumors of the tendons or aponeuroses. Microscopically, he described tumors with pale fusiform cells of epithelioid appearance with clear cytoplasm and minute vacuoles arranged in nests and fascicles. The cellular aggregates were enclosed by septa of fibrous

connective tissue that were continuous with dense collagenous structures of tendinous or aponeurotic tissue. He named these tumors clear cell sarcomas of the tendons and aponeuroses (CCS). Clinically, they were characterized by "slow but relentless growth" with a tendency to recur and metastasize.[3]

Enzinger later published a larger series of 141 CCS patients in collaboration with Chung, reporting a median age of 27 years at diagnosis, a clear predilection for the extremities (97% of primary tumors), and a slight predominance among women. 24% of the study population were alive with recurrent or metastatic disease and an additional 35% died of metastases. The mean interval from the time of surgical resection to the first recurrence was 2.6 years.[4] WeAn even larger retrospective of 489 patients from the National Cancer Database found 38% of patients had stage IV disease at diagnosis. The median overall survival (OS) of all patients from diagnosis was 57.2 months; those with stage IV disease had a dismal median survival of 8.9 months.[5]

There is no standard of care treatment for patients with advanced CCS. One report led by The Royal Marsden Hospital found of 24 CCS patients treated with traditional cytotoxic chemotherapy in the first-line metastatic setting, only one (4%) achieved a partial response (PR). In the second line, there were zero objective responses and only 8% of patients achieved stable disease (SD). The median progression-free survival (PFS) was 2.5 months and the median OS was 9 months.[6] Similar outcomes were reported by investigators at the Gustave Roussy Institute in France.[7] Most recently, Smrke and colleagues at the Royal Marsden led an international retrospective study of 55 patients with advanced clear cell sarcoma. The median PFS was reported to be 4 months with a median overall survival of 15 months.[8]

To date, the only published prospective clinical trial restricted to CCS patients involved the MET inhibitor crizotinib. The CREATE trial was a phase II open label study in 26 patients with CCS that expressed MET. One patient achieved a PR and 17 patients had SD. The median PFS was 4.3 months and median OS 9.1 months.[9] There remains an unmet medical need for the treatment of advanced CCS.

2.2 Study Agent

Tebentafusp Generates Anti-tumor Immunity in Melanoma

Tebentafusp is an Immune-mobilizing monoclonal T cell receptor (TCR) against cancer (ImmTAC) designed to target gp100. It is a bifunctional biologic comprising a soluble T cell receptor (TCR) fused to an antibody single-chain variable fragment (scFv). The former component, the TCR, functions to target and bind the drug to the glycoprotein 100 (gp100) which is over expressed and presented on the surface of cancer cells by the major histocompatibility complex (MHC). The scFv component is designed to activate T cells in physical contact with cancer via cluster of differentiation 3 (CD3), which results in an immune response targeted towards the malignant tissue. Once administered, tebentafusp is expected to bind to cancer tissue and stimulate the immune system to attack the target

tissue primarily via cytotoxic T lymphocyte (CTL) killing, but also via the stimulation of accessory immune mechanisms.

Anti-tumor activity has been observed in the Phase 1 study of IMCgp100-01, with confirmed partial responses (PRs) seen at higher doses. A total of six confirmed investigator-reported PRs have been observed, with five in Arm 1 (weekly dose expansion) and one in Arm 2 (daily × 4 dose escalation) in a patient with advanced CM. In addition to the confirmed PRs, multiple patients have experienced minor responses and prolonged disease stabilization in both CM and UM. The disease control rate (complete remission [CR], partial remission [PR], or stable disease [SD] at ≥ 24 weeks) was 40.0% (95% confidence interval [CI]: 16.3, 67.7) in the UM group and 10.3% (95% CI: 2.9, 24.2) in the non-UM group.

Based on these early clinical development findings, additional Phase 1 and 2 studies have been initiated. In UM, a Phase 1/2 study (IMCgp100-102) to evaluate the safety and efficacy of an intra-patient escalation regimen in previously treated patients has been completed. A Phase 2 study (IMCgp100-202) to assess the safety and efficacy of tebentafusp in patients with previously untreated disease is ongoing. In CM, the IMCgp100-201 study was launched to evaluate the anti-tumor activity of tebentafusp as a monotherapy or in combination with durvalumab (PD-L1 inhibitor), tremelimumab (CTLA-4 inhibitor), and the combination of durvalumab and tremelimumab in metastatic AM excluding mUM.

In the monotherapy arms, the median duration of follow-up was 8.74 months for Arm 4a and 6.34 months for Arm 4b. The median overall survival (OS) was 11.072 months (90% CI: 4.994, 14.982) in Arm 4a and 7.064 months (90% CI: 0.526, 8.641) in Arm 4b. The 1-year OS estimate was 46.5% (90% CI: 26.9, 64.1) for Arm 4a and was not evaluable (NE) for Arm 4b.

In the completed IMCgp100-102 study (N=127), 6 patients achieved PRs (4.7%), and 57 additional patients had stable disease (44.9%) as their best overall response. After a median follow-up of 19.6 months, the 12-month and 24-month OS rates were estimated at 61.8% and 37.0%, respectively. The median progression-free survival (PFS) by independent central review (ICR) was 2.8 months, with a 6-month PFS rate of 25.0%. The disease control rate was 31.7% at ≥16 weeks and 22.8% at ≥24 weeks.

In the Phase 2 IMCgp100-202 study, tebentafusp demonstrated a significant improvement in the primary endpoint of OS compared to investigator's choice, reducing the relative risk of death by 49% (hazard ratio [HR] 0.51; 95% CI: 0.37, 0.71) in HLA-A*02:01-positive patients with metastatic uveal melanoma (mUM) who had not received prior systemic therapy. Tebentafusp resulted in an approximate 15% increase in the estimated 1-year OS rate (73.2% versus 58.5%) and significantly prolonged PFS (HR 0.73; 95% CI: 0.58, 0.94; p = 0.0139). The objective response rate (ORR) by RECIST was numerically higher in the tebentafusp group compared to investigator's choice. With a minimum follow-up of 36 months, the median OS was 21.6 months in the tebentafusp group compared with 16.9 months in the control group (HR for death, 0.68; 95% CI: 0.54, 0.87). The 3-year OS rate was 27% in the tebentafusp group and 18% in the control group. Most tebentafusp-related adverse events (AEs) occurred early in treatment, and no new AEs were observed with long-term dosing. The rate of treatment discontinuation due to related AEs remained low in both treatment arms (2% for the

tebentafusp group and 5% for the control group), with no treatment-related deaths reported.

Promising OS results were also observed in the supportive Study 102 Phase 2 expansion in previously treated HLA-A*02:01-positive patients with mUM, when compared with historical controls.

As of January 1, 2023, tebentafusp is approved for the treatment of UM in 5 regions (United States, European Union, Canada, Australia, and Great Britain), under the brand name KIMMTRAK.[22]

2.3 Rationale

CCS is Characterized by an EWS-ATF1 Fusion and Expression of Melanocytic Antigens

As Enzinger noted in the 1960s, CCS cells occasionally contain discrete foci of melanin on light microscopy, which can manifest as pigmented lesions on the skin above the tumor.[10] Ultrastructural studies later found melanosomes on electron microscopy,[11] raising the possibility that CCS is actually a form of melanoma.[12] In their large case series, Chung and Enzinger found 72% of cases positively stained for intracellular melanin. They concluded that CCS represents a malignant neuroectodermal tumor derived from potentially melanogenic cells arising from the neural crest, and therefore proposed a new name for the disease: malignant melanoma of soft parts.[4]

In support of this theory, CCS were found to stain positive for S-100 on immunohistochemistry (IHC), which was initially found on astrocytes, oligodendrocytes, Schwann cells, and melanocytes, the latter two originating from the neural crest.[13] In addition, CCS stains positively for other melanoma-specific antibodies, including HMB-45, microphthalmia transcription factor (Mitf), and Melan-A.[14,15]

In 1991, Bridge et al identified a balanced translocation between chromosomes 12 and 22 in select cases of CCS.[16] The translocation t(12;22)(q13-14;q12) represents a fusion between *EWS* and *ATF1*, which contains the transactivating domain of EWS linked to most of the ATF1 protein, including a bZIP domain that mediates protein dimerization and DNA binding through dimerization with the transcription factor CREB.[17,18]

To better define the relationship between CCS and other sarcomas, Segal et al at MSKCC performed gene expression analysis to compare CCSs, melanoma, and soft tissue sarcoma. Using both hierarchical clustering and an unsupervised principal components analysis, soft tissue sarcomas clustered together, while CCS clustered with melanoma. A supervised machine-learning algorithm also categorized all CCSs as melanomas. The genes *PMEL17* (encoding gp100), *SOX10*, and *MITF* were most consistently expressed in CCS.[19] Schaefer and colleagues performed a similar analysis on CCS cell lines and other sarcoma subtypes, identifying PMEL17, MITF, and SOX10 as the most abundantly expressed genes in CCS compared to other sarcomas.[20]

Further pre-clinical work found the EWS-ATF1 fusion to constitutively activate the *MITF* promoter, leading to increased MITF expression and downstream expression of the

melanoma-associated antigens gp100 and melan-A. Forced expression of dominant negative MITF, or direct inhibition of the EWS-ATF1 fusion protein led to decreased gp100 expression, suggesting that pigment gene expression in CCS is downstream of EWS-ATF1 via direct regulation by MITF. The authors suggest that MITF is both a necessary and sufficient target gene mediating the oncogenic activity of EWS-ATF1 on CCS growth.[21]

2.4 Study Design

This is a multi-center, open label, phase II study of tebentafusp in patients with unresectable or metastatic clear cell sarcoma (CCS). Patients who screen positive for the HLA-A*02:01 haplotype and meet the eligibility requirements will be treated with weekly intravenous (IV) tebentafusp in escalating doses (20 μg on day 1, 30 μg on day 8, and then 68 μg weekly thereafter).

Radiographic assessment will occur at baseline and every subsequent 6 weeks (+/- 1 week) through 48 weeks, and then every 9 weeks thereafter. Patients will be treated until progression of disease, unacceptable toxicity, or withdrawal of consent. All patients treated with tebentafusp will undergo mandatory research biopsies at baseline and on-treatment (week 6 +/- 1 week), if it is safe and feasible to do so. Serial peripheral blood samples for correlative analysis will be collected at baseline and at various time points on treatment.

Patients who are HLA-A*02:01-negative and therefore ineligible to receive tebentafusp will be prospectively enrolled onto a separate study arm and treated with physicians' choice of systemic therapy. They will also be radiographically assessed at the same schedule (if feasible) as patients treated with tebentafusp and kept on this treatment arm until progression of disease or unacceptable toxicity on the physicians' choice regimen.

The primary study objective is to estimate the proportion of patients who are progression-free at 24 weeks. Secondary objectives include estimating the overall response rate by RECIST and Choi criteria, the duration of response (DoR), the clinical benefit rate (CBR), the progression-free survival, the overall survival (OS), and describing the safety of study treatment. An additional secondary objective will be to compare the PFS of patients who are HLA-ineligible and treated with physician's choice of therapy to the HLA-A*02:01-positive population treated with tebentafusp.

2.5 Correlative Studies Background

As clear radiologic responses to tebentafusp are infrequent[19], a complementary method of detecting change in tumor burden may provide greater insight into each patient's benefit from this immunotherapy. To that end, ctDNA measurement is a promising approach to monitor disease activity to tebentafusp noninvasively.[21,22] The feasibility of measuring *EWSR1* rearrangements in ctDNA in other sarcomas has been previously

demonstrated,[23] and targeted sequencing has proven useful for measuring ctDNA longitudinally.[24]

Given tebentafusp's immune mechanism of action, understanding the immune profile of CCS and how it varies among patients obtaining varying degrees of benefit will be critical to interpreting our results. Few broad immune profiling studies of CCS have been performed to date and there is a dearth of data to explain why it has been refractory to immunotherapeutic approaches. Further, procurement of on-treatment tissue will assess the change in the tumor microenvironment with treatment. We propose to assess the tumor microenvironment on serial biopsies to assess baseline immune characteristics of CCS tumors and to measure changes in peripheral blood T cells before and after treatment. We will utilize multiple modalities for assessment of the tumor microenvironment, including RNA sequencing and multiplex immunofluorescence. Flow cytometry will be used to characterize circulating T cell subsets.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Age ≥ 18 years

3.1.2 Histologically confirmed diagnosis of HMB-45+ clear cell sarcoma which is unresectable and/or metastatic

3.1.3 HLA-A*02:01 positive

3.1.4 ECOG Performance Status of ≤ 2 at screening

3.1.5 At least one site of measurable disease on CT/MRI scan as defined by RECIST v 1.1 criteria. Baseline imaging must be performed within 28 days of Cycle 1 Day 1 of study.

3.1.6 Adequate organ function within 28 days of Day 1 of study defined as:

- Absolute Neutrophil Count (ANC) ≥ 1.5
- Platelets ≥ 75
- ALT and AST ≤ 2.5 x institutional upper limit of normal (ULN) or ≤ 5.0 x institutional ULN if considered due to tumor
- Alkaline phosphatase ≤ 2.5 x institutional ULN unless considered due to tumor
- Serum bilirubin ≤ 1.5 x institutional ULN. **NOTE**: Patients with elevated bilirubin secondary to Gilbert's disease are eligible to participate in the study

- Serum creatinine ≤ 1.5 x institutional ULN or 24-hour creatinine clearance ≥ 50 ml/min (calculated creatinine clearance using Cockroft formula is acceptable)

3.1.7 Written, voluntary informed consent

3.1.8 Patients must demonstrate progression of disease by RECIST 1.1 within 6 months of study enrollment. Newly diagnosed patients with unresectable or metastatic disease and only one baseline scan are eligible to screen and enroll.

3.1.9 All other relevant medical conditions must be well-managed and stable, in the opinion of the investigator, for at least 28 days prior to first administration of study drug

3.2 Exclusion Criteria

3.2.1 History of sever hypersensitivity reaction (eg. anaphylaxis) to other biologic drugs or monoclonal antibodies

3.2.2 Clinically significant cardiac disease or impaired cardiac function, including any of the following:

- Clinically significant and/or uncontrolled heart disease such as congestive heart failure (New York Heart Association grade ≥ 2), uncontrolled hypertension, or clinically significant arrhythmia currently requiring medical treatment
- QTcF > 470 msec on screening electrocardiogram (ECG) or congenital long QT syndrome. NOTE: If the initial automated QTcF interval is > 470 msec at screening, for the purpose of determining eligibility, the mean QTcF, based on at least 3 ECGs obtained over a brief time interval (ie, within 30 minutes), should be manually determined by a medically qualified person.
- Acute myocardial infarction or unstable angina pectoris < 6 months prior to Screening

3.2.3 Presence of symptomatic or untreated central nervous system (CNS) metastases, or CNS metastases that require doses of corticosteroids within the prior 3 weeks to study Day 1. Patients with brain metastases are eligible if lesions have been treated with localized therapy and there is no evidence of progression for at least 4 weeks by MRI prior to the first dose of study drug

3.2.4 Active infection requiring systemic antibiotic therapy. Patients requiring systemic antibiotics for infection must have completed therapy at least 1 week prior to the first dose of study drug

3.2.5 Known history of uncontrolled human immunodeficiency virus (HIV) infection (defined as CD4 count < 200 and/or a detectable viral load). Testing for HIV status is not necessary unless clinically indicated

3.2.6 Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection per institutional protocol. Testing for HBV or HCV status is not necessary unless clinically indicated or the patient has a history of HBV or HCV infection

3.2.7 Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type

3.2.8 Any medical condition that would, in the investigator's or Sponsor's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results

3.2.9 Patients receiving systemic steroid therapy or any other immunosuppressive medication at any dose level, as these may interfere with the mechanism of action of study treatment. Local steroid therapies (eg, otic, ophthalmic, intra-articular or inhaled medications) are acceptable

3.2.10 History of adrenal insufficiency

3.2.11 Participants with clinically significant pulmonary disease or impaired lung function, including any of the following:

- An oxygen saturation of < 92% on room air, measured by pulse oximeter
- History of interstitial lung disease
- History of pneumonitis that required corticosteroid treatment or current pneumonitis
- Ongoing requirement for intermittent or continuous oxygen supplementation

3.2.12 History of colitis or inflammatory bowel disease

3.2.13 Major surgery within 2 weeks of the first dose of study drug (minimally invasive procedures such as bronchoscopy, tumor biopsy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery and are not exclusionary)

3.2.14 Radiotherapy within 2 weeks of the first dose of study drug, with the exception of palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass

3.2.15 Use of hematopoietic colony-stimulating growth factors (eg, G-CSF, GM-CSF, M-CSF) ≤ 2 weeks prior to start of study drug. An erythroid-stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment and the patient is not red blood cell transfusion dependent

3.2.16 Women who are pregnant or nursing/breastfeeding**.** Where pregnancy is defined as the state of a female after conception and until the termination of gestation.

3.2.17 Women of childbearing potential who are sexually active with a non-sterilized male partner, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during study treatment (defined in Section 7.2.3), and must agree to continue using such precautions for 6 months after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician.

3.2.18 Male patients must be surgically sterile or use double barrier contraception methods from enrollment through treatment and for 6 months following administration of the last dose of study drug

3.3 Inclusion of Women and Minorities

Men, women, and members of all ethnic and racial groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

After obtaining Informed Consent, eligible patients will be enrolled on this trial. Subjects will be registered by local sites through an electronic database and will be issued a subject unique identifying numbers for eligible participants. An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each subject treated with the investigational product in the study or registered to the study. SARC may request faxed copies of selected source documents with PHI redacted for verification of records, accuracy of electronic submissions and review of data.

While all study evaluations must be performed by the Investigator as described in Section 10, Study Evaluations and Study Calendar, only data related to the primary and secondary endpoints, as well as safety data, will be captured in the eCRFs.

4.2 Registration Process

This study uses a web based data entry system for data submission. All subject registrations and Case Report Forms (CRFs) will be submitted electronically via the study web site. All subjects must be registered on the study website prior to start of treatment. Data Managers and other authorized users will be provided with a unique user identification number and password to access the site. All study case report forms may be accessed online through the study website. In case there are problems accessing the website, please contact the SARC office directly at: Phone: 734-930-7600.

4.3 Central Pathology Review

N/A

5. TREATMENT PLAN

Pre-screening

Patients with a diagnosis of unresectable or metastatic CCS who are considered for this study will first enter the pre-screening study phase. Patients will sign a pre-screening informed consent form and undergo HLA testing in a CLIA-certified laboratory (unless this has already been done as a part of the patient's routine oncologic care). Patients who are HLA-A*02:01 will be eligible to sign consent for the interventional portion of this study and may initiate treatment after the screening phase. Patients who are HLA-ineligible will be offered the opportunity to participate in an observational study to track clinical outcomes with physician's choice of therapy.

Screening and Treatment

HLA-A*02:01 positive patients who are eligible to participate after completing screening assessments will begin tebentafusp treatment on C1D1 and C1D8 at 20 mcg and 30 mcg per week, respectively. The majority of moderate-to-severe toxicity associated with tebentafusp in previous studies were observed at these 2 dose time points and included hypotension, rash, pruritus, fever, and chills. After this initial dosing period, beginning at C1D15 and beyond, patients will receive the full dose of 68 mcg. This escalated dose administered at C1D15 will be the dose used for the remainder of the treatment period. Beginning with C1D8, tebentafusp will be administered on the scheduled day (± 2 days), and consecutive infusions of tebentafusp must be administered at least 5 days apart. A treatment cycle is defined as 21 days for the purposes of scheduling procedures and evaluations. Please refer to Section 11.0 for details of the timing of required assessments.

The first six patients treated with tebentafusp will require overnight hospitalization and a minimum of pre-dose and Q4-hour vital signs monitoring after the first administration of tebentafusp (C1D1), the second administration (C1D8), and the third escalated dose of tebentafusp (C1D15) is administered. For the first 3 administrations of tebentafusp, patients must be monitored for at least 16 hours after dosing.

If no Grade ≥ 2 episodes of cytokine release syndrome or Grade ≥ 3 infusion-related reactions among the first six patients treated with tebentafusp, subsequent patients may be treated with tebentafusp in either an inpatient or an outpatient setting for the first three study doses, at the discretion of the treating physician. Additional information regarding this 'de-escalation' of monitoring can be found in Section 5.1.3

During the course of the study visits, tests and/or procedures should occur on schedule whenever possible. A visit window of ± 2 days is allowed for all visits where study drug administration is scheduled. For all other visits, a visit window of ± 7 days is allowed, unless otherwise indicated. If the study drug infusions are delayed or otherwise moved from the scheduled day, all study assessments will be moved with the delayed study drug infusions. The only exception to moving study assessments with treatment are the radiological assessments, which must be performed ± 7 days of the scheduled date of the assessment (unless otherwise indicated) taking as reference C1D1. The protocol specified

radiologic assessments should be performed as scheduled every 6 weeks as indicated in the protocol (reference to C1D1) and should not follow delays incurred in the treatment period for the accurate assessment of PFS and duration of response endpoints. Radiologic assessments should not move if delays in treatment are incurred.

Patients will be treated until they experience unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the patient, as described in Section 5.3.

Patients receiving tebentafusp who have radiologic evidence of disease progression by RECIST and have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue treatment with tebentafusp after discussion with the Principal Investigator and re-consent (Section 12). Patients who continue on treatment after disease progression should discontinue study treatment once they have unequivocal, confirmed progression or are no longer deriving benefit as assessed by the investigator.

5.1 Agent Administration

5.1.2 Rationale for intra-patient escalation regimen

Several key observations in the first-in-human Phase I study of tebentafusp (IMCgp100-01) led to the intra-patient escalation regimen. First, the identified RP2D of the weekly dosing regimen at 50 mcg led to severe toxicity at the first or second dose in a cohort of patients with uveal melanoma in the expansion cohort. The basis for the enhanced toxicity is the high expression level of the gp100 antigen in uveal melanoma, profound lymphocyte trafficking into skin and tumor, as well as the extent of disease in these patients. From this observation, the intra-patient escalation regimen was tested with a low fixed dose at C1D1 (20 mcg) and C1D8 (30 mcg) followed by resumption of dosing at the RP2D of 50 mcg at C1D15 and beyond. This regimen was well tolerated in a subsequent cohort of patients with uveal (n=6) and cutaneous (n=1) melanoma. A review of the efficacy data from this Phase I study revealed that patients with more extensive disease had demonstrated PRs generally at doses higher than the defined RP2D of 50 mcg and specifically in uveal melanoma, the PRs were observed doses of 48–81 mcg. The Phase I of the intra-patient escalation regimen was initiated (study IMCgp100-102), to both avoid the infusion-related toxicity at Weeks 1 and 2 and to increase the exposure of IMCgp100 closer to those doses where PR were observed in uveal melanoma.

Preclinical data suggests that the residence time of tebentafusp to the HLA-A*02:01 allele is considerably longer resulting in enhanced effects compared to non-HLA-A*02:01 alleles. This is borne out in the clinical data, where patients expressing non-HLA-A*02:01 alleles appear to have fewer T cell mediated toxicities and no clinical responses have been observed. Given these preclinical and clinical data, enrollment is therefore limited to patients expressing the HLA-A*02:01 allele.

In Study IMCgp100-102, patients with advanced uveal melanoma were treated with the intra-patient escalation regimen of 20 mcg at C1D1, 30 mcg at C1D8, followed by an

escalated dose at C1D15 and beyond. To identify the escalated dose for C1D15 and beyond, a conservative escalation approach was taken (Cohort 1 at 54 mcg, Cohort 2 at 64 mcg, and escalating in increments of approximately 10 mcg). A dose level of 73 mcg was not tolerated due to elevations in hepatic transaminases with a concurrent low-grade increase in bilirubin in 2 of 4 treated patients; these events were reversible without administration of corticosteroids and all patients who experienced DLTs remained on treatment. After a dose reduction to 68 mcg, 6 patients were treated with no DLTs and no significant liver enzyme elevations. A dose of 68 mcg was identified as the MTD and was selected as the dose level for further study of the intra-patient escalation regimen.

Tebentafusp monotherapy will be administered as an intravenous (IV) infusion over 15 to 20 minutes at the standard regimen of 20 mcg on Week 1, 30 mcg on Week 2, 68 mcg on Week 3, and 68 mcg once weekly thereafter. This is the same regimen used in the randomized Phase 3 study (IMCgp100-202) in uveal melanoma and demonstrated a strong risk/benefit with an HR for OS of 0.51 and a low rate of treatment-related AEs resulting in discontinuation (2%).

5.1.3 Escalation Regimen

All patients will receive treatment with single-agent tebentafusp on C1D1 and C1D8 at 20 mcg and 30 mcg per week, respectively. The majority of moderate-to-severe toxicity associated with tebentafusp is observed at these 2 dose time points and has typically included hypotension, rash, pruritus, fever, and chills. After this initial dosing period, beginning at C1D15 and beyond, patients will receive the escalated dose of 68 mcg. This escalated dose administered at C1D15 will be the dose used for the remainder of the treatment period. Beginning with C1D8, tebentafusp will be administered on the scheduled day (± 2 days), and consecutive infusions of tebentafusp must be administered at least 5 days apart.

For the first six patients treated, this intra-patient escalation regimen requires overnight hospitalization and a minimum of pre-dose and Q4-hour vital signs monitoring after the first administration of tebentafusp (C1D1), after the second administration (C1D8), and after the escalated dose of tebentafusp on C1D15 is administered. For the first 3 administrations of tebentafusp, patients should be monitored for at least 16 hours after dosing. “Inpatient hospitalization” refers to a facility with fully functional resuscitation facilities, 24-hour monitoring, and physician availability. See Section 10.4 for additional details on vital signs monitoring.

Inpatient monitoring at C2D1 will be determined by the toxicity observed in the C1D1–C1D15 doses as follows:

1. If the escalated dose at C1D15, administered as an inpatient, does not raise safety concerns (and the patient does not experience an adverse reaction involving hypotension of grade ≥ 2), the subsequent dose at C2D1 and all subsequent doses can be administered on an outpatient basis.

2. If the patient experiences hypotension requiring any medical intervention (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] grade ≥ 2) at C1D15, then the C2D1 dose should be administered with inpatient monitoring, similar to C1D1–C1D15. If the patient does not experience hypotension requiring medical intervention at the C2D1 dose administered as an inpatient, then all subsequent doses can be administered on an outpatient basis.
3. Hospitalization at other days (eg, Cycle 2 and beyond) is determined at the discretion of the principal investigator based on the patient's history and tolerance for the initial doses of the study medication, with the exception of patients experiencing a treatment delay (please refer to bullet 4 below).
4. Patients experiencing a break or delay in treatment for any reason of more than 2 weeks AND with a history of a grade 3 or 4 event of hypotension with tebentafusp dosing during the first weeks of treatment will be monitored as an inpatient for the dose subsequent to the break in dosing, regardless of the timing of the break in dosing, with vital signs monitored at a minimum of every 4 hours and monitoring for at least 16 hours after dosing.

If none of the first six patients experience **Grade ≥ 2 CRS or Grade ≥ 3 infusion-reactions**, subsequent patients can be treated as an outpatient for their intra-patient dose escalation. However, all patients undergoing intra-patient dose escalation require monitoring in a facility with access to resuscitation equipment, rescue medications, and physician availability. Patients must be monitored for at least 8 hours post-end of infusion on C1D1, C1D8, and C1D15. Vital signs must be confirmed stable prior to discharge. Minimum thresholds are body temperature < 38.2°C, heart rate < 110 beats per minute, and oxygen saturation 92% on room air.

Antihypertensive drugs are allowed as concomitant medications; however, because transient hypotension has occurred during infusions of monoclonal antibodies and ImmTACs, the investigators should consider reducing or not administering antihypertensives for 24 hours before and after the tebentafusp administration during at least the first 3 weeks of treatment. Appropriate management of patients, especially those with more severe hypertension, receiving medications that may cause rebound hypertension when abruptly discontinued or those who are on multiple blood pressure medications should be discussed with a cardiology consultant and the Principal Investigator.

In addition, due to the risk of hypotension, IV fluids may be administered prior to tebentafusp administration and, if given, IV fluids will be recorded as a concomitant medication. The administration of IV fluids should be guided by clinical evaluation and the volume status of the patient. Pruritus is a common AE with tebentafusp, so premedication with an antihistamine may be considered. See Appendix 18.1 for further recommendations regarding treatment of skin toxicity. If a patient experiences an infusion reaction, he/she may receive premedication on subsequent dosing days after consultation with the Principal Investigator. Pre-medications should include, but are not

limited to, paracetamol/acetaminophen and antihistamine. Corticosteroid premedication should be avoided; corticosteroids should only be considered if the paracetamol/acetaminophen and antihistamine combination is not effective.

Acute allergic reactions should be treated as needed using institutional guidelines. In the event of anaphylactic/anaphylactoid reactions, any therapy necessary to restore normal cardiopulmonary status should be implemented immediately. Such acute allergic reactions will be reported to the Sponsor in an expedited manner. These should be designated as reportable as an SAE, regardless of hospitalization, as medically important events. Please refer to the SAE reporting section for details. The individual symptoms of the infusion-related reaction should be captured in order to best characterize the study drug infusion reactions, unless the investigator considers another category, such as "allergic reaction" or "anaphylaxis," more appropriate in a specific situation.

5.2 General Concomitant Medication and Supportive Care Guidelines

Acceptable Therapy

Concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed. Examples include anti-diarrheal medications, antiemetics, or electrolyte supplementation.

Patients must be told to notify the investigational site staff about any new medications, herbal remedies, or dietary supplements that he or she takes after the start of the study treatment, regardless of treatment duration. All concomitant medications and significant non-drug therapies (including physical therapy, herbal or natural medications, and blood transfusions) administered during the study must be documented on the concomitant medications list.

IV hydration prior to administration of study medications or required to manage toxicity associated with any of the study medications (eg, hypotension) should be recorded on the concomitant medications list.

Required inactivated vaccinations (ie, influenza vaccine) may be administered per investigator discretion. Inactivated (non-live) vaccine(s) should NOT be administered during first 4 weeks of tebentafusp therapy or administered within 24 hours before or after tebentafusp dosing. Vaccine(s) administered during the study should be recorded on the concomitant medications list.

Treatment with hematopoietic colony-stimulating growth factors (eg, G-CSF, GM-CSF, M-CSF, or erythroid-stimulating agents) may not be initiated during the first cycle. If a patient requires an erythropoiesis-stimulating agent prior to enrollment (beginning at least 2 weeks before start of study treatment), they may continue at the same dose.

Anti-coagulant therapy is permitted if the patients are already at stable doses for > 2 weeks at time of first dose. Low molecular weight heparin can be started during the overnight observations, if discussed and approved by the Principal Investigator in advance. The international normalized ratio should be monitored as clinically indicated

per investigator's discretion. Ongoing anti-coagulant therapy should be temporarily discontinued to allow tumor biopsy according to the institutional guidelines.
Anti-hypertensives are allowed as concomitant medications; however, because transient hypotension has occurred during infusions of tebentafusp and monoclonal antibodies, treatment with anti-hypertensive therapy should be held for 24 hours before and 24 hours after tebentafusp in the first 6 weeks of treatment, and thereafter, at the discretion of the principal investigator. Medications administered as supportive care of bony metastases, including bisphosphates and denosumab, may be administered during study therapy.

Treatment with palliative radiotherapy to tumor locations to alleviate pain is acceptable during the course of the study provided that: (1) with bony lesions, no new bone lesions are noted (representing clinically significant progression of disease) and (2) only non-target lesions are radiated. Radiation of target lesions is not permitted while receiving study treatment.

Prohibited Therapy

While on study treatment, patients may not receive other additional investigational study drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. As described above, palliative radiotherapy or surgery is allowed and bisphosphonates may be given for bone metastases. Additionally, no other therapeutic monoclonal antibodies, except for denosumab and tocilizumab if required for patient care, and no immunosuppressive medication may be administered while on this study, unless prescribed to manage toxicity as recommended in Appendix B. While systemic corticosteroid therapy will interfere with the mechanism of action of the study medications, its use is recommended in some settings. Live or attenuated vaccines are prohibited from 28 days prior to the first dose until 30 days after the final dose of the study drug.

Patients with adrenal insufficiency or patients receiving systemic steroid therapy or any other immunosuppressive medication at any dose level at Screening are excluded. Patients receiving corticosteroids may not be able to mount an appropriate physiologic cortisol response in the event of an infusion reaction with initial tebentafusp dosing. Corticosteroids and other immunosuppressives may interfere with the mechanism of action of the study drugs. The use of systemic corticosteroid therapy is permitted/recommended in the following settings: (1) infusion reactions and (2) immune-mediated toxicities and toxicity management (eg, hypotension and CRS) as directed in Appendix B (eg, hypotension not resolving with fluid support alone). Of note, patients with a pre-existing history of adrenal insufficiency are excluded from study participation. Any additional uses of systemic corticosteroid therapy during the study should be discussed with the Principal Investigator.

5.3 Duration of Therapy

Treatment may continue until one of the following criteria applies:

- Disease progression as defined by RECIST v 1.1 unless criteria for treatment beyond initial PD is met (see Section 5.3.1)
- If continuing treatment beyond initial PD, then patients must discontinue study treatment once further PD warranting treatment discontinuation is met (see Section 5.3.1)
- Initiation of alternative anti-cancer therapy including another investigational agent
- Unacceptable toxicity as defined in Appendix B or any AE that, in the opinion of the investigator, contraindicates further dosing
- Withdrawal of consent from further treatment with investigational product by the patient or the investigator
- Patient is lost to follow-up
- Patient is determined to have met 1 or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation AND continuing to receive investigational product might constitute a safety risk. Patients who fall into this category and for whom continuation of treatment is not thought to pose a safety risk, in the opinion of the investigator, may continue to receive study treatment
- Pregnancy or intent to become pregnant

At the time patients discontinue study treatment, the EOT visit should be scheduled in the appropriate window of 14 days after the last dose was administered. At this visit, all of the assessments listed for the EOT visit will be performed. If the decision to withdraw the patient occurs at a regularly scheduled visit, that date of visit may become the EOT visit rather than having the patient return for an additional visit (safety follow-up will still continue for the full 30-day observation period). An EOT disposition document should be completed at the EOT visit, giving the date and reason for stopping the study treatment.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 11. If they fail to return for these assessments for unknown reasons, every effort (eg, telephone, email, and registered letter) should be made to contact them. If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be documented.

5.3.1 Criteria for Treatment Beyond Initial RECIST v1.1 Disease Progression

Clinical evidence suggests that a minority of patients treated with immunotherapies, including tebentafusp, will derive clinical benefit after an initial assessment of PD. If initial PD based on RECIST v1.1 occurs, treatment may continue according to the protocol-specified regimen provided ALL of the following criteria continue to be met:

- Absence of signs or symptoms indicating clinically significant PD

- No decline in ECOG performance status
- No impending threat to vital organs/critical anatomical sites (eg, spinal cord compression, liver function decline) requiring urgent alternative medical intervention or where continuation of study therapy would prevent institution of such intervention
- Absence of any of the investigational product discontinuation criteria

Patients are not required to continue treatment beyond initial RECIST v1.1 PD. Both the patient and the investigator must agree continuing treatment would be in the patient's best interest. Patients continuing treatment beyond the protocol-specified RECIST v1.1 PD must provide separate consent to continue treatment after an initial assessment of PD. In addition, instances where RECIST v1.1 PD is equivocal or warrants follow-up confirmation, in the judgment of the investigator, prior to continuing study treatment, consent should be obtained at the time of initial suspicion of PD with appropriate discussion of the risk:benefit of continuing study treatment with the patient.

Patients who are treated beyond initial RECIST v1.1 PD must permanently discontinue study treatment if they experience further progression warranting treatment discontinuation. Further progression warranting treatment discontinuation is defined as ANY one of the following observed at least 4 weeks after the initial PD assessment per RECIST v1.1: 1) an additional ≥ 20% increase in tumor burden (sum of diameters of both target and new measurable lesions) accompanied by an absolute increase of ≥ 5 mm; 2) unequivocal PD of non-target lesions; or 3) new non-measurable lesions.

Treatment and assessments after an initial assessment of PD will continue to follow the treatment regimen. Imaging data will continue to be obtained until further progression warranting treatment discontinuation (as defined above) or criteria for discontinuation of study treatment following RECIST v1.1 PD are met.

5.4 Duration of Follow Up

Survival follow-up should be completed every 12 weeks until death, withdrawal from study, or until the end of the study is reached.

5.5 Criteria for Removal from Study

Patient must be withdrawn from the trial for the following reasons:

- Patient dies.
- Patient is lost to follow-up.
- Patient withdraws consent for any further participation including further survival follow-up.
- The end of study is reached

If none of these conditions are met, patients should continue to be followed for survival status. The reason for study removal and the date the patient was removed must be documented in the Case Report Form including death or lost to follow up.

6. DOSING DELAYS/DOSE MODIFICATIONS

All dose modifications should be based on the worst preceding toxicity. See Appendix B for management of tebentafusp-related AEs.

For tebentafusp, escalation steps during interpatient dose escalation (ie, increasing from 20 mcg to 30 mcg or increasing from 30 mcg to 68 mcg) may be delayed. Dose reductions from 68 mcg are not permitted.

Weekly tebentafusp doses may be omitted as needed for management of AE. After completing 3 months of treatment, the Investigator may permit occasional, infrequent dose omissions to accommodate holidays, vacations, and the like.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting in addition to routine reporting.

7.1 Adverse Event and Laboratory Abnormalities

7.1.1 Clinical AE's

7.1.1.1 Definition of Adverse Events

Per the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during a study are to be reported as AEs.

7.1.1.2 CTCAE term (AE description)

The descriptions found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a

copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

7.1.1.3 Severity

Severity of all adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events v 5.0 (CTCAE) on a five-point scale (grades 1 to 5) and reported in detail on the CRF. Adverse events not listed on the CTCAE should be graded as follows:

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death

7.1.1.4 Drug-Adverse Event relationship

The causality relationship of study drug to the adverse event will be assessed by the investigator as either:

Yes or No

If there is a reasonable suspected causal relationship to the study medication, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as **Yes**.

The following criteria should be considered in order to assess the relationship as **Yes:**

– Reasonable temporal association with drug administration

– Known response pattern to suspected drug

– Disappears or decreases on cessation or reduction in dose

– Reappears on rechallenge

The following criteria should be considered in order to assess the relationship as **No**:

– It does not follow a reasonable temporal sequence from administration of the drug.

– It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

– It does not follow a known pattern of response to the suspected drug.

- It does not reappear or worsen when the drug is readministered.

7.1.1.5 Definition of Serious Adverse Events

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any Adverse Event that at any dose fulfils at least one of the following criteria:

- is fatal; (results in death; NOTE: death is an outcome, not an event)
- is Life-Threatening (NOTE: the term "Life-Threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).
- required in-patient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above

7.1.1.6 Progression of Underlying Malignancy

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by WHO criteria, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the

symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

7.1.2 Treatment and Follow-up AEs

After the discontinuation of therapy, continue to follow up AEs as follows:

Related AEs: Follow until one of the following occurs:

- Resolved or improved to baseline
- Relationship is reassessed as unrelated
- Death
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure

Unrelated severe or life threatening AEs: Follow until one of the following occurs:

- Resolved or improved to baseline
- Severity improved to grade 2
- Death
- Start of new anti-cancer regimen
- Investigator confirms that no further improvement can be expected
- Clinical or safety data will no longer be collected, or final database closure

Unrelated Grade 1 or Grade 2 AEs: Follow as clinically indicated.

The final outcome of each adverse event must be recorded on the CRF

7.1.3 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results pages of the CRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.

Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded on the adverse event page in the CRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

7.1.4 Follow-up of Abnormal Laboratory Test

In the event of medically significant unexplained abnormal laboratory test values, the test should be repeated and followed until it has returned to the normal range, baseline value and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded in the CRF.

7.2 Handling of Safety Parameters

7.2.1 Reporting of Adverse Events

All adverse events (related and unrelated) occurring during the study and up to 30 days after the last dose of study medication must be reported. Reporting the specific time of onset of a given AE is only necessary when it occurs in relation to study drug administration.

7.2.2 Reporting of Serious Adverse Events (immediately reportable)

Any clinical adverse event or abnormal laboratory test value that is *serious* and which occurs during the course of the study (as defined in section 7.2.1.5 above), must be reported to the Principal Investigator(s), SARC and Immunocore **within *one* working day** of the investigator becoming aware of the event (expedited reporting). If only limited information is initially available, follow-up reports are required. The original SAE Form must be kept on file at the study site.

SAE's must be reported on the MedWatch Form 3500A along with the completed SAE Coversheet (operations manual) and emailed to SARC045@sarctrials.org and ImmunocorePV@ubc.com.

Related Serious Adverse Events ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated Serious Adverse Events must be collected and reported during the study and for up to 30 days after the last dose of study medication.

7.2.3 Pregnancy

Females must be instructed to stop taking the study medication and immediately inform the investigator if pregnancy occurs during the study. Pregnancies occurring up to 6 months after the completion of the study medication must also be reported to the investigator. The investigator should report all pregnancies within 24 hours to the sponsor.

The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Pregnancy occurring in the partner of a male patient participating in the study should also be reported to the investigator and the sponsor. The partner should be counseled and followed as described above.

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, can be included in the study provided they are using highly effective methods of contraception during dosing and for 6 months after the last dose of tebentafusp or Investigator's Choice.

Highly effective contraception methods include the following:

- Total abstinence from sexual relations for the duration of the treatment when applicable to the lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, this applies only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Male sterilization (at least 6 months prior to Screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
- The combination of any 2 of the following methods when both are used simultaneously:
    - Use of oral, injected, or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception

- Placement of an intrauterine device or intrauterine system
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) when used with spermicidal foam, gel, film, cream, or used of a spermicidal vaginal suppository

In case of use of oral contraception, women should have been stable on the same oral contraceptive pill for a minimum of 3 months before beginning treatment on this study.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, age appropriate, history of vasomotor symptoms), or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks prior to study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

7.3 Warnings and Precautions

7.3.1 Cytokine Release Syndrome

Cytokine release syndrome is a class effect of all T cell engagers and is due to an immune cascade following T cell activation. The tebentafusp regimen did not mandate prophylactic corticosteroids, antihistamines, or acetaminophen prior to dosing. Cytokine release syndrome was programmatically adjudicated using the ASTCT consensus grading for CRS (Lee, 2019). As of the DCO for this IB update, 344 (88.0%) of the 505 patients who received tebentafusp monotherapy across all clinical studies, experienced an AE of CRS that was considered related to study drug.
In IMCgp100-202 Study, which forms the largest dataset of programmatically derived CRS events, approximately 89% of patients following tebentafusp administration experienced CRS.

Most patients had Grade 1 (12%) or Grade 2 (76%) CRS. The incidence of Grade 3 CRS was 0.8%. There were no Grade 4 CRS or death due to CRS. The diagnosis of CRS following tebentafusp infusion was based most frequently on pyrexia followed by hypotension and infrequently hypoxia. Other commonly observed symptoms with CRS included chills, nausea, vomiting, fatigue, and headache.

Most patients experienced CRS following each of the first 3 tebentafusp infusions, with decreasing severity and frequency. In the majority of cases, CRS started on the day of infusion. Pyrexia was noted in nearly all cases of CRS, and in these patients, an increase in body temperature generally occurred within the first 8 to 10 hours after tebentafusp infusion. Cytokine release syndrome rarely (1.2%) led to treatment discontinuation. Cytokine release syndrome should be managed per the institutional protocol for CRS. In the absence of an institutional protocol, management guidance for hypotension and CRS with fluid management and IV corticosteroids has been included in all study protocols with tebentafusp. Based on the observed toxicities during the early weeks of dosing (eg,

hypotension), specific recommendations for close observation of subjects are included in each of the clinical study protocols.

7.3.2 Rash (Skin Toxicity)

Among the most frequent adverse reactions observed with tebentafusp are toxicity in the skin, most commonly rash, erythema, and pruritus. Typically, rashes were mild-to-moderate in severity and abated without systemic steroid intervention. Skin toxicity is likely related to its mechanism of action (induction of anti-gp100 T cell responses) given that melanocytes are known to express gp100, albeit at lower levels than in melanoma cells.

Across all studies, acute skin reactions occurred in 92.7% of patients treated with tebentafusp monotherapy, including any grade rash (grouped term, 85.3%), pruritus (71.5%), edema (grouped term, 28.7%), and erythema (25.1%). Most skin reactions were Grade 1 or 2 (72.3%) and some tebentafusp-treated patients experienced Grade 3 (20.4%) events. No Grade 4 or 5 events were observed.

Acute skin reactions typically occurred following each of the first 3 tebentafusp infusions, with decreasing severity and frequency. The median time to onset of acute skin reactions was 1 day in tebentafusp-treated patients and the median time to improvement to Grade $\leq$ 1 was 6 days. There were no tebentafusp discontinuations due to acute skin reactions. The majority of symptoms resolved without any systemic corticosteroid or any long-term sequalae. No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported.

Management guidance for rash is included in all study protocols. In general, patients with symptoms associated with rash (eg, pruritus) can be managed with antihistamine and topical corticosteroid therapy. For more severe cases of rash, IV corticosteroid therapy has been implemented, generally in patients with multiple associated AEs (eg, rash associated with pyrexia, chills, and hypotension).

7.3.3 Elevated Liver Enzymes

Overall, an increase in any LFT occurred in tebentafusp as well as investigator's choice arms in IMCgp100-202 Study, but did not appear to be clinically relevant in either arm. Most of the ALT/AST elevations in the tebentafusp arm were mild, occurred early, and did not result in treatment discontinuation. No deaths due to ALT/AST elevations were observed and more than 90% of patients were able to continue tebentafusp treatment beyond worst grade ALT/AST elevation. A majority (70%) of ALT/AST elevations in the tebentafusp arm occurred within the first 3 infusions. Most tebentafusp treated patients who experienced Grade 3 or 4 ALT/AST elevations had improvement to Grade $\leq$ 1 within 7 days.

Across all studies, approximately 35% of patients who received tebentafusp monotherapy have experienced LFT elevations/hepatotoxicity: 15.0% had Grade 1, 8.3% had Grade 2, 9.7% had Grade 3, and 1.8% had Grade 4 LFT elevations/hepatotoxicity. No Grade 5 events were observed. AST increased (17.6%), ALT increased (15.8%), hyperbilirubinemia (8.1%), and hepatic pain (5.5%) were the most common LFT elevations/hepatotoxicity events observed in m onotherapy patients across all studies.

Treatment can include immunosuppression using corticosteroid therapy, although most cases have resolved without therapy. Patients experiencing this transient hepatotoxicity have been re-dosed with decreased severity after additional doses and subsequent return to baseline. Chronic elevations in LFT have been associated with disease progression. Management guidance for LFT elevation with conservative dose adjustments are included in all study protocols. With observation of elevations of transaminases during dosing with tebentafusp, corticosteroid therapy can be considered as described in the clinical study protocols.

7.4 Drug Interactions

No drug-drug interactions have been observed with tebentafusp.

7.5 Use During Pregnancy and Lactation

No data are available with tebentafusp use in pregnant or lactating women. No animal reproductive and developmental toxicity studies have been conducted with tebentafusp to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if tebentafusp has the potential to be transferred to the fetus or human milk. Therefore, tebentafusp is not recommended for women who are pregnant or breast feeding, and contraception requirements are described in the individual clinical study protocols.

7.6 Overdose

No antidote is known for tebentafusp, nor has it been defined what constitutes an overdose. However, inadvertent incorrect dosing, such as administration of a higher dose than stated in the protocol, should be rigorously monitored for potential (serious) adverse reactions. Patients experiencing toxicity upon incorrect dosing or overdosing must be treated at the discretion of the treating physician with adequate supportive care as indicated by the symptoms observed in the patient which generally should include IV corticosteroid therapy. Patients will have to be followed until full recovery or confirmed stabilization of the events.

7.7 Drug Abuse and Dependency

None known.

7.8 Other Clinically Relevant Information

The other clinically relevant information section of the DCSI documents safety observations or events that may be potentially relevant in the clinical management of subjects receiving tebentafusp. A reasonable possibility of a causal association with tebentafusp and the potentially medically important observations or events listed below (in Sections 7.8.1 to 7.8.4) has not been established, and, at this time, are not considered expected for the purpose of expedited reporting. Further characterization is ongoing.

7.8.1 Tumor Flare/Pain

Pain or inflammation at the site of known tumors has been reported in the tebentafusp development program and could be due to inflammation secondary to immune activation. Clinical manifestation may vary according to the anatomic location of the tumor. For example, serious and non-serious TEAEs of dyspnea, tachypnea, pleuritic effusion, and hypoxia have been reported. Patients should be managed symptomatically as indicated and IV corticosteroid therapy should be strongly considered in cases where symptoms persist or do not respond to initial medical therapy. In addition, evaluation and management of pain should be performed as clinically appropriate.

7.8.2 Elevated Pancreatic Enzymes

Increased amylase and lipase, including Grade 3 and Grade 4 elevations, have been observed following treatment with tebentafusp in the context of CRS and/or tumor flare as a transient phenomenon.

Among the 505 patients who received tebentafusp monotherapy across all studies (as of the DCO of 13 October 2021), TEAEs of lipase increased occurred in 50 (9.9%) patients (including 18 [3.6%] patients with Grade 3 or Grade 4 events) and amylase increased occurred in 22 (4.4%) patients (including 3 [0.6%] patients with Grade 3 or Grade 4 events). Most of the events of lipase increased and amylase increased were causally related to tebentafusp. None of these events were fatal or associated with Type 1 diabetes.

7.8.3 Lymphopenia

Monitoring of white cell counts revealed that lymphocytes in patients are trafficking post-treatment. In general, lymphocyte numbers increased in the circulation soon after infusion commenced and then dropped dramatically at approximately 24 hours, sometimes manifesting in laboratory values as Grade 1–4 lymphopenia. However, it is important to note that this trafficking of lymphocytes is a desired effect of tebentafusp. Tebentafusp is expected to activate T cells at sites where it binds the target gp100 peptide, thereby causing the release of a number of inflammatory mediators including chemokines. Chemokine release will trigger the trafficking of lymphocytes to the site of inflammation. In support of this, where serial biopsies have been sampled from patients, the infiltration of lymphocytes into skin and tumor 2 days after the first dose of tebentafusp was observed. The lymphopenia has been shown to be transient and self-resolving, with lymphocyte counts returning to baseline by Day 8. Rises in C-reactive protein levels have also been noted in a number of patients at the higher dose levels. Again, elevated C-reactive protein may be considered to be a related pharmacological mechanism of action of tebentafusp-mediated inflammation.

7.8.4 Ophthalmologic and Audiologic Toxicity

Prior to initiation of Phase 1 investigation of tebentafusp, the eye and ear were identified as potential target organs for toxicity, based on expression of the antigen in these target tissues. Across the tebentafusp development program to date, there have been no clinically significant TEAEs involving vision and/or hearing.

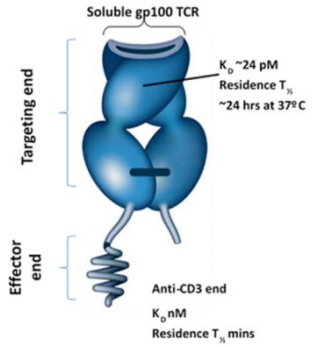
8. PHARMACEUTICAL INFORMATION

8.1 Study Agent

Tebentafusp is a 77 kDa bispecific protein with targeting and effector moieties which is manufactured in E. coli (Figure 1). The targeting portion of tebentafusp (TCR) functions to bind to the gp100 antigen as presented by MHC Class I on the surface of melanoma cells. These targeting TCRs are engineered versions of naturally occurring receptors found on the surface of T cells. In the natural situation, both diseased and healthy cells process cell proteins into peptide fragments and present these fragments at the cell surface via the Class I MHC. The system provides a means for the circulating cells of the immune system to recognize and attack diseased (or non-self) tissue. This particular function is performed by the T cell component of the immune system via the TCR.

The targeted gp100 peptide is presented by a subset of the population that express a specific variant of the MHC Class I complex known as HLA-A*02:01. This variant is carried by approximately 50% of the population in the Western World.[23] The gp100 protein is a 661 amino acid melanosomal membrane associated glycoprotein which is expressed in normal melanocytes and in the majority of melanoma tumors. The exact function of the protein is unknown, but it appears to be involved in melanosome maturation (Hoashi, 2005; Kawakami, 1997).[24,25] The gp100 antigen has been, and continues to be, the target of a number of immunotherapy based melanoma clinical trials.

Figure 1: Tebentafusp structure and functional domains



Tebentafusp is a biologic with an effector and targeting end. The targeting end is an affinity enhanced, soluble TCR recognizing the gp100 antigen and the effector end is an anti-CD3 binding domain. The kinetic measurements were generated using soluble proteins and the surface plasma on resonance (BIAcore) method. The effector function (anti-CD3) works by binding and activating T cells via CD3. These T cells can be tumor-specific cells which are already resident in the tumor (tumor infiltrating lymphocytes) but circulating polyclonal T cells may also be activated as they traffic through the tumor as part of the normal blood supply. CD4+ and CD8+ T cells are both activated by tebentafusp triggering cytolytic activity associated with release of immune mediators — potentially resulting in a cascade of anti-tumor immune effector mechanisms — and T cell proliferation. Studies on CD8 T cell subtypes have shown that effector memory, central memory, and naïve cells all respond to tebentafusp stimulation as well as CD4+ T cells. Memory T cell activation following exposure to tebentafusp is rapid (PD effects seen within hours of exposure) and naïve cell activation can take a few days, which is consistent with the biology of these cell types.

8.2 Preparation and Administration

For all study medication administration and protocol-specified inpatient hospitalizations, a physician must be present at the site or immediately available to respond to emergencies during all administrations of all study medications. Critical care and resuscitation facilities should be immediately available.

Table 1: Tebentafusp dose and schedule

Study Treatments	Pharmaceutical Form and Route of	Potency and Packaging	Dose	Frequency and/or Regimen

	Administration			
Tebentafusp	Concentrate for solution for infusion (single use vials)	0.2 mg/mL	20 mcg C1D1; 30 mcg C1D8; 68 mcg C1D15 and subsequent doses	Every week: Days 1, 8, and 15 of 21-day cycle

Tebentafusp 0.2 mg/mL drug product for IV infusion will be provided as a sterile, refrigerated solution in individual glass vials, held at 2 to 8°C. Each glass vial will contain approximately 0.5 mL (extractable volume) with a concentration of 0.2 mg/mL. Each vial is designed for single use (single-dose) only and is not to be used to treat more than one patient.

The target duration of administration of tebentafusp is 15 to 20 minutes per infusion. The entire content of the IV bag must be infused using an infusion pump. The IV line must be flushed after the contents of the IV bag are fully administered according to institutional policy to ensure the full dose is administered. It must be documented if the line was not flushed.

Detailed dose preparation instructions will be provided in the study pharmacy manual and/or in the relevant pharmacy handling instructions.

8.3 Formulation, Packaging and Labelling

Tebentafusp drug product is presented as a sterile, concentrate for solution for infusion/injection. Tebentafusp is currently available in the following configuration: 0.2 mg/mL tebentafusp for IV infusion.

8.4 Availability

Tebentafusp will be supplied by Immunocore.

8.5 Agent Ordering

Tebentafusp will be distributed by Immunocore to sites. Please refer to the operations manual for more details and a drug order form.

8.6 Agent Accountability

Accountability and patient compliance will be assessed by maintaining adequate drug dispensing and return records. Compliance with individual patient dosing is assured as the drug is administered intravenously and recorded at the clinical site.

Accurate records must be kept for each study drug provided by the sponsor. The drug dispensing log must be kept current and contain the following information:

- documentation of drug shipments received from the sponsor (date received and quantity)

- disposition of unused study drug not dispensed to patient
- the identification of the patient to whom the study medication was dispensed
- the date(s) and quantity of the study medication dispensed to the patient

This inventory must be available for inspection by the Monitor. All supplies, including partially used or empty containers and copies of the dispensing & inventory logs, must be returned to SARC/Immunocore. Monitor at the end of the study, unless alternate destruction has been authorized by SARC/Immunocore or required by local or institutional regulations (Section 8.7).

8.7 Destruction of Tebentafusp

Local or institutional regulations may require immediate destruction of used investigational product for safety reasons e.g., cytotoxicity. In these cases, it may be acceptable for investigational site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the sponsor at study start up before destruction.

Written documentation of destruction must contain the following:

- Identity (batch numbers or patient numbers) of investigational product(s) destroyed
- Quantity of investigational product(s) destroyed
- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)
- Name and signature of responsible person (or company) who destroyed investigational products(s)

A list of the adverse events and potential risks associated with Study Agent can be found in Section 7.1.

9. CORRELATIVE/SPECIAL STUDIES

9.1 Laboratory Correlative Studies

Research Blood

Peripheral blood samples for research will be obtained at baseline, C2D1, C3D1, C5D1, C9D1, and EOT. At each research blood collection time point the following samples will be collected:

- 2x10ml of peripheral venous blood will be collected in EDTA tubes
- 2x10ml of peripheral venous blood will be collected in Streck tubes

Tumor Biopsies

Archival tissue may be requested from all patients at any time after informed consent has been obtained and prior to withdrawal of consent.

Tumor biopsies for research purposes will be done at baseline and week 6, where feasible. Biopsy at the time of progression for analysis of tumor microenvironment and for potential mechanisms of immune escape will be optional.

The same tumor site will be biopsied at each time point, if feasible. Cores will be obtained with 18-gauge needles where appropriate and be of at least 1 cm in length. The quality, viability, and tumor content of biopsies will be confirmed by the on-call clinical pathologist at the time of retrieval. The goal will be to extract up to 6 cores for paraffin embedding (FFPE).

9.1.1 Collection, Handling, and Shipment of Specimens

All biospecimens collected from patients enrolled in SARC045 will be kept at a SARC designated specimen bank. Samples will be transported in compliance with current regulatory guidelines for transport of biological specimens. Sample collection and processing will be conducted as described in the SARC Operations Manual provided to each participating site. Complete details for collection, handling and shipment of specimens will be provided in the Operations Manual.

9.2 Biomarker Analyses

9.2.1 Density of Immune Infiltrate and Immune Regulatory Biomarker Expression

Multiplex immunofluorescence will be used to assess the number and composition of immune infiltrates to define the immune cell subsets present within the tumor before and after exposure to tebentafusp. Immune checkpoint expression within the tumor and on immune cells before and after exposure to tebentafusp will also be determined.

9.2.2 Gene Expression Profiling

Tumor cores will be analyzed by RNA sequencing. Software tools will be utilized to generate and perform quality control on BAM files and to quantify gene expression, including deconvolution to quantify immune cell populations. Additional analyses will include hierarchical clustering on principal components, differential gene expression, and pathway enrichment analysis, all of which may stratify patients who benefit and those who do not benefit from tebentafusp therapy.

9.2.3 Peripheral Blood Analysis for ctDNA

ctDNA will be extracted from plasma and DNA isolated from plasma will be quantified and sequenced. Baseline quantity of ctDNA and the change in ctDNA across time will be correlated with clinical endpoints.

9.2.4 Other tests

Multi-omic analysis, such as whole genome sequencing, whole exome sequencing, single-cell sequencing, methylation profiling, spatial profiling, or other techniques may be utilized as needed to better understand the molecular profile of CCS samples and the impact of tebentafusp treatment on the tumor or peripheral blood.

10. STUDY EVALUATIONS AND STUDY CALENDAR

10.1 SCREENING STUDIES

10.1.2 Pre-screening

Patients with a diagnosis of unresectable or metastatic CCS who are considered for this study will first enter the pre-screening study phase. Patients will sign a pre-screening informed consent form and undergo HLA testing in a CLIA-certified laboratory. Patients who are HLA-A*02:01 will be eligible to sign consent for the interventional portion of this study and may initiate treatment after the screening phase. Patients who have had previous HLA typing via a CLIA-certified laboratory and have documentation demonstrating these results do not need to be re-tested. Patients who are HLA-ineligible will be offered the opportunity to participate in an observational study to track clinical outcomes with physician's choice of therapy.

- Patients should not sign the Main Study informed consent form and enter Screening until the results of the HLA testing are known and the patient has been confirmed to be eligible for the screening portion of the study

10.1.3 Screening

All aspects of the screening evaluation must be completed prior to entering the study, unless otherwise noted. The following must be completed within 28 days of starting treatment:

- Signed main study informed consent for study participation
- Confirmation of disease: documented presence of unresectable and/or locally advanced clear cell sarcoma, including pathologic confirmation and measurable disease by RECIST 1.1 with demonstration of progression within 6 months of registration (if not newly diagnosed)

- Full medical history including all active conditions
- Review of concomitant medications including any relevant prior medications taken
- Physical exam (including height and weight)
    - Note: height may be documented at any time prior to registration
- Vital signs (pulse, blood pressure, temperature, respiratory rate, and oxygen saturation).
- ECOG performance status
- Complete blood count with differential
- Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, total bilirubin, total protein, AST, ALT, alkaline phosphatase, calcium), magnesium, and phosphorus
- Amylase, lipase, CK, and LDH
- PT (or INR) and aPTT
- Thyroid function tests (TSH, T4 free, T3)
- HIV-1/2 antibody test, Hepatitis B surface antigen and core antibody, and Hepatitis C antibody, with reflex PCR test if positive
- Urinalysis (dipstick)
- Serum β-HCG or urine pregnancy test for women of child-bearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required
- 12-lead electrocardiogram (ECG)
- CT scan of the chest (with or without contrast), CT abdomen and pelvis (with contrast, unless contraindicated) or MRI abdomen pelvis (with and without contrast, unless contraindicated, and CT or MR of other known sites of disease, as clinically indicated
- Research biopsy
- Research blood collection

Laboratory and radiological assessments performed as part of standard of care prior to signing the informed consent may be used if performed within the screening time window (28 days prior to C1D1).

10.2 ON STUDY EVALUATIONS

All the assessments required as part of the study are indicated in the Study Calendar organized by visit date, with assessments required indicated with an “X” at the specific visits when they should be performed. Assessments required on C1D1 that are performed as part of the screening evaluations and within 72 hours prior to the first dose of study treatment do not need to be repeated on C1D1.

The following procedures will be performed during the treatment period:

C1D1

- Physical exam (short)
- Vital signs (Please see section 10.5)
- Relevant laboratory evaluations
    - Complete blood count with differential
    - Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, total bilirubin, total protein, AST, ALT, alkaline phosphatase, calcium), magnesium, and phosphorus
    - Amylase, lipase, CK, and LDH
    - PT (or INR) and aPTT
- Concomitant medications
- Administration of tebentafusp
- Recording of adverse events

CXD8, CXD15:

- Vital signs (Please see section 10.5)
- Concomitant medications
- Administration of tebentafusp
- Recording of adverse events

Cycle 2:

- Physical exam (short one, with weight)
- Vital signs (Please see section 10.5)
- Relevant laboratory evaluations
    - Complete blood count with differential
    - Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, total bilirubin, total protein, AST, ALT, alkaline phosphatase, calcium), magnesium, and phosphorus
    - Amylase, lipase, CK, and LDH
    - PT (or INR) and aPTT
- Concomitant medications
- Administration of tebentafusp
- Recording of adverse events
- Research blood

Cycle 3, etc.:

- Physical exam (short)

- Vital signs (pulse, blood pressure, temperature, respiratory rate)
- Relevant laboratory evaluations
    - Complete blood count with differential
    - Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, total bilirubin, total protein, AST, ALT, alkaline phosphatase, calcium), magnesium, and phosphorus
    - Amylase, lipase, CK, and LDH
- PT (or INR) and aPTT

- Concomitant medications
- Thyroid function tests (D1 of odd cycles)
- Recording of adverse events
- Administration of tebentafusp
- Recording of adverse events
- Serum β-HCG or urine pregnancy test for women of child-bearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required
- Radiographic assessment
    - Occurring every 6 weeks through 48 weeks, and then every 9 weeks thereafter
- Research blood (C3D1, C5D1, C9D1 only)

- Research biopsy (Cycle 3 only)

NOTE: All visits can be obtained ±2 day of stated time point. Laboratory assessments may occur up to 2 days before infusion. Consecutive infusions of tebentafusp must be administered at least 5 days apart.

10.3 END OF TREATMENT EVALUATIONS

Final visit is to be performed at the time (or within 14 days after treatment stop date). End of treatment evaluations will include:

- Review of concomitant medications including any prior medications taken
- Physical exam (short)
- Vital signs (pulse, blood pressure, temperature, respiratory rate, and oxygen saturation).
- Relevant laboratory evaluations
    - Complete blood count with differential
    - Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, total protein, albumin, total bilirubin, total protein, AST, ALT, alkaline phosphatase, calcium), magnesium, and phosphorus

  - Amylase, lipase, CK, and LDH
  - PT (or INR) and aPTT
- Thyroid function tests (TSH, T4 free, T3)
- Urinalysis (dipstick)
- Serum β-HCG or urine pregnancy test for women of child-bearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required
- Research biopsy (if feasible)
  - EOT biopsy should be collected within 21 days of treatment stop or prior to starting next line of therapy.
- Research blood collection

Patients who complete study treatment should be followed for survival every 12 weeks until death, study withdrawal, or study end. Survival data can be collected by phone or EMR.

10.4 HLA-INELIGBILE PATIENTS

Patients who are not eligible for treatment with tebentafusp because of a non-HLA-eligible haplotype will be followed prospectively for clinical outcome. Patients may either be followed prospectively in real-time at the institution where this protocol is open and active and tracked in a database to monitor patient demographic, clinicopathologic, and treatment-related data. This includes age, sex, race, ethnicity, treatment history (e.g. number of prior therapies or surgeries and treatment location), date of initiation of systemic therapy, systemic therapy regimen, date of radiographic assessment, and date of progression. Radiographic assessment by RECIST 1.1 will occur in real-time or retrospectively. Patients who are treated at outside institutions will have their treatment records and scans requested for review, if permission has been granted.

10.5 VITAL SIGNS

Vital signs (body temperature, pulse rate, respiratory rate, and blood pressure, oxygen saturation) must be performed before dosing, and after the tebentafusp administration as indicated in Table 3 and as per institutional standards.

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the investigator if medically indicated and will be recorded as unscheduled assessment.

Table 2 Tebentafusp Post-dose Vital Signs Monitoring

C1D1, C1D8, C1D15 Inpatient monitoring required for all	Vital signs monitored per institutional standards at a minimum of every 4 hours.

dosings of the first six patients; if no Grade ≥ 2 CRS or Grade ≥ 3 infusion-reactions are seen among the first six patients, subsequent patients can be treated as outpatients	Patients should be monitored for at least 16 hours after dosing. Patients experiencing grade 2 or greater hypotension at C1D15 require inpatient monitoring for the subsequent/next C2D1 dose. Those experiencing grade 3 or 4 hypotension at C1D1, C1D8, or C1D15 require hourly vital signs monitoring for a minimum of 8 hours after dosing for any doses administered as an outpatient through C3D1. Patients who are permitted to receive dose escalation treatment as an **outpatient** must be monitored for at least 8 hours post-end of infusion on C1D1, C1D8, and C1D15. Vital signs must be confirmed stable prior to discharge. Minimum thresholds are body temperature < 38.0°C, heart rate < 100 beats per minute, and oxygen saturation ≥ 92% on room air. **Patients should be informed to reside within a 30-minute travel distance to a local emergency room. Patients will be provided a wallet card indicating their current treatment status at the time of discharge.**
C2D1 Inpatient monitoring required for exception noted	Patients experiencing a grade 2 or greater hypotension at C1D15 must be observed as an inpatient for C2D1 dose, with vital signs performed at a minimum of every 4 hours and monitoring for at least 16 hours after dosing.
C2D1 through C2D15 Monitoring requirements for exceptions noted	Patients experiencing grade 3 or 4 hypotension at C1D1, C1D8, or C1D15 require hourly vital signs monitoring for minimum of 8 hours after dosing for any doses administered as an outpatient through C3D1. If patients experienced grade ≥ 2 hypotension at C1D15, they must be monitored as an inpatient for C2D1, as noted above.
C2 and later cycles- Days 1, 8, and 15 Outpatient monitoring	For patients without grade 2 or greater hypotension at C1D15 or grade 3 or 4 hypotension at C1D1, C1D8, or C1D15, outpatient vital signs must be monitored in

	clinic for minimum of 1 hour after infusion with at least 2 post-dose vital signs measurements performed. For patients who have received outpatient treatment with tebentafusp for at least 3 months without an interruption greater than 2 weeks, outpatient monitoring in clinic may be decreased to minimum of 30 minutes after dosing.
Treatment breaks/delays	Patients with break or delay in treatment for > 2 weeks AND with history of a grade 3 or 4 event of hypotension with tebentafusp dosing during the first weeks of treatment will be monitored as an inpatient for the dose subsequent to the break in dosing, with vital signs performed at a minimum of every 4 hours and monitoring for at least 16 hours after dosing.

STUDY CALENDAR

Procedure	Pre-screen	Screening	Cycle 1			Cycle 2	Cycle 3+	EOT	Follow-up
Day of cycle		-28to -1	1	8	15	1	1		
Informed consent	X[1]	X							
HLA typing[1]	X								
Medical history		X							
Concomitant medications		X	Continually assessed						
Physical exam[2]		X	X			X	X	X	
Vital signs[3]		X	X	X	X	X	X	X	
Height		X							
Weight		X				X	X	X	
Performance status		X							
Hematology panel		X	X			X	X	X	
Chemistry panel		X	X			X	X	X	
Coagulation studies		X						X	
Urinalysis		X						X	
Thyroid function[4]		X					X (q2cycles)	X	
Pregnancy test[5]		X					X	X	
Radiographic evaluation[6]		X					X (q9weeks)		
EKG		X							
Adverse events			Continually assessed						
Biopsy[7]		X					X	X (optional)	
Research blood[8]		X				X	X	X	
Tebentafusp[9]			X	X	X	X	X		
OS assessment[10]									X

1 HLA status will be determined during the pre-screening period. Patients should not sign the Main Study Consent Form and enter Screening until the results of the central assay in Pre-Screening is known.
2 At screening and C1D1, prior to dosing, a complete physical examination will be completed. From C1D8 onwards, a short physical examination will be performed. Starting with C4D1, patients will have short physical examination performed only on day 1 of the cycle and at EOT
3 Inpatient hospitalization and frequent vital signs (at a minimum of every 4 hours [± 30 min] or more frequently according to institutional standards) are required at C1D1, C1D8, and C1D15. Inpatient monitoring at Cycle 2 Day 1 and beyond will be determined based on the toxicity observed in the individual patient in C1D1-C1D15. Patients experiencing a grade 2 or greater hypotension event at C1D15 must be observed as an inpatient for the subsequent C2D1 dose.
4 Thyroid function studies to be completed on Day 1 of every odd-numbered cycle at Cycle 3 and beyond, as well as at EOT
5 Pregnancy testing required every 6 weeks and at EOT in all WOCBP
6 Radiographic assessment via CT or MR (where CT is not feasible or per the investigator's discretion) will occur at baseline and every subsequent 6 weeks through 48 weeks, and then every 9 weeks thereafter. Progression of disease by RECIST 1.1 within 24 weeks is required for enrollment, unless the patient has a new diagnosis of CCS.
7 Mandatory biopsies are required at baseline within 28 days of study initiation and again after two cycles of treatment at C3 (+/- 7days). Biopsy at progression will be optional.
8 Research blood will be collected at baseline (during study screening or on C1D1 prior to initiating treatment), C2D1, C3D1, C5D1, C9D1, and end of treatment.
9 Tebentafusp will be administered on the scheduled day (± 2 days), and consecutive infusions of tebentafusp must be administered at least 5 days apart.
10 Survival follow-up should be completed every 12 weeks until death or until the end of the study is reached.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[1]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. Response will also be evaluated using Choi criteria (see reference), which takes changes in tumor size and density into consideration for radiographic response[2].

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with *tebentafusp*.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to*

include them, the conditions under which such lesions should be considered must be defined in the protocol.

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

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

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

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

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used

for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

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

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is

a sign of PD based on a new lesion.

b. *No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.*
c. *FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.*

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

11.1.4 RECIST Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

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

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

11.1.4.3 Evaluation of Best Overall Response

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

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

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

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

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

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

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

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

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

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

11.1.5 Choi Criteria

Table 3. Modified CT Response Evaluation Criteria

Response	Definition
CR	Disappearance of all lesions
	No new lesions
PR	A decrease in size* of ≥ 10% or a decrease in tumor density (HU) ≥ 15% on CT
	No new lesions
	No obvious progression of nonmeasurable disease
SD	Does not meet the criteria for CR, PR, or PD
	No symptomatic deterioration attributed to tumor progression
PD	An increase in tumor size of ≥ 10% and does not meet criteria of PR by tumor density (HU) on CT
	New lesions
	New intratumoral nodules or increase in the size of the existing intratumoral nodules

Abbreviations: CR, complete response; PR, partial response; HU, Hounsfield unit; CT, computed tomography; SD, stable disease; PD, progression of disease; RECIST, Response Evaluation Criteria in Solid Tumors.
*The sum of longest diameters of target lesions as defined in RECIST.[10]

11.1.6 Duration of Response

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

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

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

11.1.7 Progression-Free Survival

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

11.1.8 Response Review

N/A

12. DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

Electronic case report forms (eCRFs) will be created by SARC, the overall Principal Investigator and reviewed by the statistician. The database will be built within the Medrio system for data collection for this study.

The definition of serious adverse events (SAEs) is given in Section 7.1. Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. CTCAE v 5.0 grade 3 or 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion / exclusion criteria.

When required, and according to local law and regulations, serious adverse events must be reported to the IRB and Regulatory Authorities.
All serious adverse events should be reported to SARC within 24 hours. In the event of such an event, the investigator should refer to the Adverse Reporting section of the Operations Manual for reporting procedures.

The Investigator will report serious adverse events (SAEs) using the MedWatch 3500A form.

All reports shall be sent electronically to SARC:

SARC: SARC45@sarctrials.org

SARC will send the SAE reports and coversheets to Immunocore within 1 working day.

12.1.2 Pregnancies

The investigator must report to SARC any pregnancy occurring in a study subject, or in his partner, during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent. Please see section 7.2.3 with more information regarding pregnancy.

12.1.3 Further safety documentation

Progressive disease

If progressive disease leads to signs and symptoms that meet the criteria for an SAE (i.e., hospitalization, disability, death, or important medical event), the signs and symptoms should be reported as an SAE and not the underlying progressive disease.

Death

If any subject dies during the trial or within 30 days of the end-of-treatment visit, the investigator will inform SARC and record the cause of death in detail (using the SAE Form) within 24 hours.

12.1.4 Patient Accrual and Participating Centers

There will be approximately 4 centers collaborating to accrue patients to this study. We anticipate accrual will take approximately 3 years.

This trial will be posted at the www.clinicaltrials.gov website.

12.2 Data Safety and Monitoring

SARC is responsible for the Data Safety Monitoring for this trial. SARC Clinical Trials Review Committee convenes monthly and will provide safety oversight for this trial. The purpose of the Clinical Trials Review Committee is to review the status of the on-going SARC studies, which includes, but is not limited to:

- o Review of all safety data (Serious Adverse Events reported).
- o Review of protocol deviations/violations.
- o Review of study progress/accrual.
- o Discussion of statistical aspects of all protocols.

The committee is chaired by the SARC Medical Officer, who is responsible for leading the meeting and providing medical oversight. Attendance includes all overall study Principal Investigators on active SARC studies, SARC Research Project Managers, and a biostatistician.

12.3 Multi-Institutional Guidelines

The trial coordinating center (Operations Center) will be SARC. Patients will be registered electronically via the study website and adverse events (as defined in section 7.0) will be reported to the SARC Operations Center.

IRB approvals:

The protocol must be approved by the treating institution prior to enrolling patients. Documentation of individual IRB approval for the current protocol must be provided to the SARC Operations Center prior to enrolling patients on the trial. In addition, documentation of approval of all protocol amendments and of yearly continuing review must be provide to the Research Project Manager electronically via email.

Patient Registration:
Patient registration will be centrally managed electronically via the study website (see section 4.2).

Data Collection and Toxicity Reporting:
Registration reports will be generated by the Operations Center to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies by the SARC. Any potential problems will be brought to the attention of the study Principal Investigator(s) for discussion and action.

Access to the password protected study database will be limited to individuals involved in the clinical trial including: SARC staff, overall Study PI, participating site PIs, research nurse and data managers responsible for this trial.

Shipment and receipt of specimens and imaging studies sent for correlative studies will be entered and tracked on the study database. Details regarding handling and shipping will be outlined in the study operations manual.

12.4 Data and Participating Institution Monitoring

Data monitoring for this trial will be managed remotely. A data monitoring and site monitoring plan will be developed for this trial. Should areas of concern be identified through the remote monitoring process, an on-site monitoring visit may be warranted. Findings will be discussed with the overall study PI, participating site PIs, Clinical Trials Review Committee and the SARC medical officer.

12.5 Human Subjects Protection

12.5.1 Rationale for Subject Selection
Subjects of both genders and from all racial and ethnic groups are eligible for this trial if they meet the eligibility criteria as outlined in section 3.1. No groups will be excluded from participation in the trial.

12.5.2 Evaluation of the Benefits and Risks/Discomforts
The primary risk to patients participating in this research study is from toxicity associated with tebentafusp.

12.5.3 Management of Patient Data

All patient data will be captured and maintained in a study specific database with password-protected access. Data is entered using an assigned study subject identification number.

The data provided to those reviewing the results, for example the study statistician will include the subject identification numbers but will not include patient identifiable data.

The research samples obtained on this study will only be sent using the study subject identification number, which can only be linked to the patient at a given institution by the treating physician.

All documentation that contains personal health information that may include patient identifiable information will be maintained at the site to preserve patient confidentiality.

12.6 Premature termination of study

This study may be closed prematurely for any of the following reasons:

If risk-benefit ratio becomes unacceptable owing to, for example:

- Safety findings from this study (e.g. SAEs)
- Results of any interim analysis
- Results of parallel clinical studies
- Results of parallel animal studies

(on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).

- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.
- The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.

In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner. Details for individual subject's withdrawal can be found in Section 5.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This will be a multi-center open label phase II study of tebentafusp in patients with unresectable or metastatic CCS. CCS is an orphan disease with few efficacious systemic

treatment options and few standard of care treatment options in the unresectable or metastatic setting. This study will assess for a signal of efficacy of a novel immunotherapeutic agent (tebentafusp) in the HLA-A*02:01-positive patients and simultaneously prospectively measure real-world outcomes in the HLA-A*02:01-negative patients.

The primary endpoint is to estimate PFS rate at 24 weeks, as determined by RECIST 1.1. In the CREATE trial (one of the few prospective clinical trials in this disease), the PFS rate at 6 months (PFSr6) for patients with advanced CCS treated with crizotinib was approximately 25%.[9] In other prospective and retrospective studies of alternative systemic therapies, the median PFS was between 2 and 3 months and the PFSr6 was not reported.[6,8,32]

Van Glabbeke and colleagues[33] have previously described appropriate thresholds for PFSr6 in the design of phase II studies in soft tissue sarcoma patients refractory to first-line treatment. Based on historical controls, they conclude a PFSr6 of 8% is not promising and PFSr6 of 14% to be promising.[33] Based on all of the above, we believe PFSr6 is an appropriate and meaningful clinical endpoint in this patient population. We will consider a 10% PFSr6 as not promising and 30% to be promising.

Simon's two-stage minimax design[34] will be used. The null hypothesis that the true PFS rate at 24 weeks is 10% will be tested against a one-sided alternative that it is 30%. In the first stage, 13 patients will be accrued. If ≤ 1 of the first 13 patients enrolled is progression-free at 24 weeks, the protocol will stop enrolling patients due to futility. Otherwise, 10 additional patients will be accrued for a total of 23 patients treated. The study will be claimed positive if 5 or more of 23 patients are progression-free at 24 weeks. This design yields a one-sided type I error rate of 0.1 and power of 0.84.

All patients who have received at least one dose of study therapy will be assessable for safety. Patients evaluable for efficacy analysis will include all patients treated with tebentafusp who are assessable for response. Patients who have no assessment of response post-baseline will not be considered evaluable for response unless they missed the assessment due to progression of disease or death, in which case they will be considered non-responders for that time point. Patients with at least one post-baseline assessment who are not assessed at 24 weeks for reasons other than progression of disease, death, will be evaluated based on their last imaging assessment. For example, patients with excessive toxicity will be censored at the date of their most recent disease evaluation prior to receiving any future systemic treatment regimens. Patients who are not evaluable (excluding those who died, had progression of disease, stopped study treatment due to treatment-related toxicity, or those with at least one post-baseline assessment) may be replaced.

13.2 Accrual Rate

Clear cell sarcoma is an ultra-rare sarcoma subtype with a low incidence in the general population. To date, few prospective studies have been conducted that will allow for precise estimation of accrual rate. The CREATE trial, a multi-center

European study, enrolled 43 patients within two years. As this multi-center international study will be restricted to the HLA-A*02:01-positive population, we estimate a longer accrual time than CREATE. We anticipate an accrual rate of 6 - 12 patients per year. and the total accrual rate is estimated to range between two and four years.

13.3 Stratification Factors

Not applicable

13.4 Analysis of Secondary Endpoints

CCS is a rare tumor and approximately one-third of patients are expected to be HLA-A*02:01-positive.[35] As a secondary endpoint, we will compare the median PFS of patients treated with tebentafusp to historical controls, and we will leverage the HLA-ineligible CCS population to compare the median PFS of patients treated with physicians' choice of therapy to the HLA-A*02:01-positive population treated with tebentafusp. This secondary endpoint will provide a second point of comparison to historical controls. Prospectively enrolling 24 patients with CCS who are HLA*A-02:01-negative and treated with physicians' choice of therapy will provide 80% power to detect a HR of 2 at a one-sided type I error rate of 0.1 when compared to tebentafusp-treated CCS patients, respectively.

Additional secondary endpoints will be: to estimate the best ORR by RECIST 1.1 and by Choi criteria, to estimate the median duration of response among responders, to estimate the overall CBR and CBR at 12 and 24 weeks, to estimate the PFS at 12 weeks and median PFS, to estimate the median OS, and to further describe the safety as assessed by CTCAE version 5.0.

13.5 Exploratory Analyses

Tumor tissue
The potential effect of tebentafusp on selected biomarker expression measured in pre- and on-treatment tumor tissue will be assessed using the paired t-test for continuous variables and the McNemar test for binary variables. The significance of differences in the frequency of individual cell populations and expression of individual markers between pre- and on-treatment measurements will be evaluated using paired t-tests, and those between responders and non-responders by two-sample t-tests. We will assess the association of immune cell populations and immune suppression markers at each time point, as well as the treatment-induced change in each, by logistic regression for binary outcomes and by Cox regression with time dependent covariates for time to event outcomes. A sample size of n=23 will allow 92% (82%) power to detect a change of 0.7 (0.6) standard deviation in a biomarker expression after treatment.

Peripheral blood ctDNA analysis
The time course of the abundance of the *EWSR1::ATF1* fusion in ctDNA will be investigated numerically using summary statistics and graphically using spaghetti plots

for individual patients and in aggregate. Their trends over time will be categorized either by visual inspection (if there are clear trend groups such as monotonically increasing or monotonically decreasing) or by pattern recognition methods such as K-means clustering. If there are a reasonable number of events for each clinical outcome (such as ORR, CBR, PFS, and OS), we will assess their association with binary outcomes using generalized estimating equations and with time-to-event outcomes using Cox regression with time dependent covariates. The concordance of detected fusion sequences in ctDNA and tissue will be assessed using cross-tablulation and kappa statistics. Given the limited sample size, these analyses are exploratory in nature and for generation of hypotheses.

13.5 Reporting and Exclusions

13.4.1 Evaluation of adverse events.

All patients who received at least one dose of protocol treatment will be accessible for adverse events. The NCI CTCAE version 5 will be used to determine the type and severity of the AEs. The observed adverse events, regardless of attribution, will be summarized for the treatment arm by the maximum grade observed for a patient of a particular AE.

13.4.2 Evaluation of response.

The primary analysis will be a modified intent to treat. It will include all patients who did not withdraw prior to initiating treatments. A per-protocol analysis will be done as a sensitivity analysis. Patient will be included in the ORR analysis if they had measurable disease and a baseline tumor assessment. If a patient did not have a follow-up tumor assessment, they will be classified as a non-responder.

14. ETHICAL CONSIDERATIONS

This study will be conducted in full accordance with the principles set forth in the Declaration of Helsinki, as adopted by the World Medical Association and as current at the time of study initiation. The study will also adhere to the guidelines of the International Council for Harmonisation (ICH): Good Clinical Practice (GCP) and comply with all applicable local regulatory requirements and institutional policies.

All investigators, study staff, and involved parties will be trained in and will operate in compliance with these ethical and regulatory standards to ensure the rights, safety, and well-being of trial participants are protected, and that the data generated are credible and accurate.

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APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined in bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

Tebentafusp Toxicity Management Guidelines

Tebentafusp Toxicity Management Guidelines	
Worst Toxicity	**Recommended Dose Modifications**
Pruritus (graded per CTCAE v5.0)	
Grade 1	Continue dosing. If symptomatic, consider a systemic antihistamine regimen (see Grade 2 guidance below).
Grade 2	**May continue dosing.** Intrapatient escalation is contraindicated if symptoms have not improved to Grade ≤ 1 prior to dosing. Treat according to institutional practice and/or implement the guidance described below. Use systemic management and/or local skin management as indicated by symptoms. With bullous formation or blistering rashes consider a dermatology consultation to rule out other causes (eg, bullous pemphigoid). Oral or topical corticosteroids can be used. If bullous formation or blistering recur, consult the Medical Monitor for guidance. **Antipruritic regimen:** **A systemic antihistamine regimen** is recommended as first-line management of pruritus, eg, nonsedating, long-acting antihistamine (cetirizine, 10 mg oral or equivalent). If a sedating antihistamine is preferred (eg, evening dosing), consider diphenhydramine 25 mg oral or intravenous (IV). The use of sedating antihistamines should be minimized in participants with comorbid pulmonary pathology including pulmonary metastases or underlying inflammatory airways disease such as chronic obstructive pulmonary disease or asthma. **Topical corticosteroid regimens** Preparation of recommended regimens is as follows: • For the face and/or intertriginous areas (including genitalia), alclometasone 0.05% or hydrocortisone 2.5% creams are recommended. • For other body areas (ie, the trunk and extremities), clobetasol or betamethasone 0.05% creams are recommended. Consider a spray preparation for ease of application on the trunk. For scalp involvement, consider a foam preparation. **NOTE**: Montelukast (10 mg orally) may be considered as an adjunctive therapy in participants with persistent symptoms despite antihistamine and topical corticosteroid therapy. **Prophylaxis for subsequent doses** is generally not required after Grade 2 pruritus, but a nonsedating antihistamine may be considered, especially for recurrent or persistent symptoms.

Grade 3	**Hold all doses of tebentafusp** until returned to CTCAE Grade ≤ 1.
	• If Grade 3 pruritus resolves to ≤ Grade 1 in < 7 days,
	  o If at 20 or 30 mcg dose, stay at this dose level. Resume escalation once the current dose level is tolerated.
	  o If at 68 mcg, treatment may continue at the current dose level.
	• If Grade 3 pruritus resolves to ≤ Grade 1 in 7 to 21 days,

	○ If at 20 or 30 mcg dose, stay at this dose level. Resume escalation once the current dose level is tolerated ○ If at 68 mcg, treatment may restart at the current dose level ○ Mandatory corticosteroid prophylaxis is required for at least the next 3 doses. • If Grade 3 rash/pruritus does not resolve within 21 days, permanently discontinue all study interventions. **<u>Manage pruritus according to the institutional protocol and guidance below.</u>** **Management:** Treat according to institutional practice, which generally includes an antipruritic regimen (see Grade 2 management above). In addition, corticosteroid treatment (systemic) can be considered for pruritus that does not respond to antihistamine, topical corticosteroid, or montelukast therapy (recommend oral prednisone 20–40 mg, a single dose of 125 mg hydrocortisone IV, or the equivalent for refractory pruritus). For recommended systemic or topical regimens, refer to Grade 2 management above. **Prophylaxis:** In participants experiencing Grade 3 pruritus, administration of a nonsedating antihistamine prophylaxis dose is recommended for the subsequent dose of tebentafusp, approximately 1–2 hours prior to the tebentafusp dose being administered (eg, cetirizine 10 mg or equivalent). Prophylaxis with corticosteroid should be considered if pruritus recurs at a similar or worse severity despite antihistamine prophylaxis and is required if the initial episode does not resolve in < 7 days (recommend oral prednisone 20–40 mg, a single dose of 125 mg hydrocortisone IV, or the equivalent). If steroid prophylaxis is used, the steroid dose should be titrated to the minimum effective dose and ultimately discontinued if possible.
Grade 4	**Permanently discontinue tebentafusp** As above for Grade 3 except administer intravenous corticosteroid (eg, 2 mg/kg methylprednisolone or equivalent); additionally, consultation with a dermatologist is recommended.
Rash/Photosensitivity (graded per CTCAE v5.0)	
Grade 1	Continue dosing. If symptomatic, consider a systemic antihistamine regimen according to management guidance for pruritus (above).
Grade 2	**Hold all doses of tebentafusp** until improvement to CTCAE Grade ≤ 1. • If at 20 or 30 mcg dose, may escalate to next dose level. • If at 68 mcg, continue at this dose level **<u>Treat according to institutional practice and/or implement guidance below.</u>** Use systemic management and/or local skin management as indicated by symptoms. With bullous formation or blistering rashes, consider a dermatology consultation to rule out other causes (eg, bullous pemphigoid). Oral or topical corticosteroids can be used for bullous formations or blistering. If bullous formation or blistering recur, consult the Medical Monitor for guidance.

	Antipruritic regimen: **A systemic antihistamine regimen** is recommended as first-line management of pruritus, eg, nonsedating, long-acting antihistamine (cetirizine, 10 mg oral or equivalent). If a sedating antihistamine is preferred (eg, evening dosing) consider diphenhydramine 25 mg oral or IV. The use of sedating antihistamines should be minimized in participants with comorbid pulmonary pathology including pulmonary metastases or underlying inflammatory airway disease such as chronic obstructive pulmonary disease or asthma. **Topical corticosteroid regimens** Preparation of recommended regimens is as follows: • For the face and/or intertriginous areas (including genitalia), alclometasone 0.05% or hydrocortisone 2.5% creams are recommended. • For other body areas (ie, the trunk and extremities), clobetasol or betamethasone 0.05% creams are recommended. Consider a spray preparation for ease of application on the trunk. For scalp involvement, consider a foam preparation. **NOTE:** Montelukast (10 mg orally) may be considered as an adjunctive therapy in participants with persistent symptoms despite antihistamine and topical corticosteroid therapy. **Prophylaxis for subsequent doses** is generally not required after Grade 2 rash, but a nonsedating antihistamine may be considered, especially for recurrent or persistent symptoms. Consider performing a skin punch biopsy (Section 8.7.2) and/or photographing the affected area (Note: include a reference measurement scale, such as a ruler, in the photograph whenever possible).

Grade 3	**Hold all doses of tebentafusp** until improvement to CTCAE Grade ≤ 1.
	• If Grade 3 rash resolves to ≤ Grade 1 in < 7 days,
	  o If at 20 or 30 mcg dose, stay at this dose level. Resume escalation once the current dose level is tolerated.
	  o If at 68 mcg, treatment may continue at the current dose level.
	• If Grade 3 rash resolves to ≤ Grade 1 in 7 to 21 days,
	  o If at 20 or 30 mcg dose, stay at this dose level. Resume escalation once the current dose level is tolerated.
	  o If at 68 mcg, treatment may continue at the current dose level.
	  o Corticosteroid prophylaxis is required for at least the next 3 doses
	• If Grade 3 rash does not resolve within 21 days, permanently discontinue all study interventions.
	
	Manage rash according to the institutional protocol and guidance below.
	Management:
	Treat according to institutional practice, which generally includes an antipruritic regimen (see Grade 2 management above). In addition, corticosteroid treatment (systemic) can be considered for symptomatic rash that does not respond to antihistamine, topical corticosteroid, or montelukast therapy (recommend oral prednisone 20–40 mg, a single dose of 125 mg hydrocortisone intravenous, or the equivalent for refractory rash). For recommended systemic or topical regimens, refer to Grade 2 management above.
	Prophylaxis:

	In participants experiencing Grade 3 rash, administration of a nonsedating antihistamine prophylaxis dose is recommended for the subsequent dose of tebentafusp, approximately 1–2 hours prior to the tebentafusp dose being administered (eg, cetirizine 10 mg or equivalent). Prophylaxis with corticosteroid should be considered if rash recurs at a similar or worse severity despite antihistamine prophylaxis and is required if any episode does not resolve in < 7 days (recommend oral prednisone 20–40 mg, a single dose of 125 mg hydrocortisone intravenous, or the equivalent). If steroid prophylaxis is used, the steroid dose should be titrated to the minimum effective dose and ultimately discontinued if possible.
Grade 4	**Permanently discontinue tebentafusp.** As above for Grade 3 except administer intravenous corticosteroid (eg, 2 mg/kg methylprednisolone or equivalent); additionally, consultation with a dermatologist is recommended.
Infusion-Related Reactions/Anaphylaxis (events during infusion; graded per CTCAE v5.0)	
Any grade	Acute reactions occurring while study treatments are infused should be treated as needed using institutional guidelines. In the event of anaphylactic/anaphylactoid reactions, any therapy necessary to restore normal cardiopulmonary status should be implemented immediately.
Grade 1	Administer medications for symptomatic relief as needed. Infusion interruption may be considered until resolution of the event (up to 4 hours). The infusion rate of the study interventions may be decreased by 50%. If resolved with a decreased rate of infusion, any subsequent infusions can be administered at the reduced rate.
Grade 2	**Stop tebentafusp infusion** and keep the IV line open. Treat according to institutional practice. Provide all supportive measures as indicated. Provide supplemental oxygen and fluids, as needed. • Monitor vital signs (eg, BP, pulse rate, respiration rate, temperature, and oxygen saturation) until resolution. Administer medications for symptomatic relief as needed. Antihistamines, acetaminophen (paracetamol), or corticosteroids may be administered, as needed, at the discretion of the Investigator. • Restart infusion only once the infusion reaction resolves (within 4 hours of the initial start of infusion), ensuring there is a minimum observation period of one hour from stop of initial infusion to restart at the reduced rate. Administer oral premedication (eg, 1000 mg of acetaminophen/paracetamol, 50–100 mg diphenhydramine hydrochloride, or alternative antihistamine) 60 minutes prior to restarting the infusion, accounting for prior doses/time given for management of the initial reaction. • Restart the infusion at 50% of the previous rate under continuous observation. If the AE recurs at the reinitiated slow rate of infusion, and despite oral premedication, then permanently discontinue the participant from study treatment.
Grade 3 or 4	**Discontinue tebentafusp infusion immediately** and permanently discontinue participant from study treatment. **NOTE:** Grade 3 infusion-related reactions that improve by at least 1 grade within 6 hours of onset will not require permanent discontinuation. If treatment is continued, all guidance provided for the management of Grade 2 reactions must be followed. Manage severe infusion-related reactions per institutional standards. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (eg, BP, pulse rate, respiration rate, temperature, and oxygen saturation) until resolution.
Infusion-Related Reactions/Cytokine Release Syndrome (occurring after infusion/injection; graded per ASTCT 2019, see Table 6)	

Grade 1	• Admit for inpatient monitoring (unless already hospitalized per protocol). Assess for potential infection and treat fever and neutropenia. • Manage according to individual symptoms. Treat symptomatically as indicated, including antihistamines, antipyretics, antiemetics, and/or analgesics as needed. • Initiate bolus and/or maintenance IV fluids and carefully monitor fluid balance. • Vigilantly monitor for escalation to Grade 2 CRS with frequent vital signs monitoring (eg, assess vital signs every 2 hours) • Strongly consider early, high dose corticosteroid therapy if there is progressive worsening of vital signs (see Grade 2 below). • Consider prophylactic electrolyte supplementation for participants receiving IV fluids with low-normal serum electrolyte levels. Once symptoms resolve, at the next dose, do the following: • If at 20 or 30 mcg dose, may escalate to next dose level. • If at 68 mcg, continue at this dose level
Grade 2	• Increase monitoring with continuous cardiac and pulse oximetry monitoring and continue or increase vital signs monitoring (eg, assess vital signs every hour). • To manage hypotension, administer bolus IV fluids (recommended rate of approximately 1 L per hour) and supplemental oxygen for hypoxia or respiratory distress. If not rapidly resolved (ie, within 2-3 hours of onset) with fluids and/or supplemental oxygen, administer high dose IV corticosteroid therapy (eg, methylprednisolone 1 to 2 mg/kg initial dose or equivalent) and/or tocilizumab 8 mg/kg IV (not to exceed 800 mg/infusion) per institutional guidelines until symptoms (eg, hypotension) resolve. • Consider prophylactic electrolyte supplementation for participants receiving IV fluids with low-normal serum electrolyte levels. • Consider additional respiratory support as needed to manage ongoing or persistent respiratory distress. Once symptoms resolve, at the next dose, do the following: • Administer corticosteroid premedication (eg, dexamethasone 4 to 12 mg or equivalent) at least 30 minutes prior to the next dose • If at 20 or 30 mcg dose, may escalate to next dose level. • If at 68 mcg, continue at this dose level; monitor for at least 16 hours post-dose
Grade 3	Management as above (Grade 2) and include the following measures: • Escalate level of care (eg, intensive care unit) as clinically indicated. • Maximize immunosuppression with continued high dose IV corticosteroid (eg, methylprednisolone 2 mg/kg/day or equivalent) and/or tocilizumab 8 mg/kg IV (not to exceed 800 mg/infusion) per institutional guidelines. • For persistent hypotension, treat with a single vasopressor (with or without vasopressin). o Consider adding further immunosuppression measures or additional interventions according to the institutional cytokine release protocol (eg, administer or repeat tocilizumab if not already implemented). o Continue to manage symptoms and vigilantly monitor for escalation. • For any Grade 3 CRS, restart tebentafusp only after discussion and written approval from the Medical Monitor. Once symptoms resolve, at the next dose, do the following: • Administer corticosteroid premedication (eg, dexamethasone 4 to 12 mg or equivalent) at least 30 minutes prior to the next dose • If at 20 or 30 mcg dose, stay at this dose level. Resume escalation once the current dose level is tolerated. • If at 68 mcg, continue at this dose level; monitor for at least 16 hours post-dose

Grade 4	Management as above (Grade 3) and include the following measures. • For persistent hypotension, treat with multiple vasopressors (with or without vasopressin). • For persistent hypoxia, provide supplemental oxygen using a positive-pressure device. • If appropriate, consider additional measures according to the institutional cytokine release protocol. **Permanently discontinue tebentafusp.**
Elevated Liver Enzymes (graded per CTCAE v5.0)	
Grade 2	• Institute regular monitoring of liver enzymes until improving or resolved. • Evaluate concurrent medications for agents that may prolong or exacerbate elevated liver enzymes. • Consider IV corticosteroid therapy (eg, methylprednisolone 0.5 to 1 mg/kg/day or the equivalent) if not improving within 72 hours.
Grade 3 or 4	**Hold all doses of tebentafusp** until returned to CTCAE Grade ≤ 1. • Institute regular monitoring of liver enzymes until improving or resolved. • Administer intravenous steroids (eg, methylprednisolone 0.5 to 1 mg/kg/day or the equivalent) if no improvement within 24 hours. • Consider abdominal imaging and a hepatology consult for persistent elevated liver enzymes, onset of clinical signs or symptoms of liver dysfunction (eg, abdominal pain, nausea, vomiting, jaundice), or impact on liver synthetic function. • For any Grade 3 elevated liver enzyme elevation, restart tebentafusp only after discussion and written approval from the Medical Monitor. Once elevated liver enzymes improve to NCI CTCAE Grade ≤ 1, if restarting tebentafusp, resume treatment as follows: • If elevated liver enzymes occurred in the setting of Grade 3 CRS, resume at the current dose level. Resume escalation once the current dose level is tolerated.
	• If elevated liver enzymes occurred outside the setting of Grade 3 CRS, then resume intrapatient escalation if the current dose level is less than 68 mcg; otherwise, resume treatment at the current dose level if intrapatient escalation has been completed.
Vomiting (graded per CTCAE v5.0)	
Grade 2	• Administer antiemetic therapy as per institutional standard. • Provide IV fluid support and other supportive measures for additional AEs as needed.
Grade 3 or 4	• Consider holding all doses of tebentafusp until improvement to NCI CTCAE Grade ≤ 1. • Administer antiemetic therapy as per institutional standard. • Provide IV fluid support and other supportive measures for additional AEs. • Consider instituting antiemetic premedication for at least the next dose (eg, ondansetron 8 mg PO/IV or equivalent).
Other Clinically Significant Adverse Events (graded per CTCAE v5.0)	
Treat according to institutional practice and for potential immune-related AEs of Grade ≥ 3; treatment with corticosteroids should be considered. Consult the Medical Monitor for further guidance as needed.	
Grade 3 or 4	**Study medication(s) should be permanently discontinued** unless AEs improves to Grade 1 or 0, the Investigator believes the overall benefit-risk favors continued treatment, and there is agreement with the Medical Monitor that the participant may restart treatment at the current or reduced dose.