Abbreviated Title: STAT Trial

NIH Protocol # 20C0155

Version Date: 08/17/2022

NCT # NCT04574583

IBC # RD-20-IV-09

Title: Phase I/II Trial Investigating the Safety, Tolerability, Pharmacokinetics, Immune and Clinical Activity of **S**X-682 in Combination with Bin**T**rafusp **A**lfa (M7824 or TGF-β "Trap"/PD-L1) with CV301 **T**RICOM in Advanced Solid Tumors (STAT).

NIH Principal Investigator: James Gulley, MD, PhD
Genitourinary Malignancies Branch (GMB)
Center for Cancer Research (CCR)
National Cancer Institute (NCI)
[redacted]

Drug Name:	SX-682	Bintrafusp alfa (M7824)	MVA-BN-CV301	FPV-CV301
IND Number:	21166			
Sponsor:	CCR, NCI			
Manufacturer:	Syntrix	EMD Serono	Bavarian Nordic	Bavarian Nordic
Supplier:	Syntrix	EMD Serono	Bavarian Nordic	Bavarian Nordic

Commercial Agents: None

PRÉCIS

Background:

- Combination immunotherapy approaches are being actively explored to further improve responses, enhance clinical benefit, and overcome resistance to PD(L)-1 agents in cancer participants.
- Interleukin-8 (IL-8) is a pro-inflammatory chemokine produced by various cell types. Overexpression of IL-8 and/or its receptors CXCR1 and CXCR2, is commonly seen in many human cancers including breast, cervical, melanoma and prostate.
- SX-682 is an oral, small molecule inhibitor of the CXCR1/2 chemokine receptors that are believed involved in MDSC-recruitment to tumor and other pro-tumoral mechanisms.
- Bintrafusp alfa (M7824 or MSB0011359C) is a bifunctional protein composed of the extracellular domain of the TGF-βRII receptor (TGF-β "trap") fused to a human IgG1. Preclinical data shows bintrafusp alfa treatment increases T-cell trafficking, antigen-specific CD8+ T-cell lysis and NK cell activation.
- CV301 is a poxviral-based vaccine comprised of recombinant Modified vaccinia Ankara (MVA-BN-CV301, prime) and recombinant fowlpox (FPV-CV301, boost). CV301 contains transgenes encoding two (2) tumor-associated antigens (TAA), mucin 1 (MUC1) and carcinoembryonic antigen (CEA), as well as three costimulatory molecules (B7.1, ICAM-1 and LFA-3, designated TRICOM). A recent phase 1 clinical trial demonstrated that antigen-specific T cells to MUC1 and CEA, as well as to a cascade antigen, brachyury, were generated in most participants.
- Preclinical studies performed in LTIB with SX-682, M7824 and a CEA-based vaccine showed a significant reduction in tumor growth as well as a significant increase in tumor infiltration with CD4+ and CD8+ T cells.

Objectives:

- Arm 1 (Sequential Dose Escalation):
  - To evaluate the safety and tolerability of single agent SX-682.
  - To determine the MTD of SX-682 followed by M7824 and CV301 vaccines in participants with advanced or metastatic solid tumors. If the MTD is not reached the study will be focused to describe the safety and tolerability of SX-682 followed by M7824 and CV301 vaccines.
- Arm 2 (Combination Dose Escalation):
  - To determine the recommended phase 2 dose (RP2D) of SX-682 with M7824 and CV301 vaccines in participants with advanced or metastatic solid tumors. If the MTD is not reached the study will be focused to describe the safety and tolerability of the drug combination.
- Arm 3 (Expansion):

- To evaluate preliminary efficacy based on Objective Response Rate (ORR), in each disease cohort separately.

Eligibility:

- Age ≥ 18 years old
- Arms 1 and 2 (Dose-Escalation Cohort): Subjects with cytologically or histologically confirmed locally advanced or metastatic solid tumors.
- Arm 3 (Expansion Cohorts):
  - TNBC: Subjects with cytologically or histologically confirmed locally advanced or metastatic Triple Negative Breast Cancer that has progressed on at least one prior treatment in the advanced or in the metastatic setting.
  - HPV negative HNSCC: Subjects with cytologically or histologically confirmed locally advanced or metastatic, HPV negative head and neck squamous cell cancer (p16 negative for oropharyngeal) that has progressed on at least one prior treatment involving a platinum drug or cetuximab in advanced or in the metastatic setting.
- Prior first line systemic therapy is required unless there is no standard treatment available, the participant cannot tolerate standard first line treatment, or the participant declines standard treatment after appropriate counseling has been provided.
- ECOG performance status of 0 to 1
- Adequate renal, hepatic, and hematologic function
- Subjects in Arms 1 and 2 may have disease that is measurable or non-measurable but evaluable disease (e.g. present on bone scan, rising tumor markers, non-measurable by RECIST but visible on CT scan). Participants with third space fluid (for example pleural effusions) as only site of disease will not be eligible. Subjects in Arm 3 must have measurable disease according to RECIST 1.1

Design:

- Arm 1 is a phase I, open-label, 3+3 sequential dose escalation trial with short term, 2-week SX-682 monotherapy lead-in followed by treatment with M7824 and CV301 vaccine series in advanced solid tumors (Q2W dosing schedule) for the duration of treatment.
- Arm 2 is a phase I, open-label, 3+3 combination dose escalation trial with short term SX-682 monotherapy lead in followed by SX-682 combination with M7824 and CV301 vaccine series in advanced solid tumors (Q2W dosing schedule). Each enrolled participant will receive SX-682 as monotherapy for 2 weeks then will receive SX-682, M7824 and CV301 for the duration of treatment
- Arm 3 has two expansion cohorts. Following identification of the MTD or R2PD for the combination of SX-682, M7824 and CV301 vaccine, disease-specific phase 2 expansion cohorts will open in 1) advanced/metastatic triple negative breast cancer and 2) advanced/metastatic, platinum-refractory HPV negative head and neck squamous cell carcinoma.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objectives:

- Arm 1 (Sequential Dose Escalation):
  - To evaluate the safety and tolerability of single agent SX-682.
  - To determine the MTD of SX-682 followed by M7824 and CV301 vaccines in participants with advanced or metastatic solid tumors. If the MTD is not reached the study will be focused to describe the safety and tolerability of SX-682 followed by M7824 and CV301 vaccines.
- Arm 2 (Combination Dose Escalation):
  - To determine the RP2D of SX-682 with M7824 and CV301 vaccines in participants with advanced or metastatic solid tumors. If the MTD is not reached the study will be focused to describe the safety and tolerability of the drug combination.
- Arm 3 (Expansion):
  - To evaluate preliminary efficacy based on objective response rate (ORR), in each disease cohort separately.

1.1.2 Secondary Objectives:

- Arms 1 and 2 (Dose Escalations):
  - To characterize the PK/PD profile of SX-682 as a single agent and in combination.
- All Arms:
  - To evaluate preliminary efficacy: disease control rate (DCR; CR+PR+SD) and progression-free survival (PFS) using RECIST1.1.

1.1.3 Exploratory Objectives (may be performed on selected participants if there are adequate samples.):

- All Arms:
  - To evaluate the effect on immune cell subsets and soluble factors in peripheral blood.
  - To evaluate the effect on cytokine levels (IL-8, IL-6 and others) in peripheral blood.
  - To evaluate the effect on T cell clonality in peripheral blood and tumor samples.
  - To evaluate the effect on antigen-specific T cells responses to CEA, MUC1 and the cascade antigen brachyury in peripheral blood.
  - To evaluate the effect on antigen-specific T cell responses to CEA, MUC1 and the cascade antigen brachyury in tumor biopsies.

- To evaluate the presence of lymphocytic and myeloid cell infiltrates and other tumor markers as well as to evaluate RNA expression for IL-8, TGF-β and other soluble factors in tumor biopsies.
- To evaluate clinical responses (ORR, and DCR) per iRECIST
- To evaluate M7824 PK profile in this drug combination
- To evaluate ADA in this drug combination
- To evaluate long term (2 years after completion of treatment) clinical outcomes
- To evaluate circulating tumor cells (CTCs)

- In Arms 1 and 2 (Dose-Escalation Cohort), the following are the parameters will be evaluated, separately per dose level:
  - To evaluate ORR per RECISTv1.1
- In Arm 3 (Expansion Cohorts) the following are the parameters which will be evaluated, separately per disease-specific cohort
  - To evaluate changes in circulating free DNA (cfDNA)

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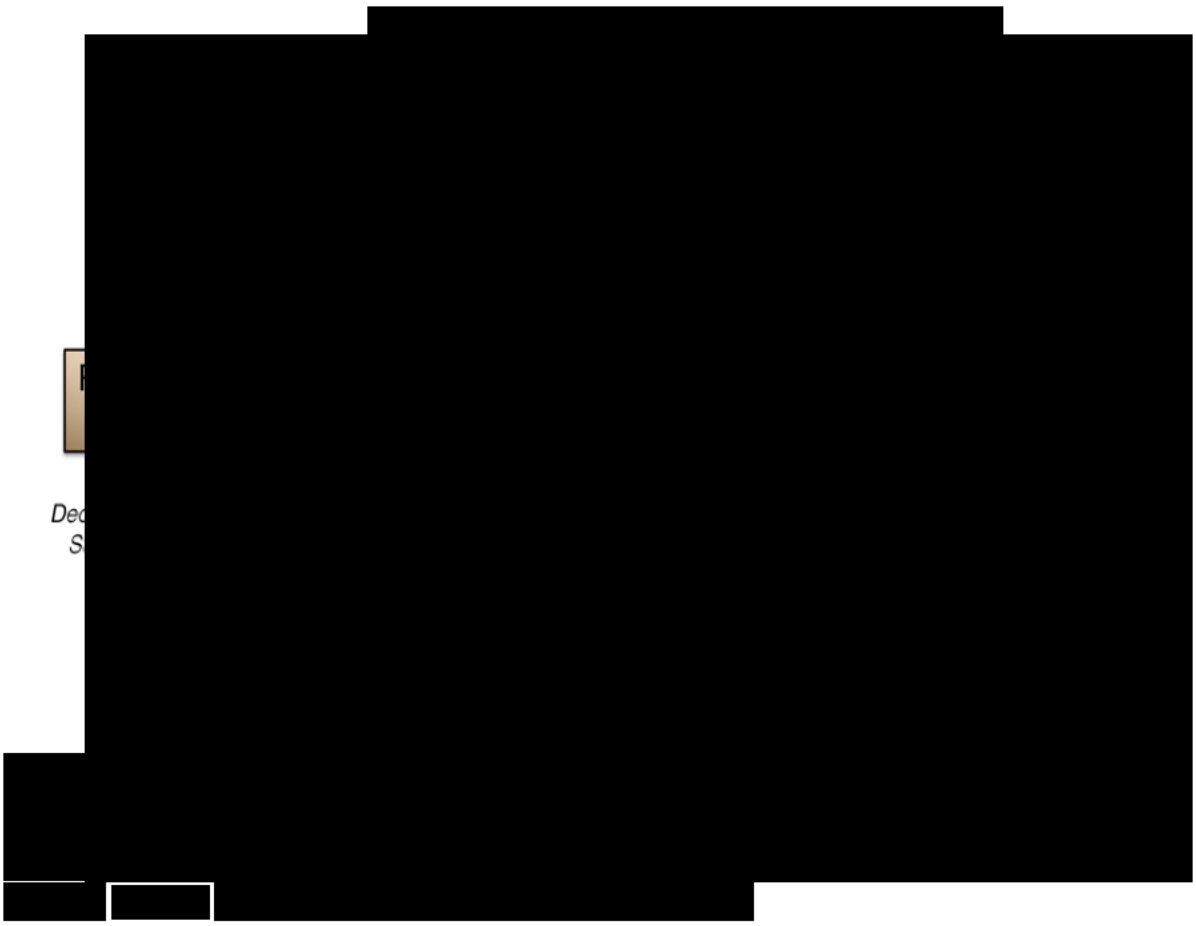

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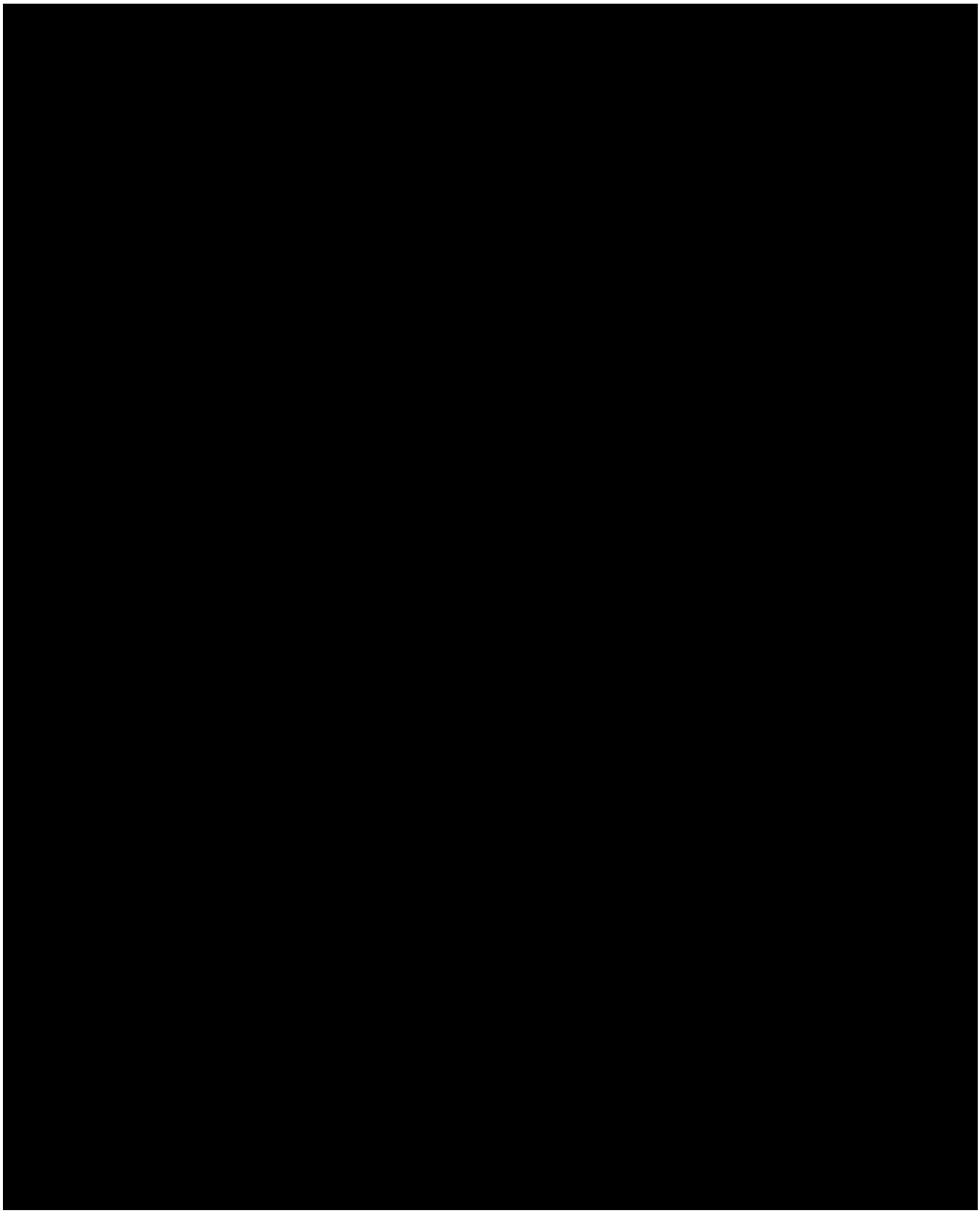

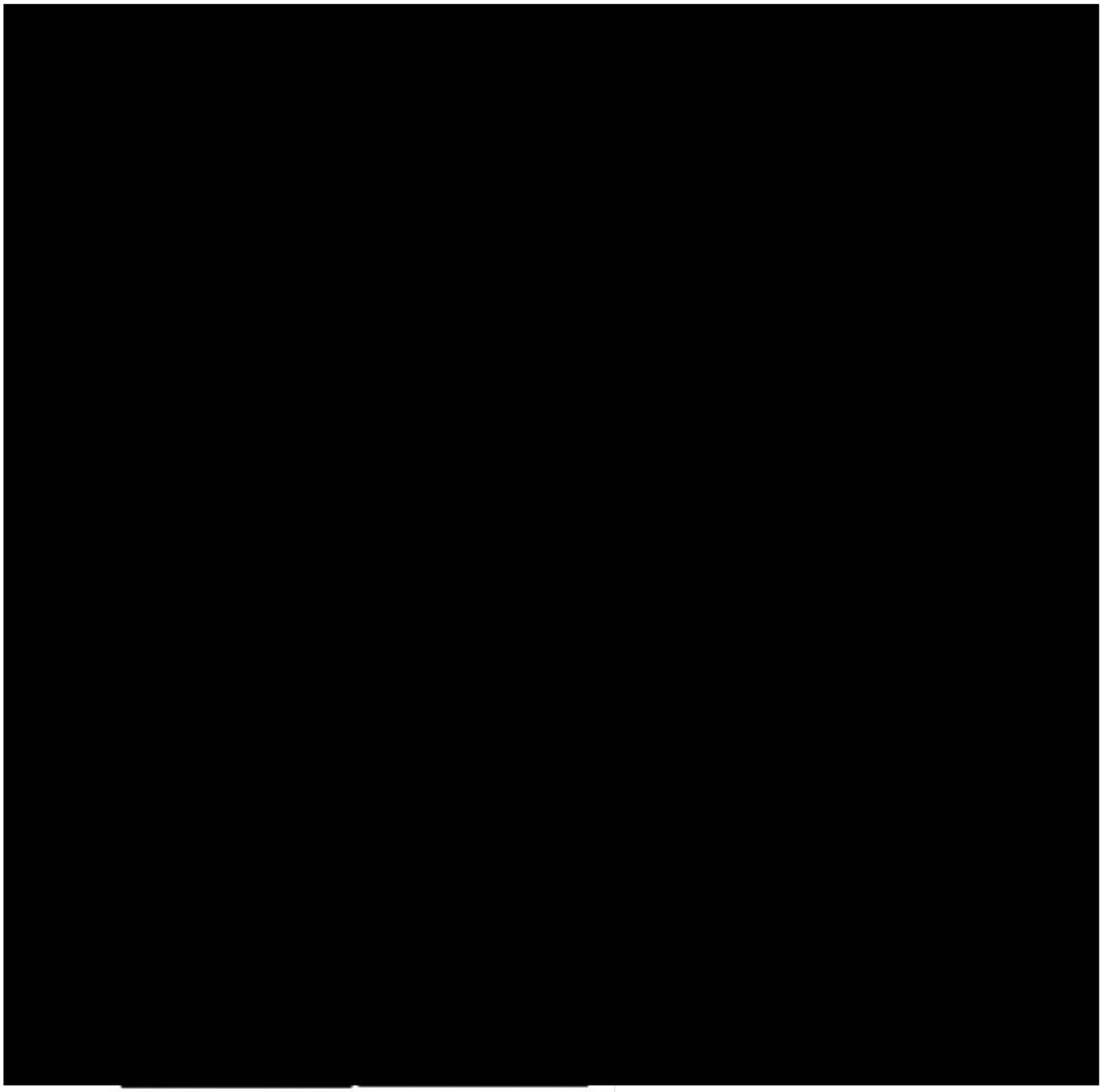

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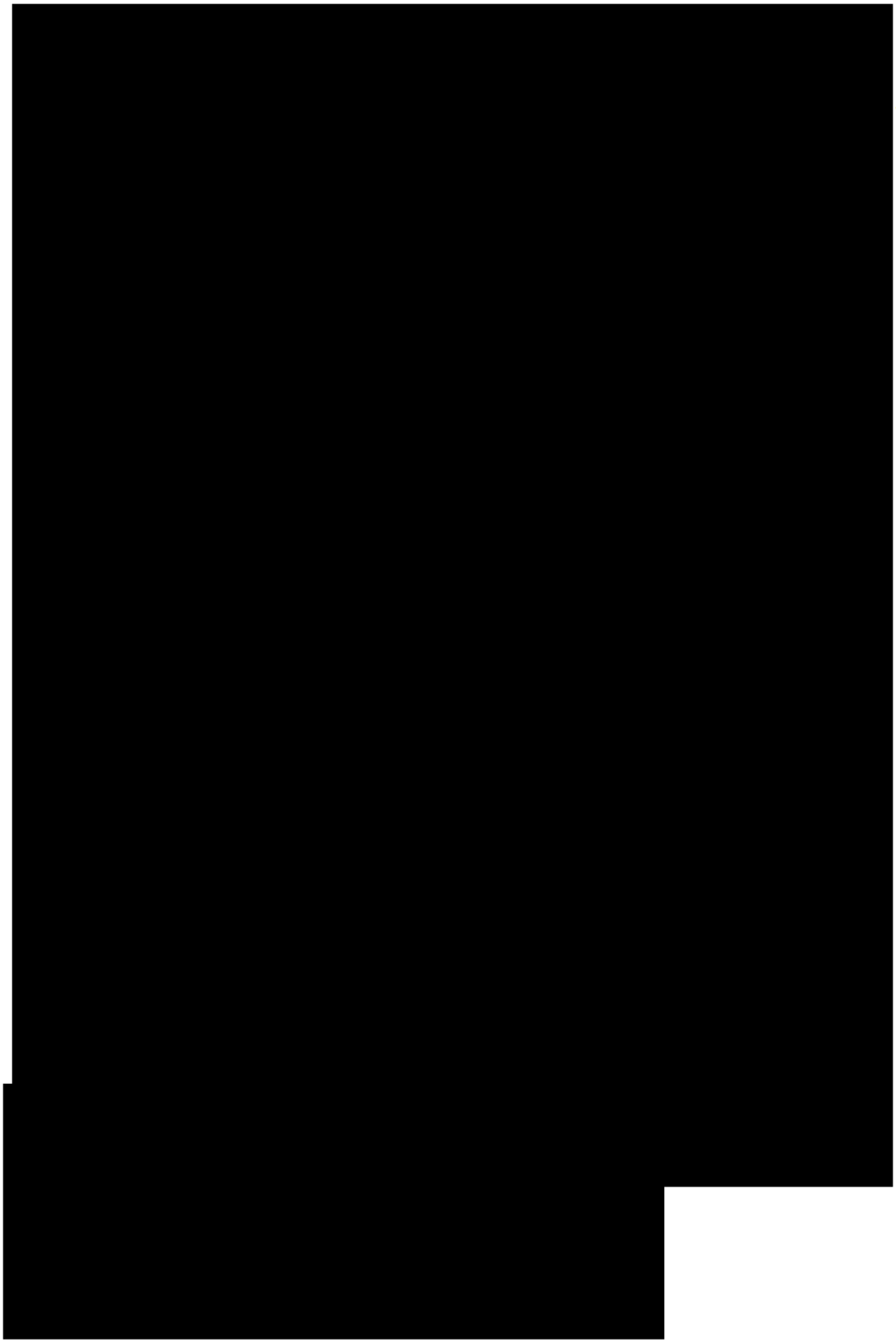

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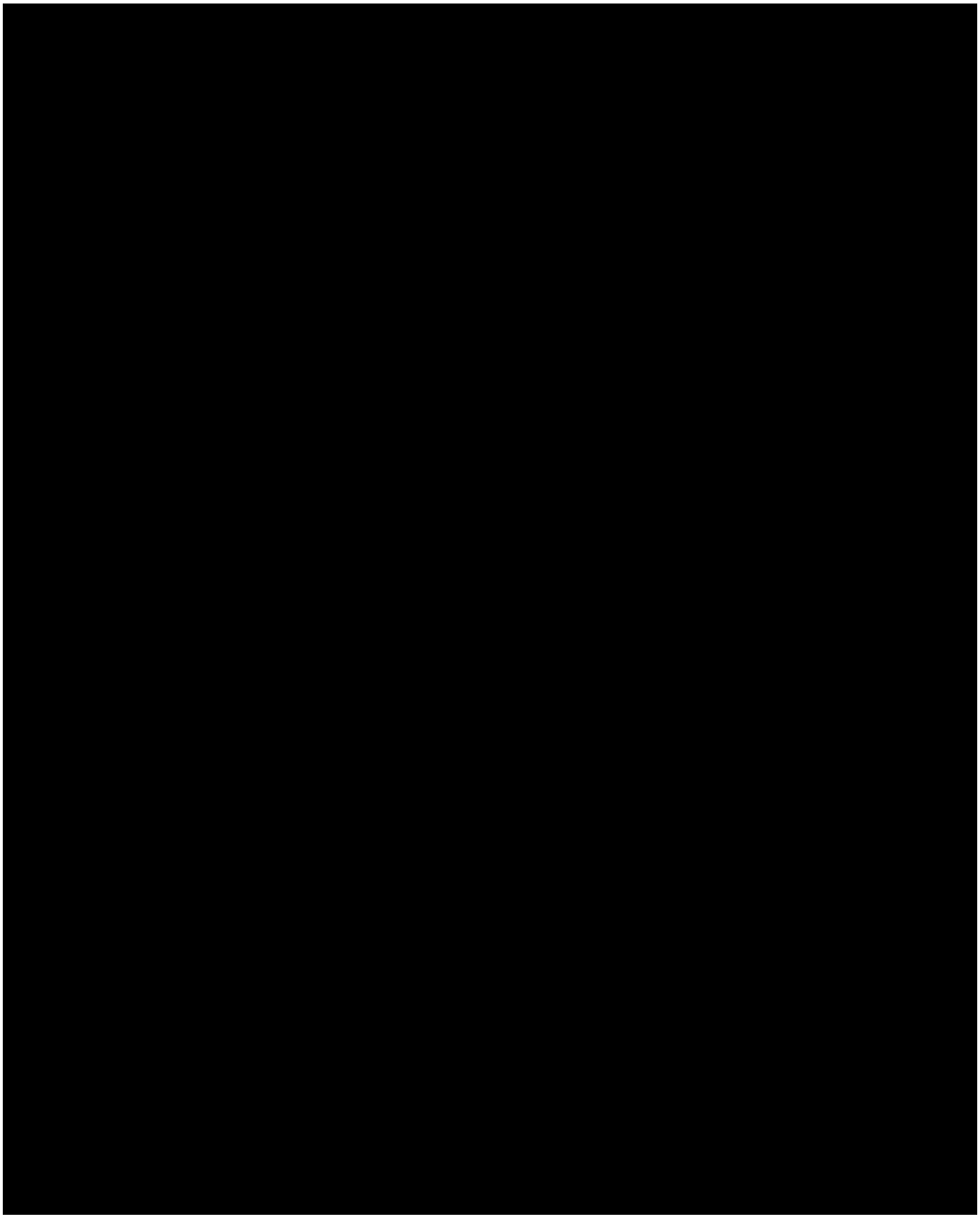

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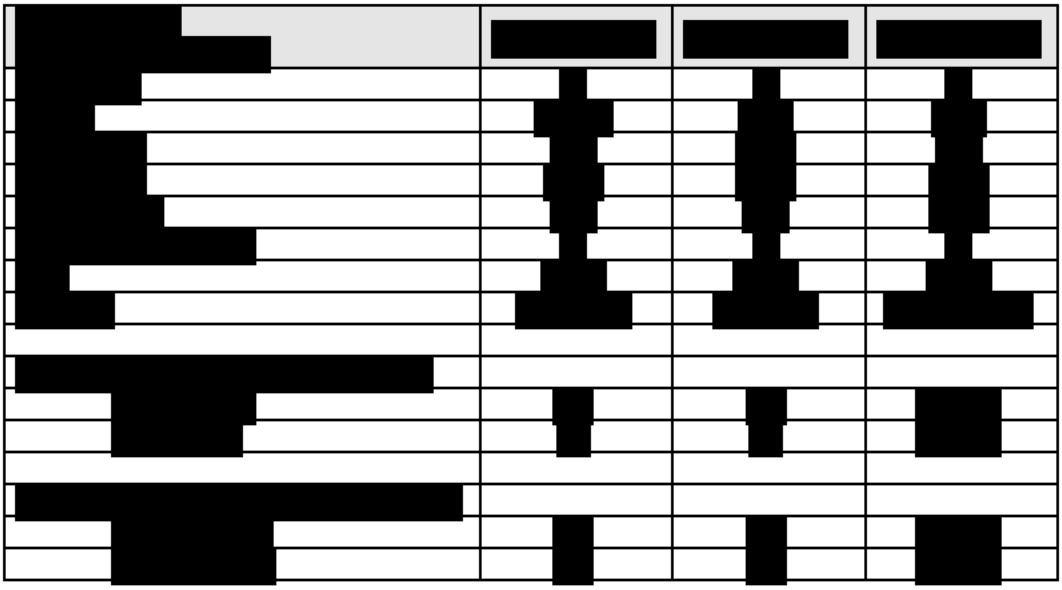

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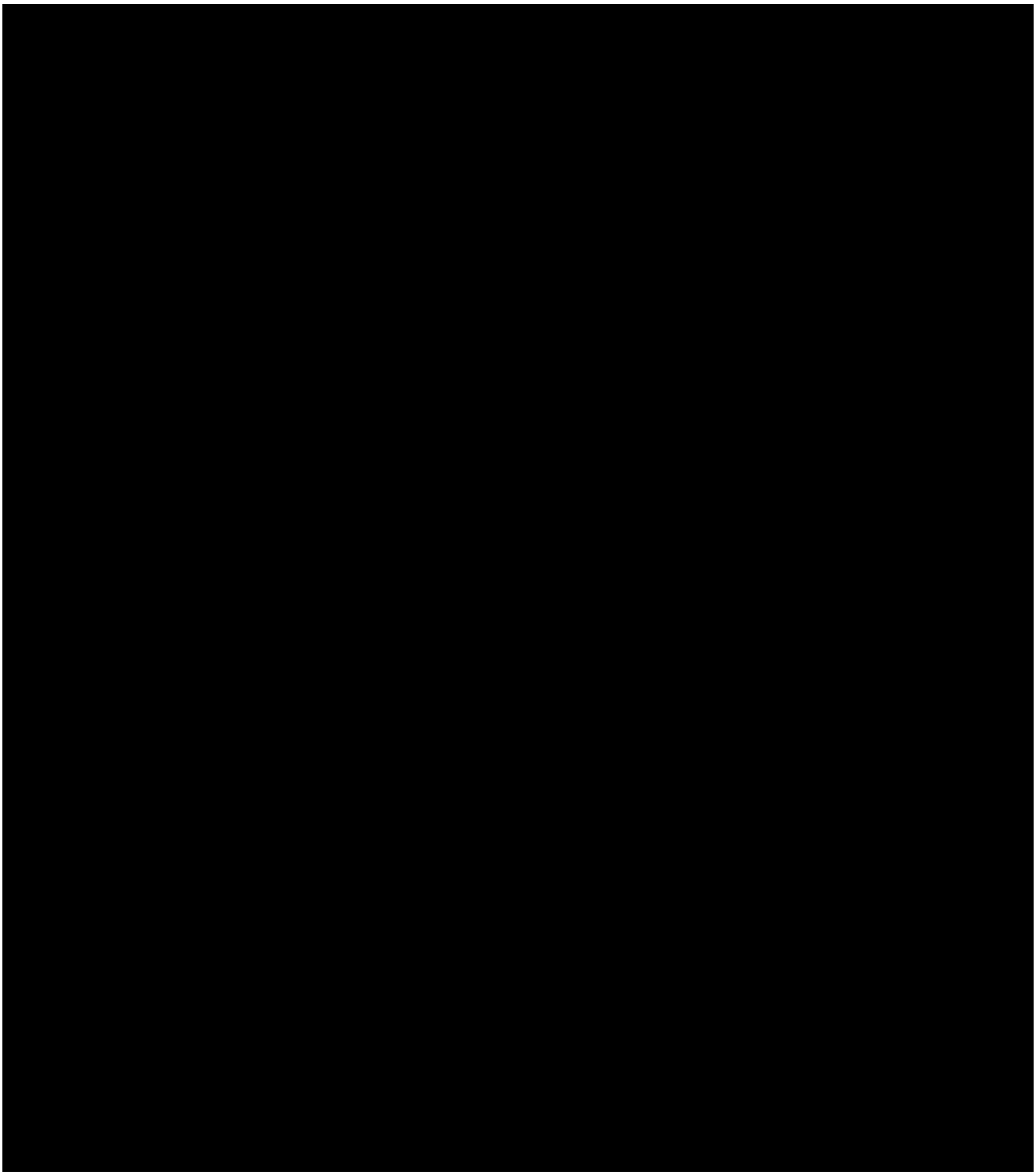

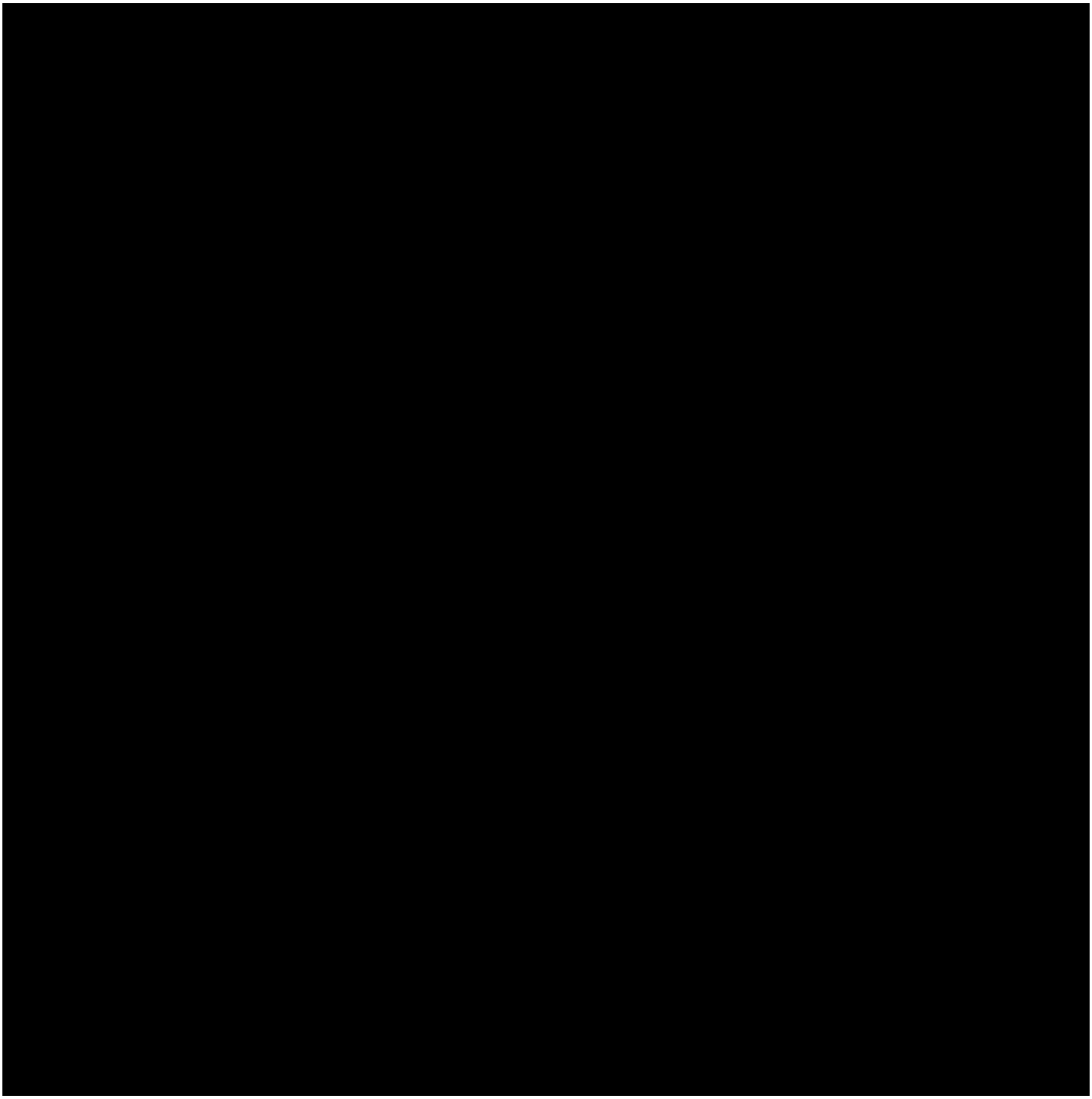

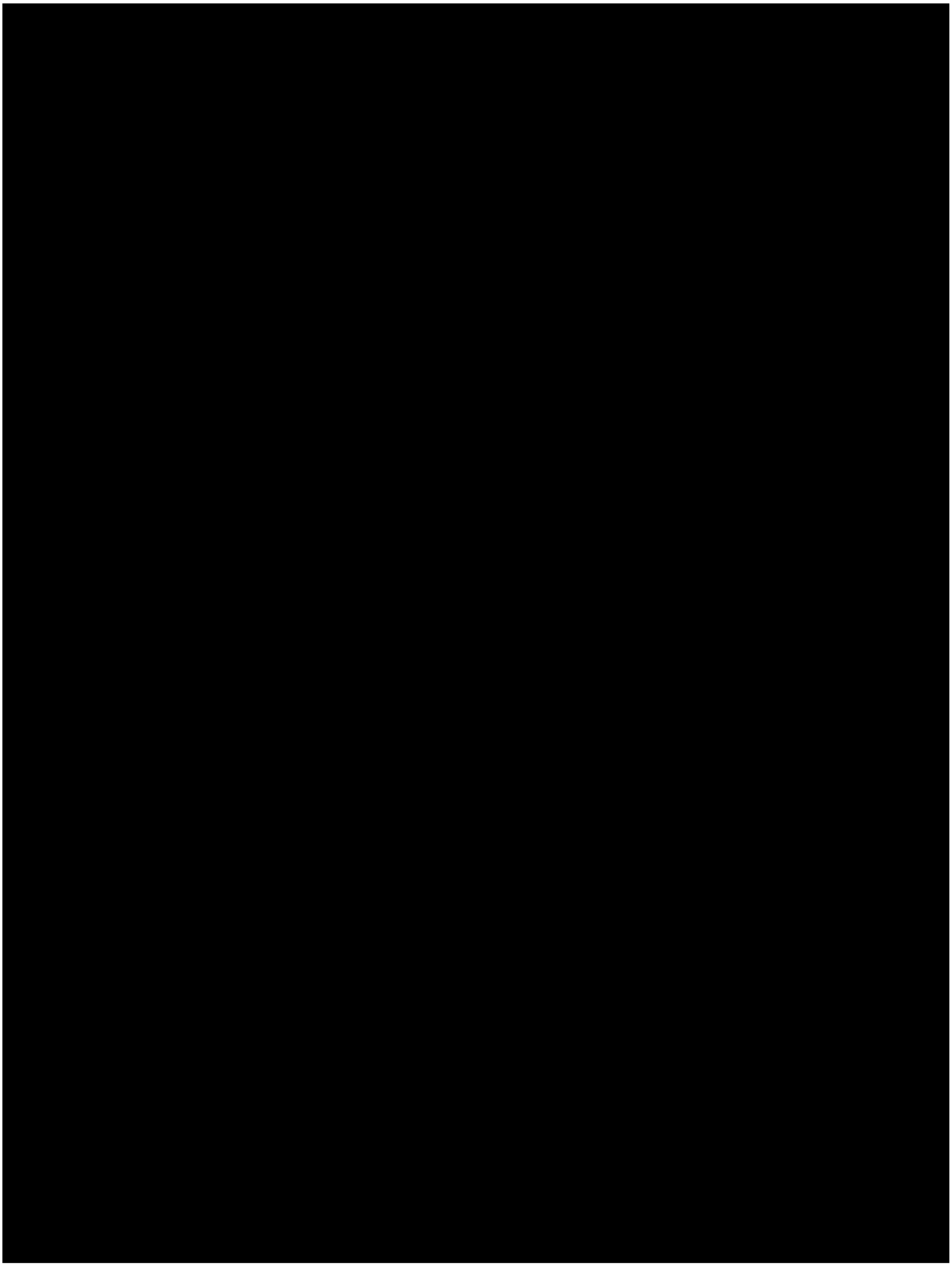

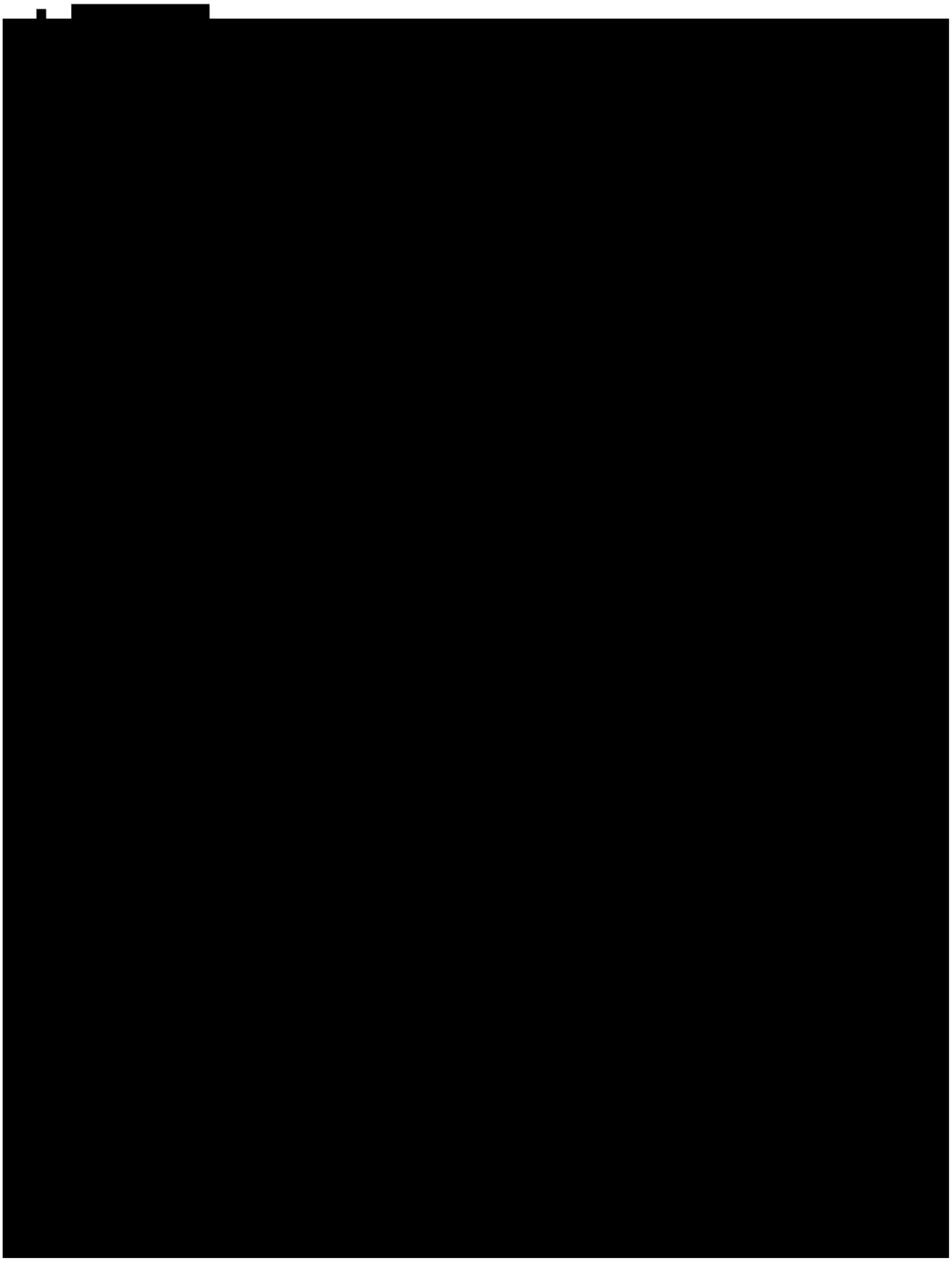

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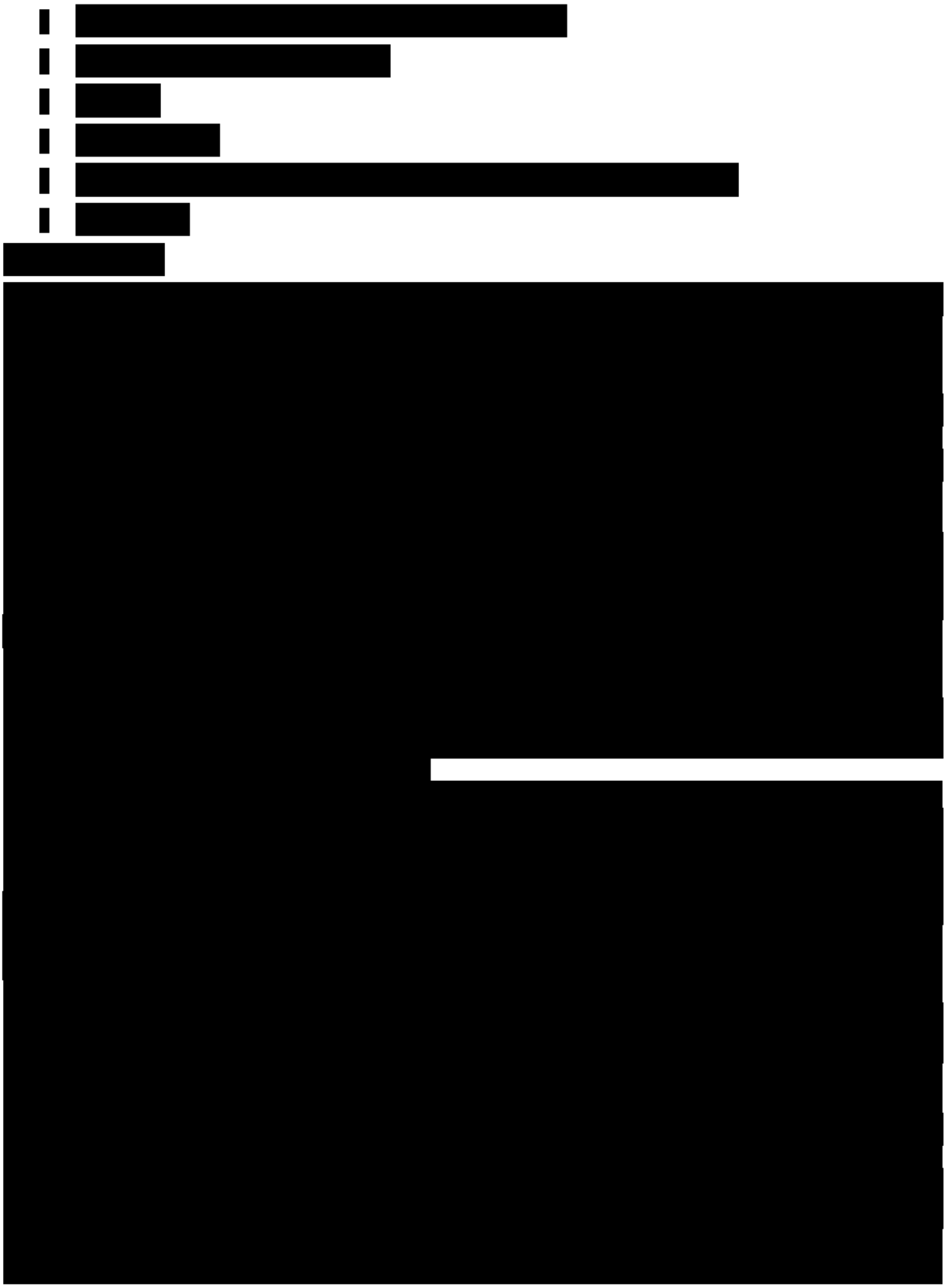

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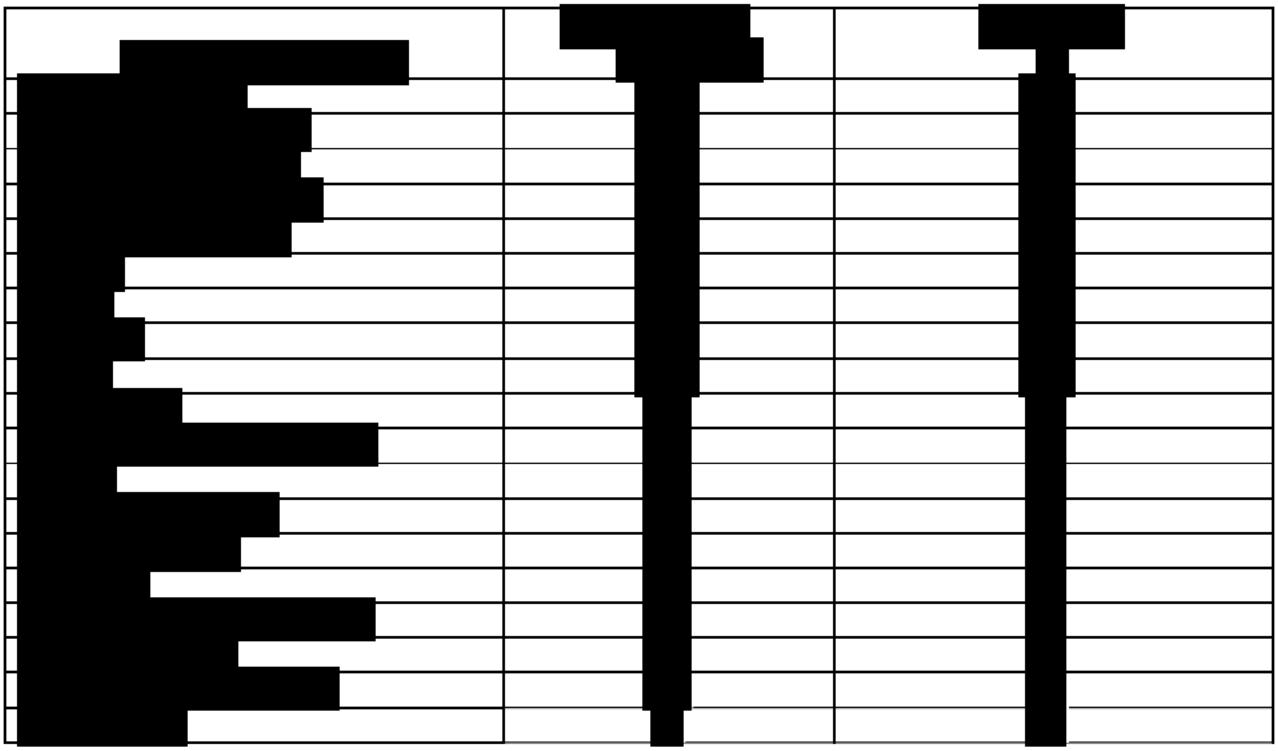

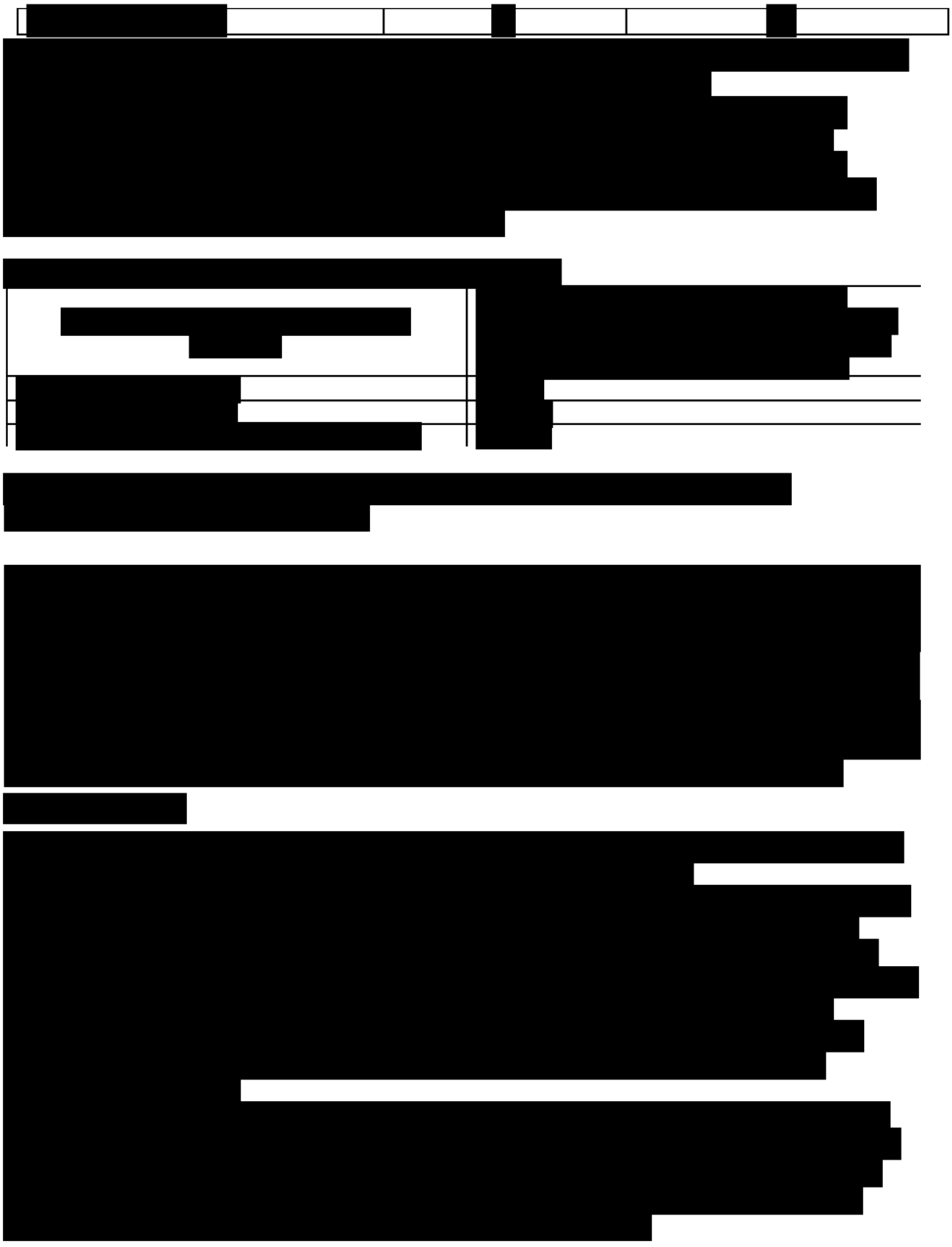

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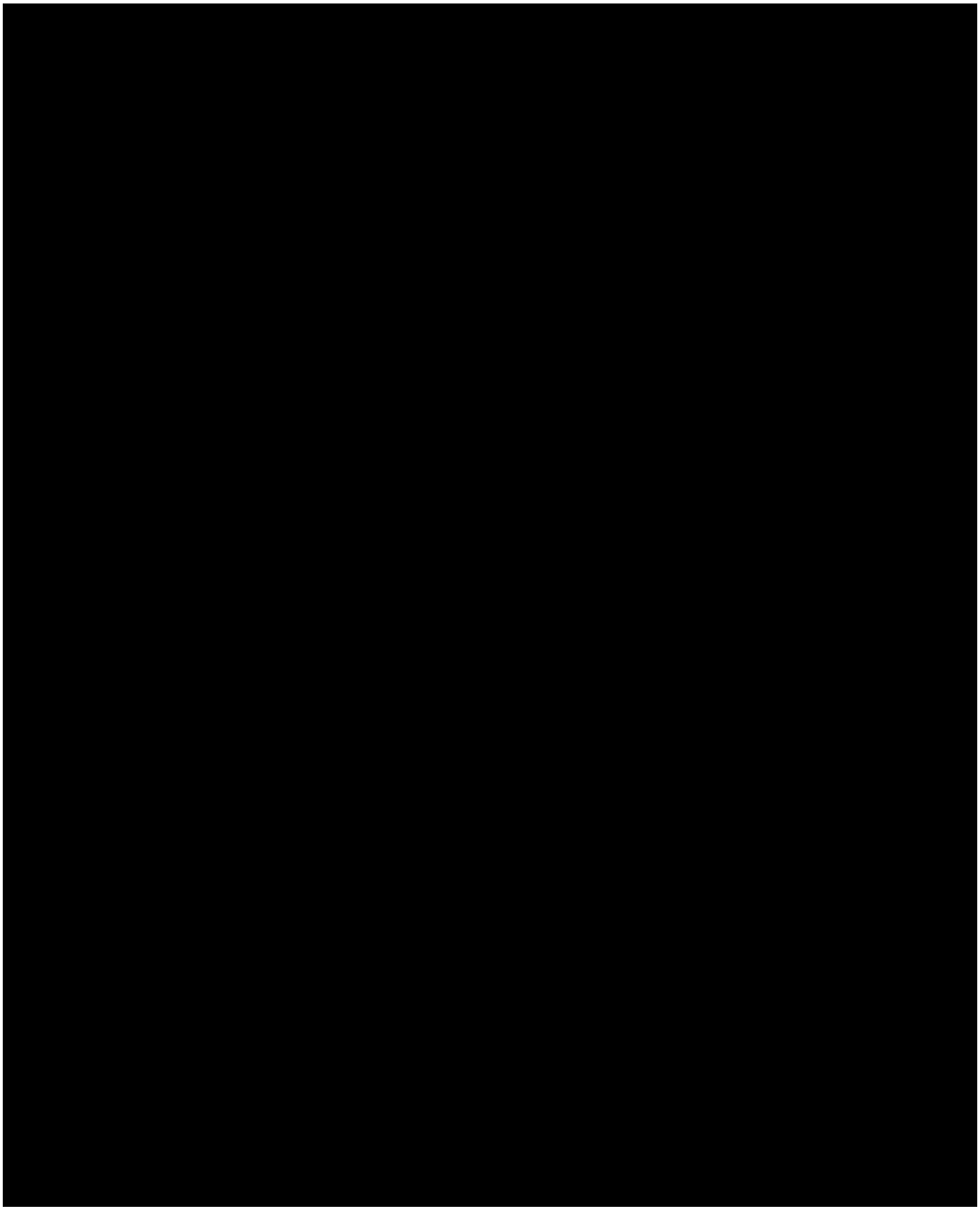

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2 ELIGBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

- Participants must have histologically or cytologically confirmed:
  - Metastatic or locally advanced, Solid tumor (Cohort 1)

OR

  - Metastatic or locally recurrent, non-resectable Triple Negative Breast Cancer (TNBC), defined as ER < 10%, PR < 10% per immunohistochemistry (IHC) and HER 2 negative. HER2 negative or unamplified breast cancer is defined as IHC 0 or 1+ or IHC 2+ with FISH average HER2 copy number < 4.0 signals per cell or HER2/CEP17 < 2.0 with average HER2 copy number < 4.0 signals per cell.[89] HER2 testing must have been performed in a laboratory accredited by the College of American Pathology (CAP) or another accrediting entity (Cohort 2).

OR

  - Metastatic or locally recurrent, non-resectable p16 negative Head and Neck Squamous Cell Cancer (HNSCC). Oropharyngeal tumors must be negative for p16 overexpression by IHC per ASCO/CAP guidelines and in a CAP accredited lab.[90] All other head and neck malignancies do not require p16 testing (Cohort 3).
- Participants must have histologically or cytologically confirmed metastatic or locally advanced disease. Historical reports from a CAP accredited lab are acceptable.
- Subjects in Arms 1 and 2 may have disease that is measurable or non-measurable but evaluable disease (e.g. present on bone scan, rising tumor markers, non-measurable by RECIST but visible on CT scan). Participants with third space fluid (for example pleural effusions) as only site of disease will not be eligible. Subjects in Arm 3 must have measurable disease according to RECIST 1.1See Section **6.3.1** for the evaluation of measurable disease.
- Participants must
  - have received at least one prior systemic therapy for metastatic or locally advanced disease, unless there is no standard treatment available,

OR

  - not tolerate standard first line treatment,

OR

  - decline standard treatment after appropriate counseling has been provided.

Note: Participants in Arm 3, Cohort 3 who have PD-L1 positive TNBC must have progressed on atezolizumab + nab-paclitaxel. Participants in Arm 3, Cohort 3 (p16 negative HNSCC) must have progressed on or been intolerant to a regimen involving a platinum drug or cetuximab monotherapy.

- Age ≥18 years.

- ECOG performance status 0 or 1 (**Appendix A**).
- Participants must have adequate organ and marrow function as defined below:
  - Absolute neutrophil count (ANC) >1,500/mcL
  - Platelets >100,000/mcL
  - Hemoglobin > 9 g/dL without a blood transfusion in the 14 days prior to enrollment.
  - Total bilirubin < 1.5X upper limit of normal (ULN) OR in subjects with Gilbert's Syndrome, a total bilirubin < 3.0 x ULN
  - AST(SGOT)/ALT(SGPT) <2.5 X institutional upper limit of normal OR in subjects with known liver metastasis, AST/ALT < 3.0 X ULN
  - An estimated creatinine clearance (CrCl) > 60 mL/min/1.73 m^2 using the Cockroft-Gault calculation (https://www.kidney.org/professionals/KDOQI/gfr_calculatorCoc).
- The effects of immunotherapies on the developing human fetus are unknown. For this reason and because immunotherapy agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) at the time of study entry, for the duration of study treatment and up to 6 months after the last dose of the study drug (s). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
- Participants with well-controlled HIV infection are eligible for trial as long as:
  - On an effective anti-retroviral therapy (ART) > 4 weeks and with evidence of viral suppression defined as HIV viral load < 400 copies/mL at enrollment
  - CD4+ count > 200 cells/μL at enrollment
- No reported opportunistic infections within 6 months prior to enrollment except for the following which will be allowed:
  - Esophageal candidiasis treated within last 6 months or currently improving with antifungal treatment
  - Oral and/or genital HSV treated within last 6 months or currently improving with antiviral treatment
  - Mycobacterium avium infection in last 6 months or that has been treated for at least 1 month.
- Immunomodulating drugs must be discontinued at least 1 weeks prior to enrollment for recent short course use (≤ 14 days) or discontinued at least 4 weeks prior to enrollment for long term use (> 14 days).
- Participants must have a received their last treatment ≥ 4 weeks or 5 half-lives of the last treatment drug, whichever is shorter before starting on trial.
- Participants with known history of hepatitis B (HBV) infection are eligible for trial as long as the HBV viral load is undetectable.

- Participants with known history of hepatitis C (HCV) infection must have been treated and cured (viral load is undetectable). For participants with HCV infection who are currently on treatment, they are eligible if they have an undetectable or unquantifiable HCV RNA 12 weeks or longer after definitive treatment completion.
- Subjects must be able to understand and be willing to sign a written informed consent document.

2.1.2 Exclusion Criteria

- Participants who are receiving any other investigational agents.
- Participants with active brain metastases or central nervous system metastasis (less than 28 days out from definitive radiotherapy or surgery of brain metastasis) are excluded from this clinical trial. However, participants with treated brain metastasis are eligible if there is no magnetic resonance imaging (MRI) evidence of progression for 6 weeks after treatment is complete and the MRI within 28 days prior to enrollment. Participants requiring immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalent) for palliation are excluded. Participants with evidence of intratumoral or peritumoral brain metastasis hemorrhage on screening imaging are also excluded unless the hemorrhage of brain metastases is grade < 1 and has been stable on two consecutive imaging scans.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to any of study drugs
- Steroid use or active autoimmune disease that might deteriorate when receiving an immunostimulatory agent with the exception of:
    - Diabetes type I, eczema, vitiligo, alopecia, psoriasis, hypo- or hyperthyroid disease or other mild autoimmune disorder not requiring immunosuppressive treatment;
    - Participants requiring hormone replacement with corticosteroid are eligible if the steroids are administered only for the purpose of adrenal insufficiency and at doses of ≤10 mg of prednisone or equivalent per day;
    - Administration of steroids for other conditions through a route known to result in a minimal systemic exposure (topical, intranasal, intro-ocular, or inhalation) is acceptable;
    - Participants on physiologic doses of systemic intravenous or oral corticosteroid therapy (≤ the equivalent of prednisone 10 mg/day.
    - The use of corticosteroids as premedication for contrast-enhanced studies which is allowed prior to enrollment.
- Participants with a history of serious intercurrent chronic or acute illness, such as cardiac or pulmonary disease, hepatic disease, bleeding diathesis or recent (within 3 months) clinically significant bleeding events or other illness considered by the Investigator as high risk for investigational drug treatment.
- History of second malignancy within 3 years of enrollment except for the following: adequately treated localized skin cancer, ductal carcinoma in situ, cervical carcinoma in situ, superficial bladder cancer or other localized malignancy which has been adequately treated.

- Receipt of any organ transplantation requiring ongoing immunosuppression including allogenic stem-cell transplant.
- Participants with bone metastases who have initiated denosumab or a bisphosphonate therapy within 28 days prior to enrollment. Continuation of prior therapy is allowed.
- Participants who have a QTcf interval > 475 msec or > 480 msec with a BBB on screening electrocardiogram.
- Participants with a personal or family history of long-QT syndrome or are on a concomitant drug that is known to cause significant QTc prolongation within 2 weeks or 5 half-lives (whichever is shorter) of enrollment (see **Appendix B** for list of drugs)
- Participants with heart failure (New York Heart Association [NYHA] class III or IV) or cerebrovascular accident within one year or acute myocardial infarction within one year.
- Participants unwilling to accept blood products or blood transfusions as medically indicated. As there is a risk of severe bleeding with M7824, participants must be willing to receive blood transfusions if medically necessary for their own safety
- Any other condition, which would, in the opinion of the Principal Investigator indicated the subject is a poor candidate for the clinical trial or would jeopardize the subject or the integrity of the data obtained.
- Pregnant women are excluded from this study because study drugs potential for teratogenic or abortifacient effects are unknown. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with study drugs, breastfeeding should be discontinued if the mother is treated with study drugs.

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites, including www.clinicaltrials.gov and the CCR website, and on NIH social media forums. Outside providers and colleagues may directly refer participants for screening into this study.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videosReview of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the study consent OR the consent for study #01-C-0129 (provided the procedure is permitted on the study) on which screening activities will be performed. Assessments performed at outside facilities or on another

NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

All screening tests and procedures must be performed within 28 days prior to initiation of study therapy, unless otherwise specified*:*

- Complete medical history and physical examination (including weight, height, vital signs, and ECOG performance status).
- CT of chest, abdomen and pelvis with contrast (preferred)
- A brain CT
- Clinical laboratory tests (within 16 days prior to enrollment)
  - Biochemical Profile: sodium, potassium, chloride magnesium, phosphorus, bicarbonate, calcium, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, and total and direct bilirubin,.
  - Hematology: complete blood count (CBC) with differential and platelets
  - CD4 (if clinically indicated)
  - TSH, free T4, lipase, amylase
  - Lymphocyte panel (TBNK)
  - Coagulation panel: PT, INR, PTT
  - Urinalysis
  - Serum pregnancy test (β-HCG) for females of childbearing-potential and women < 12 months since the onset of menopause (within 7 days prior to enrollment).
  - HBV, HCV (or HCV viral load if recently completed treatment for HCV), HIV viral load by PCR (within 3 months prior to enrollment).
- Electrocardiogram (EKG) in triplicate
- Histologic or cytologic confirmation of tumor disease (at any time point prior to enrollment). Confirmation of tumor histology in NCI Laboratory of Pathology (archival tumor samples will be requested; if unavailable, the subject may choose to undergo fresh biopsy). Pathological confirmation of diagnosis of cancer in the Laboratory of Pathology at NIH Clinical Center or Walter Reed National Military Medical Center at Bethesda. However, if no pathologic specimen is available or if participants arrived with a diagnosis from Walter Reed National Military Medical Center at Bethesda, patients may enroll with a pathologist's report showing a histologic diagnosis of metastatic cancer, TNBC or HPV negative HNSCC in a College of American Pathologists (CAP) accredited laboratory and a clinical course consistent with the disease. If there is no available tumor sample or pathology report from a CAP accredited lab, a biopsy will be performed to confirm the diagnosis in a CAP accredited lab.
- Documentation of Immunohistochemistry (IHC) confirmation of Triple Negative Breast Cancer (TNBC), defined as ER < 10%, PR < 10% and HER2 negative. HER2

negative or unamplified breast cancer is defined by IHC and FISH HER2 testing. FISH must have been performed in a laboratory accredited by the College of American Pathology (CAP) or another accrediting entity (Arm 3, Cohort 2 only) (at any time point prior to initiation of study therapy)

- Documentation of IHC confirmation of HPV negative, oropharyngeal tumor is defined by negative p16 overexpression in the tumor (Arm 3, Cohort 3 only) (at any time point prior to initiation of study therapy). Other head and neck malignancies do not require p16 testing.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a lab abnormality or temporary condition may be rescreened..

2.3.2 Treatment Assignment Procedures (for registration purpose only):

Cohorts

Number	Name	Description
1	Phase 1: Solid Tumor	Participants with any solid tumor enrolled to SX-682 escalation dose levels
2	Phase 2: TNBC Expansion	Participants with Triple Negative Breast Cancer enrolled at the RP2D of SX-682 in combination with M7824 and CV301
3	Phase 2: HPV-HNSCC Expansion	Participants with HPV negative Head and Neck Cancer enrolled at the RP2D of SX-682 in combination with M7824 and CV301

Arms

Number	Name	Description
1	Sequential Dose Escalation	Escalating doses of SX-682 for 2 weeks THEN M7824 + CV301

Number	Name	Description
2	Combination Dose Escalation	Escalating doses of SX-682 for 2 weeks THEN Escalating doses of SX-682 + M7824 + CV301
3	Disease-Specific Expansion	RP2D of SX-682 + M7824 + CV301

Participants in Cohort 1 will be sequentially assigned to Arms 1 and 2.

Participants in Cohorts 2 and 3 will be assigned to Arm 3.

2.4 BASELINE EVALUATION

Tests done at screening do not need to be repeated on baseline if performed in designated time frame prior to start of study treatment

Within 7 days prior to first dose of any study drug:

- Physical exam including height, weight, ECOG performance status and vital signs.
- Concomitant Medications and Baseline Signs and Symptoms evaluation.
- EKG
- Serum pregnancy test (β-HCG) for females of childbearing-potential and women < 12 months since the onset of natural menopause (i.e., amenorrhea not induced by chemotherapy or other medication).
- Biochemical Profile: sodium, potassium, chloride, magnesium, phosphorus, bicarbonate, calcium, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, and total and direct bilirubin.
- TSH, free T4, lipase, amylase
- Hematology: CBC with differential and platelets. Lymphocyte panel (TBNK)
- Coagulation panel: PT, INR, and PTT
- Urinalysis
- Flexible clinic-based pharyngolaryngoscopy to evaluate the airway for safety and for mucosal involvement (if clinically indicated in participants with head and neck cancers)
- Collection of archival tumor samples for research if available (any time prior to treatment).
- Optional tumor biopsy for research purposes.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is an open label Phase I/II trial, consisting of a safety run-in phase I (Arms 1 and 2) and an expansion phase II, disease-specific cohorts (Arm 3).

In Arm 1 the safety and MTD dose of short term (2 weeks) SX-682 monotherapy lead-in following by treatment with M7824 and CV301 will be determined in participants with solid

tumors (**Schema 1**). An evaluation of DLTs (eDLTs) will occur at the completion of each dose level and will be done prior to enrolling on the next dose level.

In Arm 2 the safety, MTD/RP2D of continuing treatment of SX-682 in combination with M7824 and CV301 will be determined in participants with solid tumors (**Schema 2**). An evaluation of DLTs (eDLTs) will occur at the completion of each dose level and will be done prior to enrolling on the next dose level.

During Arm 3 expansion cohorts, when RP2D of SX-682 in combination with M7824 and CV301 is estimated, we will proceed with enrollment to Cohorts 2 (participants with triple negative breast cancer) and Cohort 3 (participants with HPV negative head and neck cancer) to evaluate efficacy of the SX-682 in combination with M7824 and CV301 (**Schema 3**).

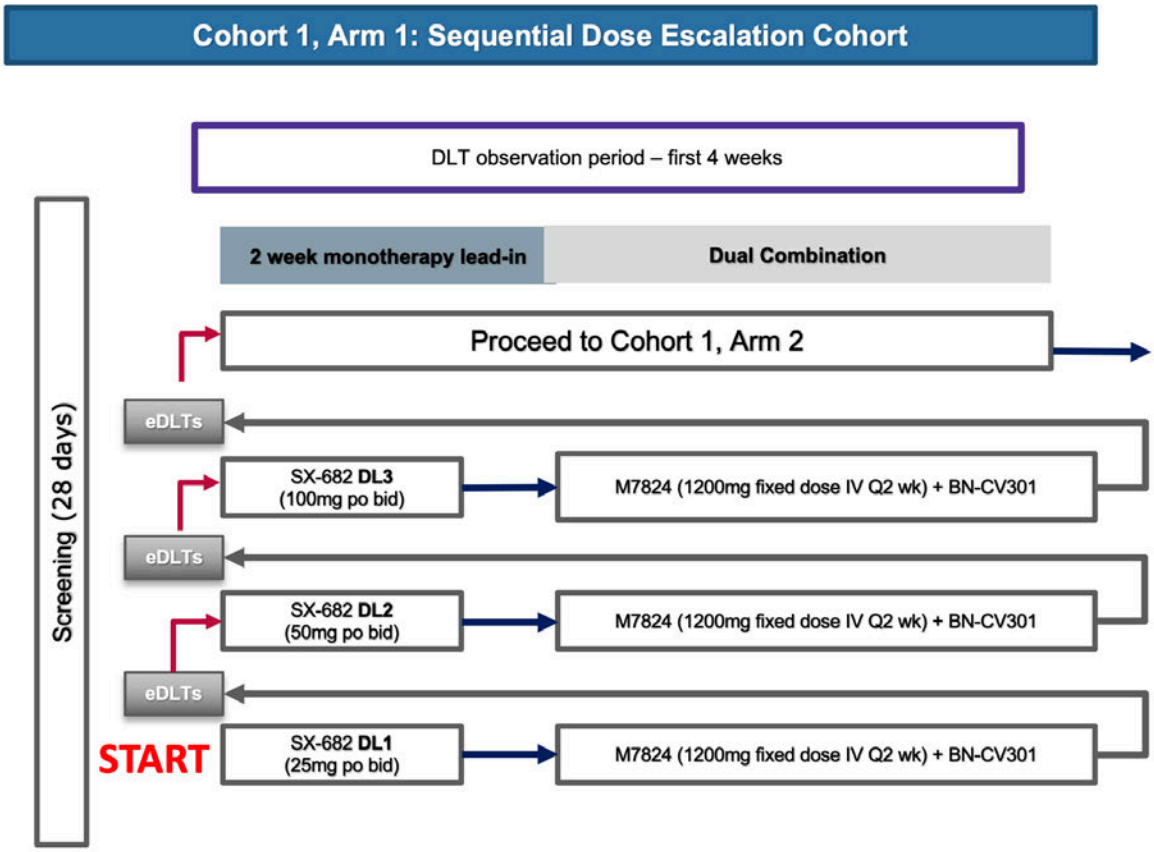
SX-682 will be self-administered by the participant orally twice daily according to designated Dose Level (**Table 4**).

Administration of M7824 will be at a flat dose of 1,200 mg every 2 weeks by IV. Participants will receive M7824 treatment every 14 (-1/+3) days.

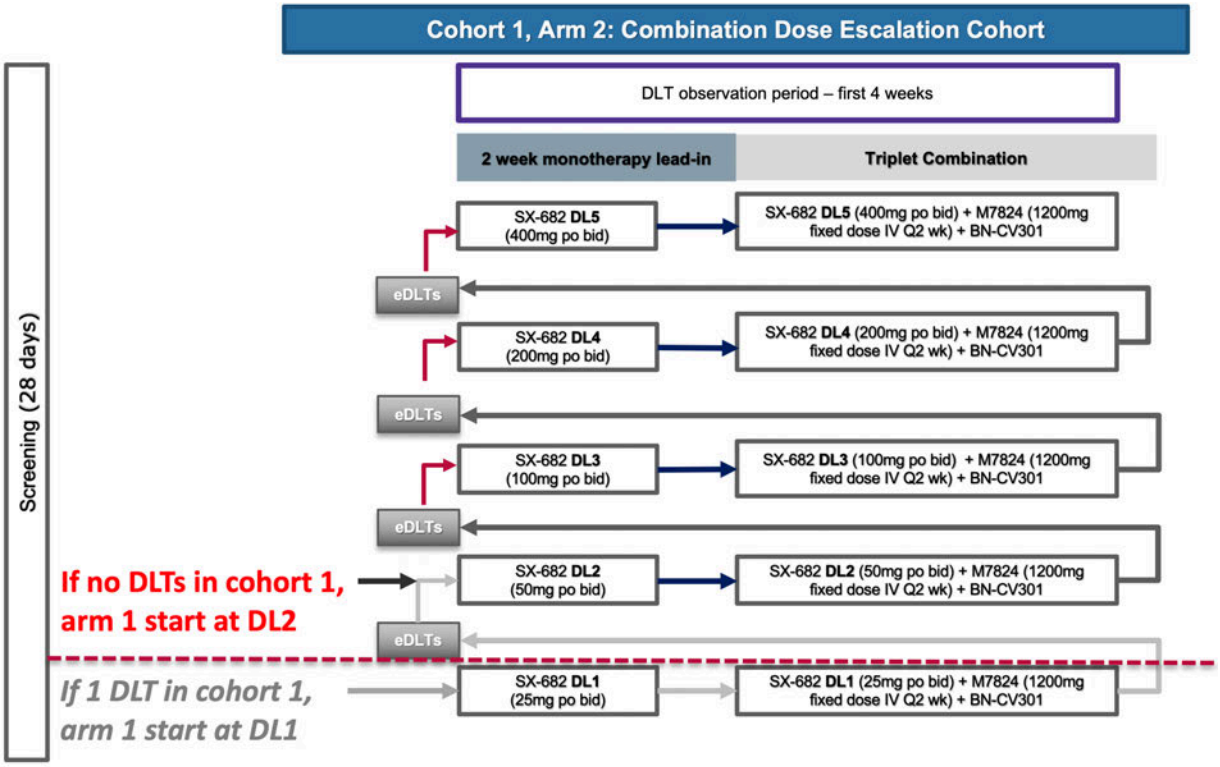
CV301 will be administered at a flat dose for both the prime and booster vaccines. The priming MVA-BN-CV301 is delivered as four subcutaneous injections of $4x10^8$ infectious units (Inf.U)/0.5 mL every 14 days for 2 doses (Cycle 1, Day 1 and Cycle 1, Day 15). FPV-CV301 is given subcutaneously at 1×10^9Inf.U/0.5 mL every 4 weeks starting on Cycle 2 Day 1 x 4 cycles then on Day 1 of every 3 cycles (every 12 weeks) for up to 1 year on trial. Participants will receive CV301 as scheduled (-1/+3) days.

Subjects on all arms will receive combined treatment with study drugs for up to 2 years (BN-CV301 will be administered for up to 1 year on trial; M7824 and SX-682 will be administered for up to 2 years on trial). Furthermore, after 2 years on treatment with M7824 and/or SX-682, the PI can discuss an additional treatment period with CRADA partners as long as in the opinion of the PI the participant continues to gain clinic benefit and is tolerating the drug regimen. Disease progression should be confirmed with a subsequent scan 4 to 8 weeks later prior to removing a participant from study therapy, unless the participant is clinically progressing or is no longer gaining benefit in the opinion of the investigator. Subjects with evidence of disease progression can remain on treatment beyond radiographic progression if in the opinion of the investigator the subject is benefiting from treatment. For complete list of off treatment criteria, see Section **3.7.2**.

Patients may undergo up to three optional biopsies for research purposes only: at baseline, at first restaging (+/- 1 week) and at time of progression.



Schema 1. Cohort 1, Arm 1



Schema 2. Cohort 1, Arm 2. Combination Dose Escalation Cohort.

3.1.1 Dose Limiting Toxicity

Dose-limiting toxicity (DLT) will be defined as any one of the following adverse events (AEs), as defined by CTCAE v5.0, possibly attributable to study drugs by the Investigator, that occur within 28 days after the start of study therapy:

- Any Grade 4 AEs, except for:
    - laboratory values that are determined to not be clinically significant or single laboratory valued that resolve to Grade ≤ 1 or baseline grade within 7 days with adequate medical management.
    - adverse drug reaction which in the opinion of the investigator is not clinically relevant or can be medically managed with minimal risk to the participant (e.g. placement of a pleural catheter for recurrent inflammatory pleural effusions)
- Average QTcf ≥ 501 msec or > 60 msec change from baseline (Grade 3)
- Any Grade 3 AEs <u>except</u> for any of the following:
    - Grade 3 flu-like symptoms or fever, as well as associated symptoms of fatigue, headaches, nausea, emesis which can be controlled with conservative medical management.
    - Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.

- Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis.
- Grade 3 Hgb decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor use does not require treatment discontinuation.
- Keratoacanthoma and squamous cell carcinoma of the skin.
- Any endocrinopathy that can be medically managed with hormone replacement
- Grade 3 neutropenia without fever
- Since the safety profile of M7824 is well characterized (see IB), a single grade 3 adverse event known to be associated with M7824, as per IB section 6.2.6 will not be considered a DLT.
    - Additionally, M7824 has a known potential to cause bleeding, with a rate of grade 3 bleeding events as high as 15.3% [92]. Therefore a grade 3 bleeding event will not be considered a DLT.
- Any grade 3 adverse drug reaction which in the opinion of the investigator is not clinically relevant or can be medically managed with minimal risk to the participant (e.g. placement of a pleural catheter for recurrent inflammatory pleural effusions)

- Any grade 3 or higher adverse event or unexpected toxicities due to the combination of therapies that would not be expected with individual agents alone, will be considered a DLT.

3.1.2 Dose Escalation Common Rules

Starting dose of SX-682 will be 25 mg by mouth twice daily (50 mg total daily dose).

The first 3 participants enrolled on a given dose level of Arms 1 and 2 will be observed for DLT. If no DLT in those 3 participants, the next dose level will open. If DLT(s) occur, see**Table 5**.

There will be an interval of at least 28 days between enrolling the last participant on a given dose level and enrolling a participant on the next dose level in Arms 1 and 2, in order to assess for DLTs.

Subjects who do not complete the DLT observation period for reasons other than a DLT will be replaced and not included in the evaluation.

Participants will be eligible for the DLT evaluation if at least ≥85 percent of SX-682 scheduled doses were taken and 100% of scheduled doses of M7824 or CV301 were administered within the DLT period.

In case of DLT, DLT will be documented and participant, per PI discretion, may continue study treatment if toxicity could be managed by interruption of the dose of study treatment or dose reductions (See section **3.4**). Participant, once having DLT, will not be used for DLT evaluation on another dose level if treated on a lower dose level.

Any of the trial drugs may be discontinued for toxicity per the discretion of the primary investigator if is it felt that the toxicity can be directly linked to a specific drug or drugs. Per PI

discretion participant can continue treatment with 2 other drugs. However, if 2 drugs or more must be discontinued, the participant will be taken off treatment.

3.1.3 Sequential Dose Escalation (Arm 1)

In Arm 1 participants will receive SX-682 as monotherapy for 2 weeks during the lead-in (Days -14L to -1L) and then continue treatment with M7824 and CV301 starting Cycle 1, Day 1.

The dose escalation will start from dose level 1 and continue until dose level 3 (**Table 4**) in sequential order using a standard 3+3 design (**Table 5**). Aside from looking at DLTs within a given dose level, the total number of DLTs will also be evaluated among the initial 3DLs in Arm 1 to guide further safety assessments. If there are 0 DLTs reported in the initial 3 DLs (minimum of 12 participants) in Arm 1, then Arm 2 can open as depicted in Schema 2 with starting at DL2. If there is 1 or more DLTs identified among all the participants in the first 3 DLs, enrollment in Arm 1 will continue with the next participants being enrolled on DL4 then DL5, using a 3+3 design in order to determine the maximally tolerated dose (MTD) before proceeding to Arm 2, DL 1.

Dose escalation will proceed in groups of 3–6 participants. The MTD is the dose level at which no more than 1 of up to 6 participants experience DLT during 28 days of treatment, and the dose below that at which at least 2 (of ≤6) participants have DLT as a result of the drug.

Table 4: Dose levels of SX-682

Dose Escalation Schedule		
Dose Level	Dose of SX-682	Total SX-682 daily dose
Level 1	25 mg by mouth twice daily	50 mg
Level 2	50 mg by mouth twice daily	100 mg
Level 3	100 mg by mouth twice daily	200 mg
Level 4	200 mg by mouth twice daily	400 mg
Level 5	400 mg by mouth twice daily	800 mg
SX-682 is dispensed as a 25mg tablet. M7824 and CV301 will be given at fixed doses.		

Table 5. Escalation Decision Rules

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule*
0 out of 3	Enter up to 3 participants at the next dose level
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter up to 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. UP to three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is the MTD and is generally the recommended phase 2 dose. At least 6 participants must be entered at the recommended phase 2 dose.

3.1.4 Combination Dose Escalation (Arm 2)

In Arm 2 participants will receive SX-682 as monotherapy for the lead-in (Days -14L to -1L) and then will continue treatment with SX-682 combined with M7824 and CV301 starting on Cycle 1 Day 1.

If 6 participants have been treated in Arm 1 at dose level 3 without DLT during DLT period, the dose escalation of SX-682 will start from dose level 2 and continue until dose level 5 (**Table 4**) in sequential order using a standard 3+3 design (**Table 5**).

If there was 1 or more DLT in Arm 1 at dose level 1 through 3 during DLT period, the dose escalation of SX-682 will start from dose level 1 and continue until dose level 5 (**Table 4**) in sequential order using a standard 3+3 design (**Table 5**).

If in Arm 1 dose level 1 or 2 are estimated as MTD, we will submit an amendment with justification for study continuation.

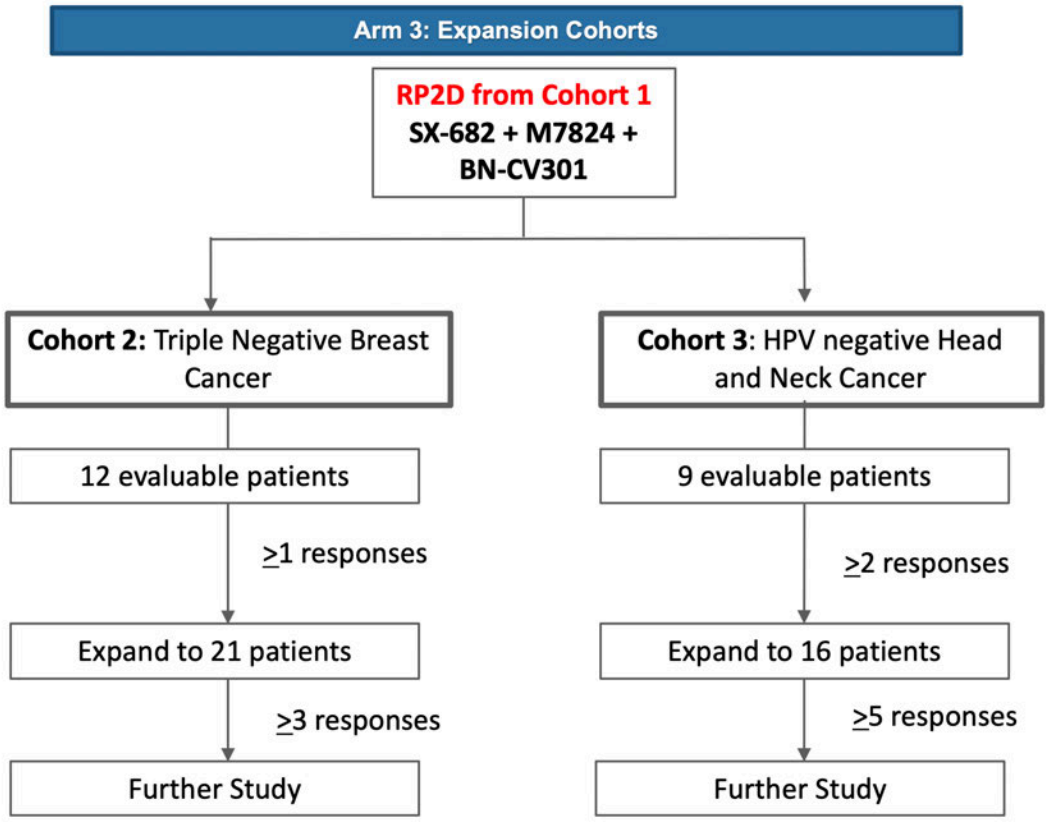
Dose escalation will proceed in groups of 3–6 participants. The MTD is the dose level at which no more than 1 of up to 6 participants experience DLT during 28 days of treatment, and the dose below that at which at least 2 (of ≤6) participants have DLT as a result of the drug. The RP2D may not necessarily be the same as the MTD.

3.1.5 Expansion Cohorts (Arm 3, Cohorts 2 and 3)

The safety, tolerability and efficacy evaluation of combination will continue with the RP2D of SX-682, M7824 and CV301 found during the dose escalation cohort (Arms 1 and 2). The dose of SX-682 used in combination with M7824 and CV301 in Arm 3 cannot exceed the highest tolerable dose for SX-682 monotherapy as determined in Arms 1 and 2.

Enrollment into the expansion cohorts can commence after the RP2D has been determined (after the 6th participant on relevant dose level completes the DLT evaluation period). For performance of the expansion cohorts, see **Schema 3**

Schema 3 Expansion Cohorts in Triple Negative Breast Cancer and HPV negative HNSCC



3.2 STUDY STOPPING RULES

For safety reasons, enrollment will be temporarily halted until an expedited safety report has been evaluated by the investigators, IND sponsor, and submitted to the FDA for either of the following events attributable to treatment regimen occurring within 30 days of receiving investigational agent:

- One occurrence of grade 5 toxicity
- Two occurrences of grade 4 toxicity
- Grade 3 or higher toxicities that occur at a higher rate than expected for each individual agent in the combination.

3.3 DRUG ADMINISTRATION

3.3.1 General Dosing Rules:

Except where stated otherwise in the study calendar a window of -1/+ 3 days for every two weeks M7824 dosing and/or study calendar a window of -1/+ 3 days for the scheduled CV301 dosing is allowed in the event of scheduling issues (i.e. holiday, bad weather or other scheduling issues). Any dose that cannot be accommodated within this window will be skipped and the dose not made up. Similar drug administrations should not be given less than 11 days from one another.

The preferred order of drug administration in the day hospital is CV301, then M7824 administration; when possible, administer the vaccine within 60 minutes prior to the M7824 administration; however, the exact timing of vaccine administration is flexible.

3.3.2 SX-682

SX-682 will be given orally at designated dose twice a day every day. SX-682 is available as a 25 mg and a 100 mg tablet. If necessary, the 100 mg tablets can be cut in half using a pill splitter; the tablets are pre-scored for this purpose. The tablets are not to be crushed, chewed, or dissolved before swallowing.

SX-682 should be taken at approximately the same times each day. Participants should take SX-682 with water once in the morning (suggested between 6-9 am) and once in the evening (suggested between 6-9 pm). For two hours before and one hour after the dose, the participant's diet should be limited to clear liquids only (no solid foods). Doses should be taken within 2 hours of the scheduled time.

In case of a missed dose (more than 2 hours late) or vomiting after taking SX-682, participants will be instructed not to make up the missed dose.

Up to 15% of scheduled doses of SX-682 can be missed per cycle unless directed by PI/AI to hold additional doses of SX-682 during a planned cycle.

Participants will complete and return Participant's Diary (**Appendix C**), which will be reviewed by research staff at the end of each cycle.

3.3.3 CV301 Vaccines

Participants will be primed with MVA-BN-CV301 twice during Cycle 1 (Days 1 and 15), followed by booster vaccines with FPV-CV301 on Day 1 of subsequent cycles (every 4 weeks) x 4 cycles (Cycle 2 through Cycle 5) then on Day 1 of every 3 cycles (Cycles 8 and Cycle 11).

A single dose of MVA-BN-CV301 is given as four subcutaneous injections with each of these injections containing $4x10^8$ Inf.U/0.5ml. Each injection will be given in a different arm or leg.

A dose of FPV-CV301 is given as one subcutaneous injection with each injection containing $1x10^9$ Inf.U/0.5ml. For participant comfort, it is generally preferred if FPV-CV301 is administered in the upper arm; however, the vaccine can be given in any extremity.

3.3.4 M7824

Subjects will be scheduled to receive M7824 at a flat dose of 1,200 mg IV on Days 1 and 15 of each cycle.

Subjects will receive M7824 via IV infusion over 1 hour (-10 minutes / +20 minutes, that is, over 50 to 80 minutes) once every 2 weeks. Infusion rate may be adjusted in the event of certain adverse events as described in section **3.4.4**. M7824 can be administered through a central line (preexisting) or a peripheral IV. A 0.2 micron in-line filter is required for administration of M7824. The preference is for M7824 to be given via peripheral line. However, if the research team documents that the main material of the port is titanium, M7824 can be administered via mediport. It is the responsibility of the research team to confirm and document this in CRIS. Once documented, the ordering physician can change the route of administration to mediport. Please refer to the pharmacy manual for a list of acceptable materials known to be compatible with M7824.

In order to mitigate potential infusion-related reactions, premedication with an antihistamine and with acetaminophen (for example, 25-50 mg diphenhydramine and 500-650 mg acetaminophen) within approximately 30 to 60 minutes prior to dosing of M7824 is optional and at the discretion of the Investigator. Steroids as premedication are not permitted.

3.4 DOSE MODIFICATIONS

3.4.1 General Rules

When, at the beginning of a treatment week, treatment delay related to one of study drugs is indicated, treatment with other drugs should not be delayed.

If, in the opinion of the investigator, a toxicity is considered to be due solely to one drug, the dose of other drugs does not require modification.

Any of the trial drugs may be held for toxicity per the discretion of the primary investigator if is it felt that the toxicity can be directly linked to a specific drug. For AEs that are attributed to a study drug, a study drug may be held or reduced (only SX-682 can be reduced) when in the opinion of the investigator doing so will minimize the risks to the participant and maximize clinic benefit (e.g., in the event of observed tumor reduction but also intolerable ADRs at the full dose).

If one drug is discontinued during first year of treatment, a participant may per PI discretion continue treatment with 2 other drugs. However, if 2 drugs must be discontinued, the participant will be taken off treatment. If one drug is discontinued during second year of treatment, a participant may per PI discretion continue treatment with the other drug.

For non-medical logistical reasons, unrelated acute illnesses, or palliative radiation, dosing with any drug can be delayed up to 2 months. Where at all possible, dosing should be restarted to keep in line with the original treatment schedule.

For AEs that are unrelated to the study drugs, study drug(s) may be held for up to 2 months at the discretion of the PI.

Any dose that would have occurred within this window will be skipped and the dose not made up.

If a participant on trial continues to gain benefit from treatment with one or more of the trial drugs at the two-year mark, the investigator can discuss with the CRADA partners the possibility of continuing the participant on treatment with the assigned trial drugs for an additional specified period of time.

In case of Grade 3 and Grade 4 AEs not study drug related, the study treatment may be interrupted based on the Investigator assessment and the subject will be medically treated for the event.

If the AE reduces to a lower tolerable grade the study treatment might be resumed in the subsequent week. If the AE remains the same despite the medical treatment until the next treatment (second cycle after the AE occurred) a consideration of a possible extension of the dose interruption for up to 1 additional cycle or a permanent withdrawal from the study treatment should be considered.

If upon the resumed study treatment, the subject experiences the same AE, permanent withdrawal from the study treatment should be considered.

Grade 3 and 4 laboratory abnormalities that do not have clinical significance and are not related to study drugs do not require dose interruption.

3.4.2 SX-682

If any SX-682 related AE observed is grade > 2 (except for electrolyte abnormalities that can be easily replenished or other lab abnormalities that have no clinical consequence or can be easily medically managed with minimal risk to the participant), treatment should be delayed by 1 week (except for hyperbilirubinemia where drug will be held for grade 2) – and up to 4 consecutive weeks. If, with a delay of up to 4 weeks, the treatment related AE resolves, then SX-682 can be resumed at the same dose level or at a lower dose level per the PI discretion.

If, after 4 weeks of delay, all treatment related AEs have still not resolved (to grade ≤ 1), then any further treatment with SX-682 should be delayed until AEs are resolved (to grade ≤ 1), and then reduced by one dose level at the time of reinitiating.

3.4.3 CV301

Dose delays or dose omissions of CV301 vaccines are allowed per PI discretion. There are no dose reductions for the CV301 vaccines.

3.4.4 M7824

Dose delays or dose omissions of M7824 are allowed per PI discretion. There are no dose reductions for M7824.

3.4.4.1 Adverse Drug Reactions (ADRs) Requiring Treatment Discontinuation

All adverse events in this trial will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Any Grade 4 ADRs require permanent treatment discontinuation <u>except for</u> any of the following:

- Single laboratory values out of normal range that do not have any clinical correlate and resolve to Grade ≤ 1 or Baseline grade within 7 days with adequate medical management.
- Grade 4 symptomatic endocrinopathies (e.g., thyroiditis or hypophysitis), treatment should be delayed, and treatment started according to best medical judgement based on the most updated professional guidelines (NCCN, EMSO, SITC, etc.). Following the initiation of appropriate medical therapy for the endocrinopathy, treatment can be resumed per PI discretion.

- Asymptomatic lab abnormalities (Grade 3 or 4) as described below in the Grade 3 ADR section.
- Grade 4 non-tumor bleeding will not require permanent treatment discontinuation if an alternative explanation for the bleeding is identified. If no alternative explanation is identified, treatment must be permanently discontinued.

Any Grade 3 ADRs require treatment temporary discontinuation <u>except</u> for any of the following:

- Transient (≤ 48 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management.
- Transient (≤ 48 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that is controlled with medical management.
- Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor.
- Any single Grade ≥ 3 drug-related transaminase, alkaline phosphatase, or bilirubin abnormality with no other associated laboratory (or other) abnormality that is not associated with symptoms or clinical manifestations of hepatitis. If the liver function abnormality not associated with symptoms or clinical manifestations of hepatitis has not resolved to Grade ≤ 1 within the subsequent 2 cycles (56 days), the subject should permanently discontinue treatment with M7824.
- Any single Grade ≥ 3 drug-related amylase or lipase abnormality with no other associated laboratory (or other) abnormality that is not associated with symptoms or clinical manifestations of pancreatitis. If the amylase or lipase abnormality not associated with symptoms or clinical manifestations of pancreatitis has not resolved to Grade ≤ 1 within the subsequent 2 cycles (56 days), the subject should permanently discontinue treatment with M7824.
- Grade 3 Hgb decrease (< 8.0 g/dL) that is clinically manageable with blood transfusions or erythroid growth factor use does not require treatment discontinuation.
- Increases in Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 3 that resolves to ≤ 2 by Day 1 of the next cycle (infusions should not be given if the ECOG PS is ≥ 3 on the day of M7824 administration and should be delayed until ECOG PS ≤ 2).
- Keratoacanthoma and squamous cell carcinoma of the skin. Any suspicious skin lesion should be biopsied for confirmation of diagnosis and be surgically removed as indicated by dermatologist and a dermatological consult obtained.
- Grade 3 non-tumor bleeding requiring intervention or hospitalization. Study treatment must be permanently discontinued unless an alternative explanation can be identified. In the case of alternative explanations for the Grade 3 bleeding event, study treatment should be held until recovery to at least Grade 1.
- Other infusion reactions and immune-related ADRs, see NCCN guidelines for the management of immune related adverse events (**Table 6**). NCCN guidelines are merely

suggestions based on current knowledge; however, given this is an evolving field, investigators are encouraged to consult professional guidelines.

- In addition to NCCN guidelines, the following recommendations should be considered when managing irAEs:
    - Permanent treatment discontinuation is required in case of immune-related Grade 4 rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, acquired thrombotic thrombocytopenic purpura inflammatory arthritis, myositis and polymyalgia-like syndrome.
    - For Grade 4 immune-related lymphopenia, permanent treatment discontinuation will be required, if lymphopenia is considered immune-related in nature, no clear alternative explanation exists for the event, and it does not resolve within 14 days. Permanent treatment discontinuation is not required when the AE is manifested by a single laboratory value out of normal range without any clinical correlates. In this case, treatment should be held until the etiology is determined. If the event is not considered immune-related and resolves to Grade $\leq$ 1, restarting treatment may be considered.
    - For Grade 1 immune-related pneumonitis: continue treatment. If clinically indicated, monitor participants weekly or more frequently as needed with history, physical examination and pulse oximetry. If symptoms appear and/or changes in the physical exam are noted, treat as Grade 2.
    - For myositis requiring management with rituximab, treatment should be discontinued.
    - For Grade 3 or 4 endocrinopathies: withhold until clinically stable or permanently discontinue depending on severity.
    - For hepatitis with no tumor involvement of the liver: withhold if total bilirubin increases to more than 1.5 and up to 3 times ULN, permanently discontinue if more than 3 times ULN
    - Hepatitis with tumor involvement of the liver: permanently discontinue if total bilirubin increases to more than 3 times ULN.

3.4.4.2 Infusion-related Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 48 hours after completion of infusion. These possible IRR are identified based on a list of MedDRA PTs and divided into reactions versus signs and symptoms.

- An IRR should be considered when onset is on the day of infusion (during or after the infusion) or the day after the infusion (irrespective of resolution date) for any infusion related reaction, drug hypersensitivity, anaphylactic reaction, hypersensitivity and/or Type 1 hypersensitivity.
- Signs and symptoms of infusion related reactions and hypersensitivity/allergic reactions should be considered when onset is on the day of infusion (during or after the infusion) and resolved completely with the end date within 2 days after onset. Signs and symptoms may include but not limited to: fever, chills or shaking, rigors, flushing, hypotension, wheezing, pruritus, rash and hypoxemia, shortness of breath, back or neck pain, facial swelling, dizziness, feeling of passing out.

Infusion-related reactions and hypersensitivity reactions (Grades 1 to 4) should be handled according to the best medical judgement based on the most updated professional guidelines (NCCN, ESMO, SITC, etc.). Guidelines provided in **Table 6** are merely suggestions based on current knowledge; however, given this is an evolving field, investigators are encouraged to consult the most updated professional guidelines.

Table 6: Treatment Modifications for Symptoms of Infusion-related Reactions

NCI-CTCAE Grade	Treatment Modification for M7824
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Consider decreasing the infusion rate of the particular agent by 50% and monitoring closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, i.e. fluids); prophylactic medications indicated for ≤ 24 hours.	Consider temporarily discontinuing infusion of the particular agent. Consider resuming infusion of the particular agent at 50% of previous rate once infusion related reaction has resolved or decreased to at least Grade 1 in severity and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening *Grade 3:* Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); hospitalization indicated for clinical sequelae. *Grade 4*: Life-threatening consequences; urgent intervention indicated.	Stop the infusion immediately and disconnect infusion tubing from the subject. For grade 3 events: Consider withdrawing immediately from treatment with that particular agent and not offering any further treatment with that agent based upon if the clinical condition can be safely managed. For grade 4 events: Withdraw immediately from treatment and do not offer further treatment with that agent.

If the infusion rate of M7824 has been decreased by 50% or interrupted due to an infusion reaction, keep it decreased for the next scheduled infusion. If no infusion reaction is observed in the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment.

If hypersensitivity reaction occurs, the subject should be treated according to the best available medical practice.

3.4.4.3 Severe Hypersensitivity Reactions and Flu-like Symptoms

If a hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice including ACLS guidelines.

Subjects should be instructed to report any delayed reactions to the Investigator immediately.

A. Symptoms

- Impaired airway
- Decreased oxygen saturation (< 92%)
- Confusion
- Lethargy
- Hypotension
- Pale / clammy skin
- Cyanosis

B. Management

- Epinephrine injection and IV dexamethasone
- Participant should be placed on cardiac, blood pressure, heart rate, and oxygen saturation monitor immediately
- Alert intensive care unit for possible transfer if required

For prophylaxis of flu-like symptoms, a NSAID, for example, ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each dose of M7824 IV infusion.

3.4.4.4 Immune-Related Adverse Events

Guidelines below are merely suggestions. If an immune-mediated reaction occurs, the subject should be treated according to the best available medical practice.

Table 7. Management of Immune Mediated Adverse Events (irAEs)

Gastrointestinal irAEs		
Severity of Diarrhea/Colitis (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Consider continuing M7824 Symptomatic treatment (e.g. loperamide)	Consider close monitoring for worsening symptoms Consider educating subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.

Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Consider withholding M7824 Symptomatic treatment	If improves to Grade ≤ 1: Consider resuming therapy If persists > 7 days or recurs: Consider treating as Grade 3 or 4.
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Consider withholding or permanently discontinuing M7824 for Grade 3 events based upon if the clinical condition can be safely managed. For grade 4 events permanently discontinue treatment. Consider 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Consider adding prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Consider continuing steroids until Grade ≤ 1, then tapering over at least 1 month; consider resuming therapy following steroids taper (for initial Grade 3). If worsens, persists > 7 days, or recurs after improvement: Consider adding infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.
Dermatological irAEs		
Grade of Rash (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 to 2 Covering ≤ 30% body surface area	Consider continuing M7824 Consider symptomatic therapy (for example, antihistamines, topical steroids)	If persists > 1 to 2 weeks or recurs: Consider withholding M7824 and OX40 therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, consider tapering steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and consider resuming M7824 therapy following steroids taper. If worsens: Consider treating as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Consider withholding or permanently discontinuing M7824 for Grade 3 events based upon if the clinical condition can be safely managed. For grade 4 events	If improves to Grade ≤ 1: Consider tapering steroids over at least 1 month; consider resuming therapy following steroids taper (for initial Grade 3).

	permanently discontinue treatment. Consider skin biopsy Consider dermatology consult Consider 1.0 to 2.0 mg/kg/day prednisone or equivalent Consider adding prophylactic antibiotics for opportunistic infections	
Pulmonary irAEs		
Grade of Pneumonitis (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Radiographic changes only	Consider withholding M7824 Consider Pulmonary and Infectious Disease consults	Consider re-assessing at least every 3 weeks If worsens: Consider treating as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Consider withhold M7824 Consider pulmonary and Infectious Disease consults Consider monitoring symptoms daily; consider hospitalization Consider 1.0 to 2.0 mg/kg/day prednisone or equivalent Consider adding prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves: When symptoms return to Grade ≤ 1, consider tapering steroids over at least 1 month, and then consider resuming therapy following steroids taper If not improving after 2 weeks or worsening: Consider treating as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Consider withholding or permanently discontinuing M7824 for Grade 3 events based upon if the clinical condition can be safely managed. For grade 4 events permanently discontinue treatment. Consider hospitalization. Consider pulmonary and Infectious Disease consults. Consider 1.0 to 2.0 mg/kg/day prednisone or equivalent Consider adding prophylactic	If improves to Grade ≤ 1: Consider tapering steroids over at least 1 month If not improving after 48 hours or worsening: Consider adding additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

	antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	
Hepatic irAEs		
Grade of Liver Test Elevation (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN	Consider continuing M7824	Consider continued liver function monitoring If worsens: Consider treating as Grade 2 or 3 to 4.
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Consider withhold M7824	If returns to Grade ≤ 1: Consider resuming therapy. If elevation persists > 7 days or worsens: Consider treating as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Consider withholding or permanently discontinuing M7824 for Grade 3 events based upon if the clinical condition can be safely managed. For grade 4 events permanently discontinue treatment. Consider 1.0 to 2.0 mg/kg/day prednisone or equivalent Consider adding prophylactic antibiotics for opportunistic infections Consider consulting gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Consider tapering steroids over at least 1 month If does not improve in > 7 days, worsens or rebounds: Consider adding mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 7 days, consider other immunosuppressants per local guidelines.
Renal irAEs		
Grade of Creatinine Increased (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Consider continuing M7824	Continue renal function monitoring If worsens: Consider treating as Grade 2 to 3 or 4.
Grade 2 Creatinine increased > 1.5 and ≤ 6 x	Consider withholding M7824 Consider 1.0 to 2.0 mg/kg/day	If returns to Grade ≤1: Consider tapering steroids over at least 1 month

ULN	prednisone or equivalent. Consider adding prophylactic antibiotics for opportunistic infections Consider renal biopsy	and consider resuming therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 3-4 Creatinine increased > 6 x ULN	Consider withholding or permanently discontinuing M7824 for Grade 3 events based upon if the clinical condition can be safely managed. For grade 4 events permanently discontinue treatment. Consider 1.0 to 2.0 mg/kg/day prednisone or equivalent. Consider adding prophylactic antibiotics for opportunistic infections Consider renal biopsy Consider Nephrology consult	If returns to Grade ≤1: Consider tapering steroids over at least 1 month.
Cardiac irAEs		
Myocarditis	**Initial Management**	**Follow-up Management**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Consider withholding or permanently discontinuing M7824 based upon if the clinical condition can be safely managed. Consider hospitalization In the presence of life-threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Consider cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, consider re-starting therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, consider managing as immune-mediated myocarditis.
Immune-mediated myocarditis	Consider withholding or permanently discontinuing M7824 based upon if the clinical condition can be safely managed. Consider guideline based supportive treatment as appropriate as per cardiology consult. Consider 1.0 to 2.0 mg/kg/day prednisone or equivalent Consider adding prophylactic antibiotics for opportunistic infections.	Once improving, consider tapering steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A).

1 *Local guidelines, or e.g. ESC or AHA guidelines
2 ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines
3 AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

Endocrine irAEs

Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Consider continuing M7824 Consider endocrinology consult if needed Consider starting thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Consider ruling-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Consider continuing hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Consider withholding or permanently discontinuing M7824 for Grade 3 events based upon if the clinical condition can be safely managed. For grade 4 events permanently discontinue treatment Consider hospitalization Consider endocrinology consult Consider starting thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Consider ruling-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Consider resuming therapy once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Consider continuing hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH): • Consider referring to endocrinologist for dynamic testing as indicated and	Consider resuming therapy once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, consider resuming M7824 only once shrinkage of the pituitary gland on MRI/CT scan is documented.

	measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Consider hormone replacement/suppressive therapy as appropriate • Consider performing pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue M7824 if mild symptoms • Consider withholding M7824 if moderate, severe or life-threatening symptoms of hypophysitis. Consider hospitalization. Consider initiating corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Consider adding prophylactic antibiotics for opportunistic infections.	Consider continuing hormone replacement/suppression therapy as appropriate.
Other irAEs (not described above)		
Grade of other irAEs (NCI-CTCAE v5)	**Initial Management**	**Follow-up Management**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Consider withholding M7824 pending clinical investigation	If irAE is ruled out, consider managing as appropriate according to the diagnosis and consider re-starting therapy If irAE is confirmed, consider treating as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Consider withholding M7824 based upon if the clinical condition can be safely managed. Consider 1.0 to 2.0 mg/kg/day prednisone or equivalent Consider adding prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Consider tapering steroids over at least 1 month and resuming therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Consider permanently discontinuing M7824 based upon if the clinical	If improves to Grade ≤ 1: Consider tapering steroids over at least 1

	condition can be safely managed; Consider 1.0 to 2.0 mg/kg/day prednisone or equivalent Consider adding prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	month.
Grade 4	Permanently discontinue M7824; Consider 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Consider adding prophylactic antibiotics for opportunistic infections Consider specialty consult as appropriate	If improves to Grade ≤ 1: Consider tapering steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Consider permanently discontinuing M7824 Consider specialty consult as appropriate	

3.4.4.4.1 Rash with Hyperkeratosis / Keratoacanthoma / Squamous Cell Carcinoma of the Skin

Dermatological consults will be requested on a case-by-case basis as needed with potential biopsy of suspicious skin lesions.

3.4.4.4.2 Suggested Evaluation of Suspected Bleeding or Hemorrhage Events and Treatment Modification

For anemia or hemorrhage events assessed as treatment-related, items queried may include but are not limited to detailed relevant past medical and treatment history, bruising tendency, history of blood transfusions and/or dependency, and a request for an updated participant history including details such as concomitant medications, all laboratory data, updated dosing information and recent tumor evaluation scans.

In this protocol, anemia may be due to M7824 (documented in 29% of patients based on pooled safety analysis set from a total of 765 participants, refer to IBv7) and/or SX-682. For M7824 anemia is an AESI and important identified risk (see Investigators' Brochure). Notably, there are many reasons for hemorrhage and/or anemia in patients with advanced cancer, and Hb level of at least 9 g/dL is required for this study. A thorough investigation of new anemia cases of unspecified etiology is recommended:

- Participants must enter the study with Hgb values at least 9 g/dL and baseline anemia evaluation is conducted per **recommendations below.**
- **Consider hematology consult for severe and or refractory anemias.**

- All relevant hematologic testing for treatment related anemias should be done prior to blood transfusion, if clinically feasible.
- Transfusion should be performed at the discretion of the investigator, based on clinical assessment and considered when participant experiences significant anemia.
- Guidance for evaluation of baseline anemia or suspected treatment-related anemias is provided below. Investigators may consider the following laboratory evaluations in participants with anemia.
    - Hb and CBC with differential (e.g. MCV, RDW, ANC, hematocrit, reticulocytes counts)
    - Peripheral blood smear for cell morphological assessment
    - Complete metabolic panel including liver panel-LFTs, bilirubin, LDH, renal function, and serum folate, B12 values and other chemistries
    - Coagulation factors (PT, PTT, INR)
    - Urinalysis including culture
    - Iron panel (TIBC, ferritin, Fe)
- Discuss further management with Principal Investigator for clinically significant treatment related anemias.

Multiple protocols using M7824, several mucosal bleeding events ranging from low grade gingival bleeding and epistaxis to more serious hemoptysis, GI bleeding and hematuria have been observed. Some of these events can be attributed to bleeding events related to cancer directly and others bleeding events can be attributed to an inflammatory process (e.g. colitis) which is a known toxicity of anti-PD-L1 agents including M7824. However, there remains the possibility that M7824 may increase the overall risk of bleeding in ways that may not be directly related to direct tumor bleeding or inflammatory bleeding events described with checkpoint inhibitors like M7824. However, there is no evidence of a negative effect on coagulation or platelet number or function. It is hypothesized that this possible increased mucosal bleeding risk may be due to the known mucoprotective effects of TGFβ. Accordingly, participants will be closely monitored for mucosal bleeding (e.g., gum bleeding, nose bleeds, coughing up blood, blood in their urine, or blood in the stool).

3.5 STUDY CALENDAR

	Screening	Baseline[1]	Lead-In (Days -14L to -1L)	Cycles [2] Cycle=28 (-1/+ 3) days		EOT[6]	Safety FU [7]	Long Term FU [8]
				Day 1	Day 15			
SX-682[3]			X	X	X			
M7824[4]				X	X			
MVA-BN-CV301 (Cycle 1 only)[5]				X	X			
FPV-CV301(Cycle 2 onward)[5]				X				
Medical History	X							
Height	X	X						
ECOG	X	X				X		
Clinical Assessment - physical exam, vital signs[18], weight	X	X		X	X	X	X	
HIV, HCV, HBV viral load by PCR	X							
CD4	X							
EKG [9]	X	X		X	X	X	X	
CBC w/differential with platelets	X	X		X	X	X	X	

	Screening	**Baseline**[1]	**Lead-In (Days -14L to -1L)**	**Cycles** [2] **Cycle=28 (-1/+ 3) days**		**EOT**[6]	**Safety FU** [7]	**Long Term FU** [8]
				Day 1	**Day 15**			
Biochemical profile[10]	X	X		X	X	X	X	
Lymphocyte profiling (TBNK), TSH, Free T4, lipase, amylase, urinalysis[11]	X	X		X				
Pregnancy testing in women of childbearing potential[12]	X	X		X		X		
PT/PTT/INR[11]	X	X		X				
Flexible clinic-based pharyngolaryngoscopy (HNSCC only) if clinically indicated	X	X		*as needed*				
Tumor evaluation (CT Scan / MRI, if clinically indicated)[13]	X			X				X
A brain CT / MRI scan (if clinically indicated) [14]	X							
Nuclear bone scan (if clinically indicated)	X							
Concomitant medications	X	X		X	X	X	X	
Adverse event evaluation				X	X	X	X	
Baseline signs and symptoms		X						

	Screening	Baseline[1]	Lead-In (Days -14L to -1L)	Cycles [2] Cycle=28 (-1/+ 3) days		EOT[6]	Safety FU [7]	Long Term FU [8]
				Day 1	Day 15			
Tumor biopsy (optional)[15]		X		X		X (at disease progression)		
Research blood [16]		See **Table 9** (Arm 1), **Table 10** (Arm 2), and **Table 11** (Arm 3)						
Telephone or E-mail Follow Up								X
Collection of archival tumor samples for research if available		X						
Diet Order (may be ordered during visits if clinically indicated)			X	X	X			
Confirmation of disease [17]	X							

[1]Baseline evaluations do not need to be repeated if performed at screening within 7 days of any first drug administration. If treatment does not start within 28 days after enrollment (or if specific longer), screening evaluations will be repeated.

[2] Participants will be seen in clinic every 2 weeks while on treatment. If treatment is being held, clinic visits may be missed and the associated labs will be deferred per the discretion of the PI. Due to COVID-19 pandemic, outside of the DLT period, if the participant is not able to return to the NIH CC for treatment/follow-up, remote visits will be conducted in compliance with NIH guidelines and FDA regulations. A participant may be referred to their local provider or asked to come to the NIH CC for an in-person assessment, if clinically indicated, and at the discretion of the PI. In the case of any visits with participants' local providers, records will be obtained.

[3] Arm 1: during Lead-In only. Arms 2 and 3: during Lead-In (Arm 2 only) and every day of every cycle. See **Table 8**

[4] On days 1 and 15 of every cycle. Can be -1/+3 days due to holidays, inclement weather, conflicts, or similar reasons except where explicitly noted elsewhere. M7824 drug administrations should not be given less than 11 days apart. See **Table 8**

[5] MVA-BN-CV301 will be given on days 1 and 15 of Cycle 1. FPV-CV301 will be given Day 1 of Cycles 2 through 5 then Day 1 of Cycle 8 and Cycle 11. Can be -1/+3 days due to holidays, inclement weather, conflicts, or similar reasons except where explicitly noted elsewhere. CV301 administrations should not be given less than 11 days apart. See **Table 8**

[6] EOT – End of treatment visit: Where feasible, on the day of or within 30 days of the decision to discontinue treatment prematurely before completion of one year of treatment. Does not need to be completed if drug is withheld after one year of treatment. Research labs will be collected if feasible. Participants continuing to experience toxicity at the off-treatment visit will be contacted for additional assessments until the toxicity has resolved or is deemed irreversible. Participants must remain on the study to have additional assessments completed

[7] 30 days (+/- 7 days) after last treatment. If subjects are not willing to come to NIH to FU visit, they will be contacted by phone to assess adverse events. Does not need to be repeated if EOT performed within this time frame.

[8] Participants who are taken off treatment for reasons other than disease progression, will be invited for optional imaging studies every 3 months (+/- 2 weeks) until they experience PD in order to assess PFS. If participants unable to come, participants will be followed by phone or email and outside images will be requested. Participants who opt out of these scans will have their data censored in data analysis at the time they become unfollowable for PFS. After progression and 30 days Safety Follow up visit, participants will be followed by phone or email for long-term clinical outcomes, and further tumor therapy every year for 2 years.

[9] EKGs will be done in triplicate on screening, before SX-682 administration at baseline and then every two weeks until cycle 6, at EOT and at the safety FU visit.

[10] Biochemical profile: sodium, potassium, magnesium, phosphorus, chloride, bicarbonate, calcium, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, and total and direct bilirubin.

[11] Performed every 8 weeks: Lymphocyte panel (TBNK), TSH, Free T4, lipase, amylase, urinalysis, PT/PTT/INR, unless there is a clinical concern that warrants evaluation on a more frequent basis

[12] For women of childbearing potential at screening and baseline serum pregnancy test must be performed, but on day 1 of each cycle and EOT, urine pregnancy test can also be used.

[13] In Arms 1 and 2, the first restaging will occur 6 weeks after starting treatment (+/- 1 week) and then every eight weeks (+/- 1 week). In Arm 3, restaging will occur every eight weeks (+/- 1 week). In the event of a PR or CR tumor imaging assessments may be performed every 3 months (+/- 2 weeks) at the discretion of the investigator. Tumor assessment should be continued beyond end of treatment in participants who have not experienced PD until they experience PD in order to assess PFS. In addition to a baseline scan, confirmatory scans can also be obtained 4 to 8 weeks following initial documentation of objective response per the discretion of the primary investigator. MRI of chest, abdomen and pelvis (if participant has contradiction to CT).

[14] Brain CT/MRI if there is a history of prior CNS metastasis or there is a concern for CNS involvement.

[15] Optional biopsies at baseline and as close as logistically feasible to first imaging restaging (+/- 1 week if possible). Optional biopsy also at time of progression. In addition, tissue collected during unscheduled procedures may also be collected for research purposes.

[16] Where feasible, research blood for all study assessments will be collected as per **Table 9, Table 10,** and **Table 11** below. The exact collection time for PK samples will be recorded
[17] See Section **2.2.2**
[18] Arms 1 & 2: Day -14, SX-682 oral administration; collect full set of vital signs pre dose and (180 minutes) 3 hours post dose at the time of last PK blood collection.

All 3 Arms: All cycles with CV301 & M7824 administration; collect a full set of vital signs pre CV301 vaccine administration and prior to start of M7824 infusion. During the M7824 infusion, collect a full set of vital signs every 30 minutes and at the end of the 60 minute observation period, for C1D1 and C1D15 doses. For the 3rd M7824 dose, C2D1 and all subsequent M7824 doses, the observation period is 30 minutes, a full set of vital signs will be collected at that time.

Table 8: Study Drug Administration

Arm 1:

Lead-In (days)	**Cycle 1**		**Cycle 2 until Progression**	
Days -14L to -1L	**C1D1**	**C1D15**	**CxD1**	**CxD15**
SX-682				
	M7824	M7824	M7824	M7824
	MVA-BN-CV301	MVA-BN-CV301	FPV-CV301*	

*Given every cycle for 4 cycles, then every 3 cycles for 2 additional doses (total of 1 year of vaccines).

Arm 2:

Lead-In (days)	**Cycle 1**		**Cycle 2 until Progression**	
Days -14L to -1L	**C1D1**	**C1D15**	**CxD1**	**CxD15**
SX-682	SX-682 → → → → → → → → → → → → → → →			
	M7824	M7824	M7824	M7824
	MVA-BN-CV301	MVA-BN-CV301	FPV-CV301*	

*Given every cycle for 4 cycles, then every 3 cycles for 2 additional doses (total of 1 year of vaccines).

Arm 3:

Cycle 1		**Cycle 2 until Progression**	
C1D1	**C1D15**	**CxD1**	**CxD15**
SX-682 Continuous			
M7824	M7824	M7824	M7824
MVA-BN-CV301	MVA-BN-CV301	FPV-CV301*	

*Given every cycle for 4 cycles, then every 3 cycles for 2 additional doses (total of 1 year of vaccines).

Table 9 Arm 1 Research Blood Draws

Cycle (Day)	**Time**	**SX-682**	**M7824**		**Immune and Other Analyses**		
		PK	**PK**	**ADA**	**Soluble Factors**	**Immune phenotyping/ RNA analysis, Antigen-specific response, T-cell clonality**	**CTCs**
Lead-In (-14L)	predose	X	Not given until C1D1	Not given until C1D1	X	X	X
	30 minutes	X					
	60 minutes	X					
	120 minutes	X					
	180 minutes	X					
	< 6 hours of 2nd dose	X					
Lead-In (-7L) *	predose	X					

Cycle (Day)	**Time**	**SX-682**	**M7824**		**Immune and Other Analyses**		
		PK	**PK**	**ADA**	**Soluble Factors**	**Immune phenotyping/ RNA analysis, Antigen-specific response, T-cell clonality**	**CTCs**
	30 minutes	X					
Cycle 1 (1)	predose	X	X	X	X	X	X
	End of Infusion (EOI)	X	X				
Cycle 1 (15)		X			X	X	
Cycle 2 (1)	predose	X			X	X	X
Cycle 3 (1)**	predose	X	X**	X**	X	X	
EOT			X	X	X	X	

*Lead-In, Day -14L labs only for Cohort 1, Arm 1 (Sequential Dose Escalation).
**The last M7824 PK/ADA timepoint should be Cycle 3, Day 1 predose or EOT, whichever comes first.

Table 10: Arm 2 Research Blood Draws

Cycle (Day)	**Time**	**SX-682**	**M7824**		**Immune and Other Analyses**		
		PK	**PK**	**ADA**	**Soluble Factors**	**Immune phenotyping/ RNA analysis, Antigen-specific response, T-cell clonality**	**CTCs**

Cycle (Day)	**Time**	**SX-682**	**M7824**		**Immune and Other Analyses**		
		PK	**PK**	**ADA**	**Soluble Factors**	**Immune phenotyping/ RNA analysis, Antigen-specific response, T-cell clonality**	**CTCs**
Lead-In (-14L)	predose	X	Not given until C1D1	Not given until C1D1	X	X	X
Cycle 1 (1)	predose	X	X	X	X	X	X
	EOI	X	X				
Cycle 1 (15)		X			X	X	
Cycle 2 (1)	predose	X	X	X	X	X	X
Cycle 3 (1)*	predose	X	X*	X*	X	X	
EOT		X	X	X	X	X	

*The last M7824 PK/ADA timepoint should be Cycle 3, Day 1 predose or EOT, whichever comes first.

Table 11: Arm 3 Research Blood Draws

Cycle (Day)	**Time**	**Immune and Other Analyses**			
		Soluble Factors	**Immune phenotyping/ RNA analysis, Antigen-specific response, T-cell clonality**	**CfDNA**	**CTCs**

Cycle (Day)	**Time**	**Immune and Other Analyses**			
		Soluble Factors	**Immune phenotyping/ RNA analysis, Antigen-specific response, T-cell clonality**	**CfDNA**	**CTCs**
Cycle 1 (1)	predose	X	X	X	X
Cycle 1 (15)	predose	X	X	X	
Cycle 2 (1)	predose	X	X	X	X
Cycle 3 (1)	predose	X	X	X	
EOT		X	X	X	

3.6 COST AND COMPENSATION

3.6.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.6.2 Compensation

There will no compensation provided in this study.

3.6.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.7 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, efforts must be made to have all subjects complete a safety visit approximately 30 days (+/- 7 days) following the last dose of study therapy.

3.7.1 Criteria for Removal from Protocol Therapy

- Participant request to be withdrawn from active therapy
- Confirmed clinical or radiographic progression of disease except when the investigator feels the subject is still benefiting from treatment. **NOTE:** treatment may be continued despite progression according to RECIST 1.1 at any time if:
  - There are no new or concerning symptoms.
  - There is no decrease in ECOG PS.
  - The Investigator does not consider it necessary to administer a salvage therapy.
- Unacceptable Toxicity as described in sections **3.3**
- Investigator discretion
- Positive pregnancy test
- Need to use restricted medication, section **4.1**
- Completion of 2 years of therapy unless the PI feels that the participant continues to gain benefit from two or more of the trial drugs and discusses continuing on trial with the CRADA partners for an additional specified period of time.

3.7.2 Off -Study Criteria

- Completion of 2 years follow-up period after confirmed disease progression
- PI decision to end the study
- Participant lost to follow up

- Investigator discretion
- Death
- Participant request to be withdrawn from the study
- Screen Failure

3.7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, an IRB approved certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

Any medications (other than those excluded by the clinical trial protocol) that are considered necessary to protect subject welfare or alleviate symptoms and will not interfere with the trial medications may be given at the Investigator's discretion.

Palliative radiotherapy delivered in a normal organ-spearing technique may be administered during the trial. The assessment of PD will not be based on the necessity for palliative radiotherapy.

4.1 THE FOLLOWING TREATMENTS SHOULD NOT BE ADMINISTERED DURING THE TRIAL:

- Other immunotherapies or immunosuppressive drugs for example, chemotherapy or systemic corticosteroids except for prophylaxis or treatment of allergic reactions, endocrine replacement therapy at low dose prednisone [≤ 10 mg daily] or equivalent, for the treatment of irAEs, or for short courses (≤ 14 days) as appropriate medical therapy for unrelated medical conditions (e.g. asthma). Steroids with no or minimal systemic effect (topical, inhalation) are allowed.
- Prophylactic use of corticosteroids for infusion related reactions. Corticosteroid administration prior to CT scans in participants with intravenous contrast allergy is allowed.

- QTc prolonging drugs: The drug-drug interactions of SX-682 in humans have not yet been determined. However, due to its in vitro inhibition of hERG, concomitant dosing of SX0682 with drugs known to have a clinically significant prolongation the QT interval (See **Appendix B**), such as pimozide and thioridazine, should be avoided until further human EKG data is gathered. Drugs that may conditionally prolong QTc that are not included in **Appendix B**, maybe be used with caution after reviewing the risks/benefits and potential alternative options. QTc prolonging agents are not prohibited in participants no longer receiving SX-682.
- In vitro studies indicate SX-682 inhibits CYP2C8. Medications that are substrates of this enzyme may have altered metabolism when administered concurrently with SX-682. CYP2C8 substrates will be evaluated on a case-by-case basis prior to concurrent use with SX-682. Updated drug-information resources should be consulted

  (e.g. https://drug-interactions.medicine.iu.edu/MainTable.aspx).
- Any live vaccine therapies for the prevention of infectious disease. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines). Locally approved COVID vaccines are permitted.
- Systemic anticancer treatment other than the investigational agents in this trial except for disease specific appropriate hormonal therapies (e.g., ADT for prostate cancer, anti-estrogen for breast cancer, somatostatin analogue for neuroendocrine cancer).
- All anticoagulation drugs will be reviewed by the investigator to determine the potential for interactions or potential safety concerns with the investigational agents. Any anticoagulation agent deemed to have a potentially clinically significant interaction with the investigational agent(s) by the investigator should not be administered while on the clinical trial.
- All herbal supplements will be reviewed by the investigator to determine the potential for herbal interactions or potential safety concerns with the investigational agents. Any herbal supplement deemed to have a potentially clinically significant interaction with the investigational agent(s) by the investigator should not be administered while on the clinical trial.

5 CORRELATIVE STUDIES FOR RESEARCH

Biospecimens will be evaluated to help identify the effect of the study dugs on the immune response before and after treatment, to gain insight into potential biomarkers, and help improve the administered therapy.

5.1 SAMPLES

5.1.1 Tumor Samples

Where available, archival tumor samples will be requested.

Optional biopsies may be performed as per Study Calendar **3.5**. Attempts will be made to obtain up to six cores (18G or 20G preferred) or direct biopsies with biopsy forceps if safe and feasible. These tumor core biopsies will be obtained percutaneously by interventional radiology as long as considered minimal procedural risk. Direct biopsies with biopsy forceps will be obtained by Otolaryngology as long as considered minimal procedural risk. Two 3-millimeter punch biopsies

of skin will be acceptable in lieu of 18-gauge core biopsies for participants with skin involvement.

- Cores/biopsies 1 and 2: Formalin-Fixed Paraffin-Embedded (FFPE)
- Cores/biopsies 3 and 4: Fresh frozen
- Cores/biopsies 5 and 6: Fresh for flow cytometry or TIL culture

Tissue samples will be sent to Laboratory of Pathology for disease evaluation first, remaining samples will be processed and stored for research. If fresh-frozen cores are obtained, they will be processed and stored in CSP. Samples will be picked up and delivered for processing and storage by:

[redacted]

If fresh tissue to be used for flow cytometry or TIL culture are obtained, they will be processed and stored in the Translational Tumor Immunology Program (TTIP) Laboratory ([redacted]

[redacted]

5.1.2 Blood samples

The amount of blood that may be drawn from adult participants (i.e., those persons 18 years of age or older) for research purposes will not exceed 10.5 mL/kg or 550 mL, whichever is smaller, over any eight-week period. Please, see Study Calendar **3.5** for collection time points.

5.2 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

The following tests may be performed on selected participants' peripheral blood samples if there are adequate samples. If collected samples are not sufficient, the correlative studies will be performed in the order of priority as detailed below in the table. These correlative studies will be done in an exploratory fashion.

Research samples will be sent either to Blood Processing Core (BPC), or Clinical Services Program – Leidos Biomedical Research, Inc. (CSP) or the TTIP Laboratory for barcoding, initial processing and storage. From these facilities samples will be sent to the designated places for analysis in batch shipments or upon request.

All samples collected for correlative studies will be stored in locked rooms with limited access to study personnel.

Test/assay	**Volume (approx.)**	**Type of tube[a]**	**Collection point**	**Location of specimen analysis (processing/storage location)**
Functional Analysis of immune cell subsets by FACS	60-80 mL blood for PBMCs	Sodium heparin (green	Study Calendar **3.5**	LTIB, TTIP (CSP)

Test/assay	Volume (approx.)	Type of tube[a]	Collection point	Location of specimen analysis (processing/storage location)
Antigen Specific Immune Response by cytokine staining assay		top) tubes		LTIB (CSP)
T cell clonality by immunoSeq platform				NCI Frederick Genomic Core Facility (CSP)
RNA expression, Nanostring				NCI Frederick Genomic Core Facility, Nanostring (CSP)
Soluble Factors by ELISA	8 mL blood for serum	SST		LTIB (CSP)
SX-682 Pharmacokinetics	3-6 mL blood for plasma	EDTA		Syntrix, (BPC)
M7824 Pharmacokinetics	4 mL blood for serum	SST		EMD Serono (BPC)
ADA	4 mL blood for serum	SST		EMD Serono (BPC)
cfDNA	10 mL blood	EDTA (lavender top) tubes		Dr Liang Cao (CSP)
CTCs	10 ml blood	CellSave		Dr Jane Trepel
Analyses of Immune Markers by IHC and/or multiplex immunofluorescence	Tumor samples			LTIB (LP, CSP)
T cell clonality by immunoSeq platform	Tumor samples			NCI Frederick Genomic Core Facility (LP, CSP)
RNA expression, Nanostring	Tumor samples			NCI Frederick Genomic Core Facility, Nanostring (LP, CSP)
Analysis of immune	Tumor			TTIP (TTIP)

Test/assay	Volume (approx.)	Type of tube[a]	Collection point	Location of specimen analysis (processing/storage location)
infiltration by flow cytometry/ELISA	samples			

a. Please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator.

5.2.1 Immune Phenotyping

Exploratory immunologic studies will be conducted to evaluate the study drug's effect on the immune response before and after treatment, to gain insight into potential biomarkers, and help improve the administered therapy. The following immune assays may be performed:

1. PBMCs may be analyzed for changes in standard immune cell types (CD4 and CD8 T cells, natural killer [NK] cells, regulatory T cells [Tregs], myeloid-derived suppressor cells [MDSCs], and dendritic cells) as well as 123 immune cell subsets, using multi-color flow cytometry.
2. PBMCs from selected subjects may be analyzed for function of specific immune cell subsets, including CD4 and CD8 T cells, NK cells, Tregs, and MDSCs using flow-based assays.
3. PBMCs may be analyzed for tumor antigen-specific immune responses using an intracellular cytokine staining assay. PBMCs will be stimulated in vitro with overlapping 15-mer peptide pools encoding the tumor-associated antigens such as CEA, MUC-1 and Brachyury; control peptide pools will involve the use of human leukocyte antigen peptide as a negative control and CEFT peptide mix as a positive control. CEFT is a mixture of peptides of CMV, Epstein-Barr virus, influenza, and tetanus toxin. Post-stimulation analyses of CD4 and CD8 T cells will involve the production of IFN-γ, IL-2, TNF, and the degranulation marker CD107a. If sufficient PBMCs are available, assays may also be performed for the development of T cells to other tumor-associated antigens.

5.2.2 Soluble Factors

-Sera and/or plasma may be analyzed pre- and post-therapy for the following soluble factors: sCD27, sCD40 ligand using commercial ELISA kits.

-Sera and/or plasma may be analyzed for changes in cytokines (IFN-γ, IL-8, IL-6, IL-10, IL-12, IL-2, IL-4, etc.), chemokines, antibodies, tumor-associated antigens, and/or other markers using ELISA or multiplexed assays (e.g. Mesoscale, Luminex, cytokine bead array).

5.2.3 Pharmacokinetics

Plasma and Serum samples may be analyzed by a validated immunoassay to quantitate SX-682 and M7824 concentration, respectively. Samples may be further tested in qualified or validated PK characterization assays. Coded, linked samples will be shipped to Syntrix and EMD Serono for analysis under existing CRADAs with these companies.

5.2.4 ADA

Serum samples may be analyzed by a validated electrochemiluminescence immunoassay (ECLA) to detect the presence of anti-M7824. Samples that screen positive will be subsequently tested in a confirmatory assay. Those confirmed positive will be titered for a quasi-quantitative result. Samples may be further tested in qualified or validated immunogenicity characterization methods. The investigation will be done by Syntrix and EMD Serono for analysis under existing CRADAs with these companies.

5.2.5 Analyses of Tumor Tissue for Immune Markers

Biopsy samples may be used to study immune infiltration as well as PD-L1 status within the tumor microenvironment pre vs. post treatment by IHC and/or multiplex immunofluorescence. Biopsies may be subjected to dissociation and analysis by flow cytometry to determine immune infiltration. Tumor infiltrating lymphocytes may be cultured from biopsies for assessment of T cell clonality and antigen specificity.

Tumor samples will be sent to the Laboratory of Pathology at NIH for disease evaluation; remaining samples will be used for research.

5.2.5.1 Antigen-specific T cell responses to CEA, MUC1 and the cascade antigen brachyury in tumor biopsies.

Tumor infiltrating lymphocytes (TIL) may be cultured from tumor fragments in standard T cell media with high dose recombinant human IL-2 (6000 U/mL). CD8 and CD4 TIL will be purified from cultured TIL using pan T cell negative magnetic selection. B cells will be sorted from PBMC using negative magnetic isolation and will be expanded using flt3-expressing 3T3 cells and IL-7. Expanded B cells will serve as autologous antigen presenting cells for coincubation assays. B cells will be electroporated with full length capped and tailed mRNA encoding for MUC1, CEA or the cascade antigen brachyury. Autologous B cells loaded with mRNA will be co-incubated with TIL cultured from tumor fragments (2:1 APC: T cell ratio) and IFNg production will be measured by ELISA.

5.3 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.3.1 RNA and T-cell Receptor Clonality Analysis of Blood and Tumor Tissue

RNA expression and T-cell receptor clonality analysis may be done on the peripheral blood as well as archived tumor tissue or optional biopsies to help further evaluate changes in immune response and RNA expression levels with treatment as well as to determine tumor and infiltrating lymphocyte characteristics which may be predictive of response to treatment. In addition, these analyses will also be used to gauge resistance mechanisms and additional targets for future therapy. Digital Spatial Profiling (DSP) including RNA in situ hybridization may also be performed on tissue for spatially resolved high plex profiling of RNA and protein targets. De-identified, coded samples may be analyzed for RNA expression levels and DSP using the Nanostring platform and T-cell receptor clonality using the ImmunoSeq platform (LTIB and NCI Frederick Genomic Core Facility).

NCI Fredrick Genomic Core Facility:

Leidos Biomedical Research, Inc:

[redacted]

[redacted]

5.3.2 Plasma analysis for circulating free DNA (cfDNA):

Plasma may be analyzed pre- and post-therapy in [redacted] for circulating free tumor DNA using PCR-based techniques.

5.3.3 Analysis for Circulating Tumor Cells (CTCs)

Plasma may be analyzed pre- and post-therapy in [redacted] for circulating tumor cells. TCs enumeration will be investigated using ferrofluidic enrichment and multi-parameter flow cytometric detection. CTCs are identified by positive expression of epithelial markers and a viability marker and negative expression of hematopoietic markers.

5.4 Sample Storage, Tracking and Disposition

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside the National Institutes for Health (NIH) without appropriate approvals and/or agreements, if required.

5.4.1 Sample Management and Storage at Clinical Services Program – Leidos Biomedical Research, Inc. (CSP)

Clinical Services Program - Leidos Biomedical Research, Inc.

[redacted]

All data associated with the participant samples is protected by using a secure database. All samples drawn at the NIH Clinical Center will be transported to the Clinical Support Laboratory at the Frederick National Laboratory for Cancer Research by couriers.

Samples will be tracked and managed by Central Repository database, where there is no link to personal identifiable information. All samples will be stored in either a -80ºC freezer or vapor phase liquid nitrogen. These freezers are located at NCI Frederick Central Repository in Frederick, Maryland.

NCI Frederick Central Repositories (managed under a subcontract) store, among other things, biological specimens in support of NIH clinical studies. All specimens are stored in secure, limited-access facilities with sufficient security, backup, and emergency support capability and monitoring to ensure long-term integrity of the specimens for research.

Specimens are stored in accordance with applicable HHS and FDA Protection of Human Subjects Regulations in accordance with the subcontractor's Federal-wide Assurance. The subcontractor's role limited to clinical research databases and repositories containing participant specimens. The subcontractor does not conduct or have any vested interest in research on human subjects but does provide services and support the efforts of its customers, many of which are involved in research on human subjects. The subcontractor's IRB reviews policies and procedures for labeling, data collection and storage, access, and security. The IRB will review protection of privacy issues prior to acceptance of any new work and in the event of change impacting privacy issues in existing work.

It is the intent and purpose of the subcontractor to accept only de-identified samples and sample information. To the limit of our ability, every effort will be made to ensure that protected information is not sent electronically or by hard copy or on vial labels.

Sample data is stored in the BioSpecimen Inventory System II (BSI). This inventory tracking system is used to manage the storage and retrieval of specimens as well as to maintain specimen data. BSI is designed for controlled, concurrent access. It provides a real-time, multi-user environment for tracking millions of specimens. The system controls how and in what order database updates and searches are performed. This control prevents deadlocks and race conditions. For security, BSI has user password access, 3 types of user access levels, and 36 user permissions (levels of access) that can be set to control access to the system functions. BSI provides audit tracking for processes that are done to specimens including shipping, returning to inventory, aliquoting, thawing, additives, and other processes. BSI tracks the ancestry of specimens as they are aliquoted, as well as discrepancies and discrepancy resolution for specimens received by the repository. If a specimen goes out of the inventory, the system maintains data associated with the withdrawal request. Vials are labeled with a unique BSI ID which is printed in both eye-readable and bar-coded format. No participant-specific information is encoded in this ID.

Investigators are granted view, input, and withdrawal authority only for their specimens. They may not view specimen data or access specimens for which they have not been authorized.

Access to specimen storage is confined to repository staff. Visitors to the repositories are escorted by repository staff at all times.

[redacted]

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to participants without Labmatrix access. The data recorded for each sample includes the participant ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Participant demographics associated with the clinical center participant number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

Sample bar-codes are linked to participant demographics and limited clinical information. This information will only be provided to investigators listed on this protocol, via registered use of the Labmatrix. It is critical that the sample remains linked to participant information such as race, age, dates of diagnosis and death, and histological information about the tumor, in order to correlate genotype with these variables.

5.4.2.3 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80^{0}C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in Labmatrix. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the NIH Intramural IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with NIH Intramural IRB approval.

Following completion of this study, samples will remain in storage as detailed above. Access to these samples will only be granted following NIH Intramural IRB approval of an additional protocol, granting the rights to use the material.

If, at any time, a participant withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the participant, if so requested)

The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be made per the requirements of section **7.2**.

5.4.3 Translational Tumor Immunology Program (TTIP) Laboratory, [redacted]

All samples are physically stored in [redacted] in secure, limited-access facilities with sufficient security, backup, and emergency support capability and monitoring to ensure long-term integrity of the specimens for research. Samples are logged, barcoded and tracked using Freezerworks Summit. This data storage software allows secure tracking of specimens that are completely de-identified, coded linked and tracked with barcodes only. Freezerworks has the capacity to fully audit all individual specimen processes such as location, aliquoting, thawing and shipping. Acquired samples are immediately transported to the NIDCD tissue core where

they are processed and barcoded. The participant sticker that was used for transport is immediately destroyed. Unique barcodes generated for each individual sample are linked to participant identification numbers given to laboratory staff by NIDCD research nurses. These unique participant numbers correspond to participant information that is stored in CTDM. Protected participant information in CTDM will be recorded by NIDCD Research Nurses. Aside from the participant label that is immediately destroyed after specimen transport, laboratory staff will not have access to protected participant information.

Investigators are granted view, input, and withdrawal authority only for their specimens. They may not view specimen data or access specimens for which they have not been authorized. Access to specimen storage is confined to repository staff. Visitors to the repositories are escorted by repository staff at all times

Tissue biopsies will be ordered in CRIS and any linked protected participant data will be stored in the Clinical Trial Data Management (CTDM) system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. All tissue biopsies collected will be coded and stored in the NIDCD Biospecimen Tissue Bank.

[redacted]

5.4.4 Procedures for Storage of Tissue Specimens in the Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly, and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissue that is not embedded in paraffin is stored in formalin for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the participant was enrolled.

[redacted]

5.4.5.2 Sample Processing

Samples will be processed immediately upon receipt by the [redacted]. Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and

participant confidentiality. Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented, and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. Specimen labels will indicate protocol number, order in which the participant enrolled on the trial, type of sample, as appropriate. The inventory process contains other security provisions sufficient to safeguard participant privacy and confidentiality. Access to the inventory system and associated documents is restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved by the trial Principal Investigator. SOPs ensure that any changes in informed consent made by a participant and relayed to the trial Principal Investigator will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel are trained to adhere to SOPs and are monitored for high-quality performance. Samples are stored in labeled boxes in secured freezers (i.e., -80°C, liquid nitrogen or other, as appropriate) according to stability requirements. These freezers are located in the [redacted]

5.4.6 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described in sections above. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed.

The PI will record any loss or unanticipated destruction of samples as a deviation. Reports will be per the requirements of section **7.2**.

If the participant withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event.

Document AEs from the administration of the first study intervention through 30 after the study agent (s) was/were last administered. Beyond 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be recorded in the database as an AE only if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study

- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

Adverse Events of grade 1 will not be collected.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, his will be reported expeditiously per requirements in section **7.2.1**

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

The PI will share coded linked human data generated in this research for future research

- in a NIH-funded or approved public repository clinicaltrials.gov and dbGaP
- in BTRIS
- in publication and/or public presentations
- with approved outside collaborators under appropriate agreements
- at the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy.

6.3 RESPONSE CRITERIA

For the purposes of this study, participants should be re-evaluated for response according to schedule in the Study Calendar, section **3.5**.

In the event of a PR or CR tumor imaging assessments may be performed every 3 months (+/- 2 weeks) at the discretion of the investigator. In addition to a baseline scan, confirmatory scans can also be obtained 4 to 8 weeks following initial documentation of objective response per the discretion of the primary investigator.

The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT of the chest without contrast and MRI scan of the abdomen/pelvis is preferred. Additional assessment of tumor response may include the following evaluations; nuclear bone scan for subjects with known/suspected bone lesions; and CT or MRI scan of the brain (only as clinically warranted based on symptoms/findings).

Brain CT / MRI scan should be performed, if clinically indicated by development of new specific symptoms or on the discretion of the Primary Investigator. For each subject, the Investigator will

designate 1 or more of the following measures of tumor status to follow for determining response: CT or MRI images of primary and / or metastatic tumor masses, physical examination findings, and the results of other assessments. All available images collected during the trial period will be considered. The most appropriate measures to evaluate the tumor status of a subject should be used. The measure(s) to be chosen for sequential evaluation during the trial have to correspond to the measures used to document the progressive tumor status that qualifies the subject for enrollment.

Progressive disease should be confirmed by imaging 4 to 8 weeks (preferably at 4 weeks, but not more than 8 weeks) after progression has been diagnosed according to RECIST 1.1. before the participant is removed from treatment [93]. If progression is based on the occurrence of a new lesion in an area not scanned at Baseline, a further on-study scan 4 to 8 weeks later should be considered before performing the 28-Day Safety Follow-up visit.

Tumor responses to treatment will be assigned based on the evaluation of the response of target, non-target, and new lesions according to RECIST 1.1 (all measurements should be recorded in metric notation).

To assess objective response, the tumor burden at baseline will be estimated and used for comparison with subsequent measurements. At baseline, tumor lesions will be categorized in target and non-target lesions according to RECIST 1.1.

Results for these evaluations will be recorded with as much specificity as possible so that pre and post-treatment results will provide the best opportunity for evaluating tumor response.

The Investigator may perform scans in addition to a scheduled trial scan for medical reasons or if the Investigator suspects PD.

iRECIST will also be used for exploratory endpoints (See section **6.3.3)**

For the primary endpoint antitumor activity will be evaluated with target and/or non-target lesions according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. [93].

Palliative radiotherapy delivered in a normal organ-spearing technique may be administered during this trial. The assessment of PD will not be based on the necessity for palliative radiotherapy.

If a target lesion is radiated during the course of treatment, this target lesion will no longer be considered a measurable lesion and will be removed from the target lesion sum moving forward as is recommended in RECISTv1.1.

6.3.1 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:

- By chest x-ray: ≥20 mm;
- By CT scan:
    - Scan slice thickness 5 mm or under: as ≥10 mm
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Tumor lesions that are situated in a previously irradiated area may be considered measurable if there is demonstrated progression in the radiated lesion prior to starting on the trial.

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 participant, 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.

6.3.2 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 not acceptable as measurable lesions.

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 participant 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. [94-96] 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.[97]

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

Evaluation of Target Lesions

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

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

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

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

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

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

Evaluation of Best Overall Response

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

Table 12. Response Criteria for Participants 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 to 8 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 to 8 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: Participants 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 Participants 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		

6.3.3 iRECIST

As an exploratory endpoint antitumor activity will also be evaluated according to iRECIST.[98] Using iRECIST criteria the following will be incorporated into the assessment:

- An increase in the sum of target lesions of more than 20%, unequivocal increase in the non-target lesions or new lesions result in iUPD (unconfirmed progression disease); iUPD can be assigned multiple ties as long as iCPD (confirmed progressive disease) is not confirmed at the next assessment.
- Progression is confirmed in the target lesion category if the next imaging assessment after iUPD (4-8 weeks later) confirms a further increase in sum of measures of target disease from iUPD, with an increase of at least 5mm. Progression is confirmed in the non-target lesion category if subsequent imaging, done every 4-8 weeks after iUPD shows a further unequivocal increase in non-target lesions. Progression is confirmed in the new lesions category if at next assessment additional new lesions appear or an increase in the size of previously seen new lesions is seen (≥5 mm for sum of new target lesion).

However, the criteria for iCPD (after iUPD) are not considered to have been met if complete response, partial response or stable disease criteria (compared with baseline and as defined by RECIST 1.1) are met at the next assessment after iUPD. The status is reset (unlike RECIST 1.1, in which any progression precludes later complete response, partial response, or stable disease). iCR, iPR, or iSD should then be assigned; and if no change is detected, then the timepoint response is iUPD.

6.3.4 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.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met.

6.3.5 Progression-Free Survival (PFS)

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

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found at: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#Policies&Guidance-800Series-ComplianceandResearchEventReportingRequirements.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in the NIH eIRB system will also be reported to the NCI Clinical Director/designee; therefore, a separate submission for these reports is not necessary.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death t[redacted]

7.4 INSTITUTIONAL BIOSAFETY COMMITTEE (IBC) REPORTING CRITERIA

7.4.1 Serious Adverse Event Reports to IBC

The Principal Investigator (or delegate) will notify IBC of any unexpected fatal or life-threatening experience associated with the use of CV301 vaccines as soon as possible but in no

event later than 7 calendar days of initial receipt of the information. Serious adverse events that are unexpected and associated with the use of the CV301 vaccines, but are not fatal or life-threatening, must be reported to the NIH IBC as soon as possible, but not later than 15 calendar days after the investigator's initial receipt of the information. Adverse events may be reported by using the FDA Form 3500a.

7.4.2 Annual Reports to IBC

Within 60 days after the one-year anniversary of the date on which the IBC approved the initial protocol, and after each subsequent anniversary until the trial is completed, the Principal Investigator (or delegate) shall submit the information described below. Alternatively, the IRB continuing review report can be sent to the IBC in lieu of a separate report. Please include the IBC protocol number on the report.

7.4.3 Clinical Trial Information

A brief summary of the status of the trial in progress or completed during the previous year. The summary is required to include the following information:

- the title and purpose of the trial
- clinical site
- the Principal Investigator
- clinical protocol identifiers;
- participant population (such as disease indication and general age group, e.g., adult or pediatric);
- the total number of participants planned for inclusion in the trial; the number entered into the trial to date whose participation in the trial was completed; and the number who dropped out of the trial with a brief description of the reasons
- the status of the trial, e.g., open to accrual of subjects, closed but data collection ongoing, or fully completed,
- if the trial has been completed, a brief description of any study results.

7.4.4 Progress Report and Data Analysis

Information obtained during the previous year's clinical and non-clinical investigations, including:

- a narrative or tabular summary showing the most frequent and most serious adverse experiences by body system
- a summary of all serious adverse events submitted during the past year
- a summary of serious adverse events that were expected or considered to have causes not associated with the use of the gene transfer product such as disease progression or concurrent medications
- if any deaths have occurred, the number of participants who died during participation in the investigation and causes of death

a brief description of any information obtained that is pertinent to an understanding of the gene transfer product's actions, including, for example, information about dose-response, information from controlled trials, and information about bioavailability.

7.5 NIH Required Data and Safety Monitoring Plan

7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when participants are being actively treated on the trial to discuss each participant. Decisions about dose level enrollment and dose escalation will be made based on the toxicity data from prior participants. Evaluation of DLTs (eDLTs; Schema 1 and 2) will occur after all participants are enrolled on a given dose level.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7.5.2 Data Safety Monitoring Board (DSMB)

The DSMB is an independent group of at least 3 experts that monitors participant safety and advises The Sponsor. DSMB members will be separate and independent of study staff participating in this trial and should not have scientific, financial, or other conflicts of interest related to this trial. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of data from this trial. A quorum will consist of a simple majority.
The DSMB will review cumulative safety data from this trial at least annually.
The DSMB will meet when trial halting criteria (see Section **3.2)** are met, or as requested by the sponsor or PI.
The DSMB will have a final review meeting at the end of the study.
Procedures for DSMB reviews/meetings will be defined in the DSMB charter. The DSMB will review applicable data, including, but not limited to, enrollment, demographics, dosing data, clinical laboratory data, and safety data, at scheduled timepoints during this trial as defined in the DSMB charter. The DSMB will review blinded aggregate data in the open session of the DSMB meetings.
Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by the Sponsor. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study product administration, and to continue, modify, or terminate this trial.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Event

Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (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 related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization:
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for participant convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 5.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.

- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product(s) and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs assessed as severe allows ongoing surveillance of these events to characterize and understand them in association with the use of these investigational products. Only AESIs that match the definition of SAE will be reported within 7 days from the knowledge of event. Other non-SAE AESIs do not need to be reported to OSRO but only collected in the clinical database.
The adverse events related to mucosal bleeding, regardless of site, will be collected as an AESI to enable evaluation of potential risk factors, such as site/past radiation/associated infection at site/recent instrumentation and other variables such as time to onset, exposure history, grade of bleeding, anatomical sites, etc. can be collected.

8.2 Assessment of Safety Events

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the Sponsor with the exception of any listed in section **8.4**.

8.3 Reporting of Serious Adverse Events

Any AE that meets a protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form. Any exceptions to the expedited reporting requirements are found in section **8.4**

All SAE reporting must include the elements described in **8.2**.

[redacted]

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 WAIVER OF EXPEDITED REPORTING TO CCR

As death due to disease progression is part of the study objectives (PFS), and captured as an endpoint in this study, death due to disease progression will not be reported in expedited manner to the sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3**.

Hospitalization that is deemed to be due to disease progression, and not attributable to the intervention will not be reported as an SAE. The event, and the assessment that it was caused by disease progression will be documented in the medical records. The causality assessment of hospitalization will be re-evaluated any time when new information is received. If the causality assessment changes from disease progression to related to the study intervention, SAE report will be sent to the Sponsor in an expedited manner according to section **8.3**. If there is any uncertainty whether the intervention is a contributing factor to the event, the event should be reported as AE or SAE as appropriate.

8.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

Reporting will be per the collaborative agreement.

8.6 REPORTING PREGNANCY

[redacted]

8.6.1 Maternal exposure

If a participant becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies should be followed up and documented.

8.6.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study treatment and for 6 months after the last dose of study drug (s).

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies occurring from the date of the first dose until 6 months after the last dose should, if possible, be followed up and documented. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

A Protocol Deviation is defined as any non-compliance with the clinical trial Protocol, Manual of Operational Procedures (MOP) and other Sponsor approved study related documents, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements.

In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

- that the rights of the participants are protected;
- that the study is implemented per the approved protocol, Good Clinical Practice and standard operating procedures; and
- the quality and integrity of study data and data collection methods are maintained.

Monitoring for this study will be performed by NCI CCR Office of Sponsor and Regulatory Oversight (OSRO) Sponsor and Regulatory Oversight Support (SROS) Services contractor. Clinical site monitoring activities will be based on OSRO standards, FDA Guidance E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) March 2018, and applicable regulatory requirements.

Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP) developed by OSRO. CMPs will be protocol-specific, risk-based and tailored to address human subject protections and integrity of the study data. OSRO will determine the intensity and frequency of monitoring based on several factors, including study type, phase, risk, complexity, expected enrollment rate, and any unique attributes of the study and the site. The Sponsor will conduct a periodic review of the CMP to confirm the plan's continued appropriateness. A change to the protocol, significant or pervasive non-compliance with GCP, or the protocol may trigger CMP updates.

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit (SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

Some monitoring activities may be performed remotely, while others will occur at the study site(s). Monitoring visit reports will describe visit activities, observations, and associated action items or follow-up required for resolution of any issues, discrepancies, or deviations. Monitoring reports will be distributed to the study PI, NCI CCR QA, CCR Protocol Support Office, coordinating center (if applicable), and the Sponsor regulatory file.

The site Monitor will inform the study team of any deviations observed during monitoring visits. If unresolved, the Monitor will request that the site Staff enter the deviations in the CCR Protocol Deviation Tracking System (PDTS) for deviation reporting to the Sponsor and as applicable per institutional and IRB guidance.

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10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

Primary Objectives:

- Arm 1 (Sequential Dose Escalation):
  - To evaluate the safety and tolerability of single agent SX-682.
  - To determine the MTD of SX-682 followed by M7824 and CV301 in participants with advanced or metastatic solid tumors. If the MTD is not reached the study will be focused to describe the safety and tolerability of SX-682 followed by M7824 and CV301.
- Arm 2 (Combination Dose Escalation):
  - To determine the RP2D of SX-682 with M7824 and CV301 in participants with advanced or metastatic solid tumors. If the MTD is not reached the study will be focused to describe the safety and tolerability of the drug combination.
- Arm 3 (Expansion):
  - To evaluate preliminary efficacy based on Objective Response Rate (ORR), in each disease cohort separately.

Secondary Objectives:

- Arms 1 and 2 (Dose Escalations):
  - To characterize the PK/PD profile of SX-682 as a single agent and in combination.
- All Arms:
  - To evaluate preliminary efficacy: Disease control rate (DCR) and Progression-free survival (PFS) using RECIST1.1

10.2 SAMPLE SIZE DETERMINATION

The trial will begin with two phase I evaluations (Cohort 1, Arms 1 and 2; Dose Escalation) as follows: initially participants will be enrolled in Arm 1 involving monotherapy with SX-682 followed by M7824 + CV301. This will initially include up to 3 dose levels, with 3 participants per dose level if no DLTs are experienced. However, if in any of the dose levels, a DLT is identified in the 3 participants, 3 more participants will be enrolled in that dose level, with subsequent escalation only if there are <=1 DLTs in 6 participants. Thus, up to 18 participants may be enrolled in these first 3 dose levels. If there is one or more DLTs identified in in the first 3 dose levels, escalation will continue to DL4 and 5 using the above 3+3 design. If there are no DLTs in the first 3 dose levels, then participants will be enrolled to Arm 2. As a result, depending on toxicities identified, between 9 and 30 participants may be treated within this sequential dose escalation arm.

In Arm 2, a combination arm with SX-682 followed by the triplet combination (SX-682, M7824, CV301), up to 5 dose levels may be explored. Using a standard 3+3 design, up to 5x6=30 participants may be included in this arm. Thus, up to 30+30=60 total participants may be treated in the phase I portion (Cohort 1, Arms 1 and 2) of the trial.

The phase II evaluation (Arm 3) will take place separately in two cohorts:

TNBC:

Based on prior studies [70-72], the clinical response rate for similar participants with advanced disease receiving a single agent checkpoint inhibitor is expected to be 8-10%. Thus, an observed response rate of approximately 15% or higher would be desirable.

In Arm 3, Cohort 2 (TNBC), the trial will be conducted using a Simon minimax two-stage phase II trial design [99] to rule out an unacceptably low response rate (CR+PR) of 5% (p0=0.05) in favor of an improved response rate of 20% (p1=0.20). With alfa=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.20 (probability of rejecting a good treatment=0.20), the first stage will enroll 12 evaluable participants, and if 0 of the 12 has a response, then no further participants will be accrued in that cohort. If 1 or more of the first 12 participants has a response, then accrual would continue until a total of 21 evaluable participants have been treated in that cohort. As it may take up to several months to determine if a participant has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are 1-2 participants with a response out of 21 participants in this cohort, this would be an uninterestingly low response rate. If there were 3 or more of 21 (14.3%) who experienced a response, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (5% response rate), the probability of early termination is 54.0%.

HPV negative HNSCC:

Based on prior studies [82, 87, 88], the clinical response rate for similar participants with this disease is expected to be 13-18%. Thus, an observed response rate of greater than 25% would be desirable.

In Arm 3, Cohort 3 (HPV negative HNSCC), the trial will be conducted using a Simon minimax two-stage phase II trial design[99] to rule out an unacceptably low response rate (CR+PR) of 15% (p0=0.15) in favor of an improved response rate of 40% (p1=0.40). With alfa=0.10(probability of accepting a poor treatment=0.10) and beta = 0.20 (probability of rejecting a good treatment=0.20), the first stage will enroll 9 evaluable participants, and if 0 to 1 of the 9 have a response, then no further participants will be accrued in that cohort. If 2 or more of the first 9 participants have a response, then accrual would continue until a total of 16 evaluable participants have been treated in that cohort. As it may take up to several months to determine if a participant has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. If there are 2-4 participants with a response out of 16 participants in this cohort, this would be an uninterestingly low response rate. If there were 5 or more of 16 (31.3%) who experienced a response, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (15% response rate), the probability of early termination is 60.0%.

It is expected that up to 1.5 years may be required to enroll up to 60 participants in Arms 1 and 2. It is then expected that 2-3 years may be required to complete accrual to Arm 3. Thus, accrual is expected to be completed in 4-5 years. The total number of evaluable participants is no more than 60+21+16=97. To allow for a small number of inevaluable participants, the accrual ceiling for treated participants in the dose escalation and expansion cohorts combined will be set at 105 participants

10.3 POPULATIONS FOR ANALYSES

Intention to treat: any subjects who enroll onto the trial and provide consent and who receive at least 1 dose of SX-682, will be included in safety analyses in Arms 1 and 2.

In Arm 3, any participants who receive at least one cycle (defined as 28 days) of SX-682, M7824, and CV301 will be included in safety evaluations as well as efficacy evaluations for the appropriate cohort.

10.3.1 Evaluable for toxicity

All participants will be evaluable for toxicity from the time of their first treatment with SX-682. Participant will be eligible for the DLT evaluation if at least ≥85 percent of SX-682 scheduled doses were taken and 100% of scheduled doses of M7824 or CV301 were administered within the DLT period.

10.3.2 Evaluable for objective response

Only those participants 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 participants will have their response classified according to the definitions in section **6.3**). (Note: Participants who receive at least treatment cycle and exhibit objective disease progression prior to the first restaging will also be considered evaluable.)

10.3.3 Evaluable Non-Target Disease Response

Participants 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.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

Following a determination of safety, tolerability, and the MTD in Arms 1 and 2, the fraction of participants who experience a response in each disease-specific cohort of Arm 3 will be reported along with confidence intervals.

10.4.2 Analysis of the Primary Endpoints

The toxicity grades per participant will be tabulated and reported by dose level during dose escalation (Arms 1 and 2). This will also include separate evaluations for the initial monotherapy evaluations preceding the evaluation of the combination at each dose level.

In Arm 3, the fraction of participants who experience a response in each disease-specific cohort will be reported along with 95% two-sided confidence intervals.

10.4.3 Analysis of the Secondary Endpoint(s)

10.4.4 PK evaluations will be performed on participants in both dose escalation Arms (both for single agent SX-682 and the combination of agents); results will be reported using standard descriptive statistics. In Arm 3, separately by cohort, the disease control rate (DCR; CR+PR+SD) will be reported as the fraction of participants who experience this outcome, along with a 95% two-sided confidence interval for each fraction. Progression free survival (PFS) will be calculated using the Kaplan-Meier method, including progressions or death without progression as events. Participants who come off study for reasons other than progression and choose not to participate in optional imaging will be censored in data analysis at the time when they become unfollowable for PFS.

10.4.5 Safety Analyses

The fraction of participants who experience a toxicity, by grade and type of toxicity, will be tabulated per dose level (both single agent and combination of agents) during the Arms 1 and 2 portion of the trial. Participants who take one dose or more of SX-682 will be evaluable for safety.

10.4.6 Baseline Descriptive Statistics

Baseline demographic characteristics will be reported.

10.4.7 Planned Interim Analyses

As indicated in the two-stage designs, the number of responses after 9 or 12 evaluable participants have been treated in the appropriate cohort will be noted and will be used to determine if enrollment to the second stage of accrual may proceed for that cohort.

10.4.8 Sub-Group Analyses

In Arm 3, analyses will be performed separately by histology.

10.4.9 Tabulation of individual Participant Data

None

10.4.10 Exploratory Analyses

All Arms:

- To evaluate response via iRECIST
- To evaluate the effect on immune cell subsets and soluble factors in peripheral blood.
- To evaluate the effect on serum cytokine levels (IL-8, IL-6 and others) in peripheral blood.
- To evaluate the effect on T cell clonality in peripheral blood and tumor samples.
- To evaluate the effect on antigen-specific T cells responses to CEA, MUC1 and the cascade antigen brachyury in peripheral blood.
- To evaluate the effect on antigen-specific T cell responses to CEA, MUC1 and the cascade antigen brachyury in the tumor biopsies.
- To evaluate the presence of lymphocytic infiltrates and other tumor markers as well as to evaluate RNA in situ hybridization for IL-8, TGF-β and other soluble factors in tumor biopsies.
- To evaluate M7824 PK profile in this drug combination
- To evaluate ADA in this drug combination
- To evaluate long term (2 years after completion of treatment) clinical outcomes
- To evaluate CTCs

In Arms 1 and 2 (Dose-Escalations), the following are the parameters will be evaluated, separately per dose level:

- To evaluate ORR per RECISTv1.1

In Arm 3 (Expansions) the following are the parameters will be evaluated, separately per cohort.

- To evaluate changes in circulating free DNA.

Any exploratory evaluations which generate quantitative measures will be done using descriptive statistics including confidence intervals when appropriate. Any statistical tests performed for evaluation of exploratory objectives will be done without formal adjustment for multiple comparisons, but in the context of the number of tests performed.

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

A CRADA (03153) is in place with Syntrix for the supply of SX-682.

A CRADA (02666) is in place with EMD Serono for the supply of M7824.

A CRADA (02561) is in place with Bavarian Nordic for the supply of CV301.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

No individual who meets the criteria for eligibility will be excluded from participation based on their race, ethnicity, gender, or socioeconomic status. Particular attention will be made to acquire a broad and diversified population.

12.2 PARTICIPATION OF CHILDREN

Children (younger than 18 years) will not be included in this protocol due to the limited data on study drugs in children and the different biology of childhood malignancy.

12.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (Section **12.4.2**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify an LAR as needed. .

Please see section **12.5.1** for consent procedure.

12.4 RISK/BENEFIT ASSESSMENT FOR ALL PARTICIPANTS

12.4.1 Known Potential Risks

12.4.1.1 Study Drug Risks

Risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document or sections **1.2.2.2, 1.2.3.1, 1.2.4.1** of this protocol document. Frequent monitoring for adverse effects will help to minimize the risks associated with administration of the study agents.

12.4.1.2 Risk of Biopsy

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent.

12.4.1.3 Risks of local anesthesia and/or light sedation.

Biopsies will be done under local anesthesia and/or light sedation. Potential side effects of sedation include headache, nausea and drowsiness. These side effects usually go away quickly.

12.4.1.4 Risks of contrast dye used in CT scans

There is a chance of developing an allergic reaction from the contrast material, which may cause symptoms ranging from mild itching or a rash to severe difficulty breathing, shock or rarely, death. The contrast material may also cause kidney problems.

For IV contrast: Potential side effects include discomfort when the contrast material is injected, feeling warm, flushed, a metallic taste, or rarely vomiting or nausea.

For oral contrast: Potential side effects include vomiting, nausea, cramping, bloating, constipation or diarrhea after drinking the contrast.

12.4.1.5 Risks of exposure to Ionizing Radiation

This research study involves up to nine (9) CT scans (C/A/P) and up to three (3) CT guided biopsies (optional) collected for research purposes only. Subjects undergoing these scans and optional biopsies collection will be exposed up to 12.3 rem.

The CT scans that participant will get in this study will expose them to the roughly the same amount of radiation as 41 years of background radiation. The risk of getting cancer from the radiation exposure in this study is 1.2 out of 100 (1.2 %) and of getting a fatal cancer is 0.6 out of 100 (0.6 %)

12.4.1.6 Risks of MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe to have an MRI scan for participants with pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye.
People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. There are no known long-term risks of MRI scans.

12.4.1.7 Risks of Gadolinium

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.
Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure.
People with kidney disease are at risk for a serious reaction to gadolinium contrast called “nephrogenic systemic fibrosis (NSF)”. This condition always involves the skin and can also involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths.

Most of the gadolinium contrast leaves the body in the urine. However, the FDA has issued a safety alert that indicates small amounts of gadolinium may remain in the body for months to years. The long-term effects of the retained gadolinium are not known. Some types of gadolinium contrast drugs are less likely to remain in the body than others. The gadolinium contrast drugs that are less likely to remain in the body will be used on this study.

12.4.1.8 Research Blood Collection Risks

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting and infection. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

12.4.1.9 Risk of Rapid Progression

Three large studies of bintrafusp alfa were recently stopped when the drug manufacturer reviewed data that suggested that the studies would not be likely to prove the study treatment better than standard treatments. This data also suggested that there may be a portion of patients that have either no benefit from bintrafusp alfa, or that bintrafusp alfa will make the tumor grow faster. This has been described with other immunotherapy approaches also with studies suggesting this happens in about 15% of cases.

12.4.1.10 Other Risks

Risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document or this protocol document. Frequent monitoring for adverse effects will help to minimize the risks associated with administration of the study agents.

12.4.2 Known Potential Benefits

The study drugs may help to control the disease. The results may help the investigators learn more about the disease and develop new treatments for participants with this disease.

12.4.3 Assessment of Potential Risks and Benefits

Solid tumors treatment needs improved therapy options. Current studies suggest that study therapy may have tremendous anti-tumor efficacy.

A number of clinically appropriate strategies to minimize risks to participants have been built into the protocol through the means of inclusion/exclusion criteria, monitoring strategies, and management guidelines. Overall, the potential benefit of the study therapy in subjects with solid tumors outweigh the risks associated with this drug.

The potential benefit to a participant that participates in this study is better control of their tumor growth and disease recurrence which may or may not have a favorable impact on symptoms and/or survival.

Potential adverse reactions attributable to the administration of the study drug utilized in this trial are discussed in Sections **1.2.2.2, 1.2.3.1, 1.2.4.1**. All care will be taken to minimize side effects, but they can be unpredictable in nature and severity

12.5 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.
The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy including HRPP policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant) or as described below, with a manual (non-electronic) signature on the electronic document. When required, witness signature will be obtained similarly as described for the investigator and participant.

Manual (non-electronic) signature on electronic document:

When a manual signature on an electronic document is used for the documentation of consent at the NIH Clinical Center, this study will use the following to obtain the required signatures:

- Adobe platform (which is not 21 CFR Part 11 compliant); or,
- iMedConsent platform (which is 21 CFR Part 11 compliant)

During the consent process, participants and investigators will view individual copies of the approved consent document on screens at their respective locations (if remote consent); the same screen may be used when in the same location but is not required.
Both the investigator and the participant will sign the document using a finger, stylus or mouse.
Note: Refer to the CCR SOP PM-2, Obtaining and Documenting the Informed Consent Process for additional information (e.g., verification of participant identity when obtaining consent remotely) found at: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

12.5.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.5**

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

Clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and

conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 SX-682 (IND#21166)

14.1.1 Acquisition and Accountability

Investigational SX-682 is manufactured and supplied for the trial by Syntrix. Drug will be delivered directly to the NIH Pharmacy. Individual bottles with tablets will be prepared for each study participant according to assigned dose by NIH Pharmacy personnel. Participants will pick

up bottles at NIH Pharmacy and will return bottles and not-used tablets after completion of every cycle together with Medication Diary to Study Coordinator. After review of leftover tablets and Medication Diary, unused tablets will be returned to pharmacy and disposed by pharmacy personnel

14.1.2 Formulation, Appearance, Packaging, and Labeling

SX-682 is dispensed as either 25 mg or 100 mg tablets for oral administration.

SX-682 exhibits 99.4% protein binding.

The anticipated half-life of the drug varies by dose administered with a 25mg flat dose resulting in a half-life of 2.6 hours and a 200 mg flat dose resulting in a half-life is 14 hours.

14.1.3 Product Storage and Stability

Store SX-682 between 15 to 30°C. On the basis of available stability data for the API and a drug product demonstration batch, SX-682 is projected stable for at least 2 years when stored as above.

14.1.4 Preparation

SX-682 is dispensed as 25 mg or 100 mg tablets for oral administration. If necessary, the 100 mg tablets can be cut in half using a pill splitter; the tablets are pre-scored for this purpose. The tablets should not be crushed, chewed, or dissolved before being swallowed.

14.1.5 Administration

Please see Section **3.3.2**

14.2 M7824 (IND#21166)

14.2.1 Acquisition and Accountability

M7824 is manufactured and supplied for the trial by EMD Serono Research and Development Institute. Drug will be delivered directly to the NIH Pharmacy. Individual IV bags will be prepared for each study participant according to assigned dose by NIH Pharmacy personnel. IV bags will be delivered from NIH Pharmacy to participant unit where drug will be infused to the participant.

14.2.2 Formulation, Appearance, Packaging, and Labeling

M7824 is provided as a sterile liquid formulation and packaged at a 10 mg/mL concentration in USP/ Ph Eur type I 50R vials that are filled with drug product solution to allow an extractable volume of 60 mL (600 mg/60 mL). The vials are closed with rubber stoppers in serum format complying with USP and Ph Eur with an aluminum crimp seal closure. Each single-use vial contains 600mg of M7824, formulated as 10mg/mL of active, 6% (w/v) Trehalose, 40 mM NaCl, 5 mM Methionine, 0.05% (w/v) Tween 20, 10 mM LHistidine at pH 5.5.

The liquid formulation is diluted directly with 0.9% sodium chloride solution for injection. The estimated volumes of delivery are anticipated to be no more than 250mL. The verified concentration range in the infusion solution is 0.16 mg/mL to 9.6 mg/mL.

14.2.3 Product Storage and Stability

M7824 drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing longterm stability studies with M7824. M7824 drug product stored at room

(23°C to 27°C) or higher temperatures for extended periods of time might be subject to degradation.

The chemical and physical in-use stability for the infusion solution of M7824 in 0.9% saline solution has been demonstrated for a total of 72 hours at room temperature. However, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to administration are the responsibility of the user. Do not freeze or shake the diluted solution.

No other drugs should be added to the infusion containers containing M7824.

14.2.4 Preparation

Preparation is described in pharmacy manual.

14.2.5 Administration

Please see Section **3.3.4**

14.3 CV301 (IND#21166)

14.3.1 Acquisition and Accountability

Investigational CV301 vaccines (MVA-BN-CV301 and FPV-CV301) will be supplied by the manufacturer, Bavarian Nordic. Drug will be delivered directly to the NIH Pharmacy. Individual syringes with the drugs will be prepared for each study participant by NIH Pharmacy personnel. Syringes will be delivered from NIH Pharmacy to participant unit where drug will be injected to the participant.

14.3.2 Formulation, Appearance, Packaging, and Labeling

The manufacturing department of Bavarian Nordic will supply MVA-BN-CV301 and FPV-CV301, with each vaccine provided in 2 mL type I borosilicate glass vials closed with sterile bromobutyl rubber stoppers, crimped with aluminum caps and covered with polypropylene closures.

14.3.3 Product Storage and Stability

Supplies of both the MVA-BN-CV301 and the FPV-CV301 vaccines will be shipped temperature controlled and monitored to the clinical trial site. Once at the site, the package should be handed over to personnel in charge of vaccine preparation (e.g., the pharmacist or representative). Site personnel are responsible for proper storage of vaccine upon receipt.

Both the MVA-BN-CV301 and the FPV-CV301 vaccines must be shipped to site and stored at a minimum temperature of -4°F +/- 9°F (-20°C +/- 5°C) or -80ºC ± 10ºC, avoiding direct light. A vial must not be re-frozen once it has been thawed. A provisional shelf life of 2 years at -80°C ± 10°C has been given. Expiry date may be extended due to real time stability data. Storage at -20°C ± 5°C is limited to 12 months after moving from -80°C ± 10°C to -20°C ± 5°C.

14.3.4 Preparation

MVA-BN-CV301 and FPV-CV301 encode the human MUC-1 and the human CEA gene in combination with human TRICOM. No marker gene is present in both recombinant viruses.

MVA-BN-CV301 is a liquid-frozen, highly attenuated, live recombinant virus based on the viral vector MVA-BN. It is administered as s.c. injection. Packaging and vials will be labeled according to the respective product specifications.

One MVA-BN-CV301 vaccine vial has a nominal titer of 4 x 10^8 infectious units (Inf.U) in 0.5 mL of the drug product.

FPV-CV301 is a liquid-frozen, highly attenuated, live recombinant virus. It is administered as s.c. injection. The packages and vials will be labeled according to the respective product specifications.

One FPV-CV301 vaccine vial has a nominal virus titer of 1 x 10^9 Inf.U in 0.5 mL of the drug product.

14.3.5 Administration

Please see Section **3.3.3.**

15 REFERENCES

1. Palena, C., D.H. Hamilton, and R.I. Fernando, *Influence of IL-8 on the epithelial-mesenchymal transition and the tumor microenvironment.* Future Oncol, 2012. **8**(6): p. 713-22.
2. David, J.M., et al., *The IL-8/IL-8R Axis: A Double Agent in Tumor Immune Resistance.* Vaccines (Basel), 2016. **4**(3).
3. Xie, K., *Interleukin-8 and human cancer biology.* Cytokine Growth Factor Rev, 2001. **12**(4): p. 375-91.
4. Fernando, R.I., et al., *IL-8 signaling plays a critical role in the epithelial-mesenchymal transition of human carcinoma cells.* Cancer Res, 2011. **71**(15): p. 5296-306.
5. Fernando, R.I., et al., *IL-8 signaling is involved in resistance of lung carcinoma cells to erlotinib.* Oncotarget, 2016. **7**(27): p. 42031-42044.
6. Dominguez, C., et al., *Neutralization of IL-8 decreases tumor PMN-MDSCs and reduces mesenchymalization of claudin-low triple-negative breast cancer.* JCI Insight, 2017. **2**(21).
7. Ginestier, C., et al., *CXCR1 blockade selectively targets human breast cancer stem cells in vitro and in xenografts.* J Clin Invest, 2010. **120**(2): p. 485-97.
8. Posner, M.R., et al., *Survival and human papillomavirus in oropharynx cancer in TAX 324: a subset analysis from an international phase III trial.* Ann Oncol, 2011. **22**(5): p. 1071-7.
9. Ang, K.K., et al., *Human papillomavirus and survival of patients with oropharyngeal cancer.* N Engl J Med, 2010. **363**(1): p. 24-35.
10. Bilusic, M., et al., *Phase I trial of HuMax-IL8 (BMS-986253), an anti-IL-8 monoclonal antibody, in patients with metastatic or unresectable solid tumors.* J Immunother Cancer, 2019. **7**(1): p. 240.
11. Kirsten, A.M., et al., *The safety and tolerability of oral AZD5069, a selective CXCR2 antagonist, in patients with moderate-to-severe COPD.* Pulm Pharmacol Ther, 2015. **31**: p. 36-41.
12. O'Byrne, P.M., et al., *Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial.* Lancet Respir Med, 2016. **4**(10): p. 797-806.
13. Jurcevic, S., et al., *The effect of a selective CXCR2 antagonist (AZD5069) on human blood neutrophil count and innate immune functions.* Br J Clin Pharmacol, 2015. **80**(6): p. 1324-36.
14. Miller, B.E., et al., *The pharmacokinetics and pharmacodynamics of danirixin (GSK1325756)--a selective CXCR2 antagonist --in healthy adult subjects.* BMC Pharmacol Toxicol, 2015. **16**: p. 18.

15. Madan, A., et al., *Efficacy and Safety of Danirixin (GSK1325756) Co-administered With Standard-of-Care Antiviral (Oseltamivir): A Phase 2b, Global, Randomized Study of Adults Hospitalized With Influenza.* Open Forum Infect Dis, 2019. **6**(4): p. ofz163.

16. Roberts, G., et al., *Randomized, Double-Blind, Placebo-Controlled Study of the Safety, Tolerability, and Clinical Effect of Danirixin in Adults With Acute, Uncomplicated Influenza.* Open Forum Infect Dis, 2019. **6**(4): p. ofz072.

17. Schott, A.F., et al., *Phase Ib Pilot Study to Evaluate Reparixin in Combination with Weekly Paclitaxel in Patients with HER-2-Negative Metastatic Breast Cancer.* Clin Cancer Res, 2017. **23**(18): p. 5358-5365.

18. Goldstein, L., et al. *A randomized, placebo-controlled phase 2 study paclitaxel in combination with reparixin compared to paclitaxel alone as front-line therapy for metastatic Triple-Negative Breast Cancer (fRida)*. in *San Antonio Breast Cancer Symposium*. 2019. San Antonio, Tx.

19. Blobe, G.C., W.P. Schiemann, and H.F. Lodish, *Role of transforming growth factor beta in human disease.* N Engl J Med, 2000. **342**(18): p. 1350-8.

20. Dumont, N. and C.L. Arteaga, *Transforming growth factor-beta and breast cancer: Tumor promoting effects of transforming growth factor-beta.* Breast Cancer Res, 2000. **2**(2): p. 125-32.

21. Formenti, S.C., et al., *Focal Irradiation and Systemic TGFbeta Blockade in Metastatic Breast Cancer.* Clin Cancer Res, 2018. **24**(11): p. 2493-2504.

22. Ivanovic, V., et al., *Elevated plasma levels of TGF-beta 1 in patients with invasive prostate cancer.* Nat Med, 1995. **1**(4): p. 282-4.

23. Shen, M., et al., *FASN-TGF-beta1-PD-L1 axis contributes to the development of resistance to NK cell cytotoxicity of cisplatin-resistant lung cancer cells.* Biochim Biophys Acta Mol Cell Biol Lipids, 2018. **1863**(3): p. 313-322.

24. Tsushima, H., et al., *High levels of transforming growth factor beta 1 in patients with colorectal cancer: association with disease progression.* Gastroenterology, 1996. **110**(2): p. 375-82.

25. Terabe, M., et al., *Blockade of only TGF-beta 1 and 2 is sufficient to enhance the efficacy of vaccine and PD-1 checkpoint blockade immunotherapy.* Oncoimmunology, 2017. **6**(5): p. e1308616.

26. Vanpouille-Box, C. and S.C. Formenti, *Dual Transforming Growth Factor-beta and Programmed Death-1 Blockade: A Strategy for Immune-Excluded Tumors?* Trends Immunol, 2018. **39**(6): p. 435-437.

27. Grenga, I., et al., *Anti-PD-L1/TGFbetaR2 (M7824) fusion protein induces immunogenic modulation of human urothelial carcinoma cell lines, rendering them more susceptible to immune-mediated recognition and lysis.* Urol Oncol, 2018. **36**(3): p. 93 e1-93 e11.

28. Jochems, C., et al., *Analyses of functions of an anti-PD-L1/TGFbetaR2 bispecific fusion protein (M7824).* Oncotarget, 2017. **8**(43): p. 75217-75231.

29. Knudson, K.M., et al., *M7824, a novel bifunctional anti-PD-L1/TGFbeta Trap fusion protein, promotes anti-tumor efficacy as monotherapy and in combination with vaccine.* Oncoimmunology, 2018. **7**(5): p. e1426519.

30. Lan, Y., et al., *Enhanced preclinical antitumor activity of M7824, a bifunctional fusion protein simultaneously targeting PD-L1 and TGF-beta.* Sci Transl Med, 2018. **10**(424).

31. Ravi, R., et al., *Bifunctional immune checkpoint-targeted antibody-ligand traps that simultaneously disable TGFbeta enhance the efficacy of cancer immunotherapy.* Nat Commun, 2018. **9**(1): p. 741.

32. David, J.M., et al., *A novel bifunctional anti-PD-L1/TGF-beta Trap fusion protein (M7824) efficiently reverts mesenchymalization of human lung cancer cells.* Oncoimmunology, 2017. **6**(10): p. e1349589.

33. Strauss, J., et al., *Phase 1 trial of M7824 (MSB0011359C), a bifunctional fusion protein targeting PD-L1 and TGF-beta, in advanced solid tumors.* Clin Cancer Res, 2018.

34. Goudie, D.R., et al., *Multiple self-healing squamous epithelioma is caused by a disease-specific spectrum of mutations in TGFBR1.* Nat Genet, 2011. **43**(4): p. 365-9.

35. Morris, J.C., et al., *Phase I study of GC1008 (fresolimumab): a human anti-transforming growth factor-beta (TGFβ) monoclonal antibody in patients with advanced malignant melanoma or renal cell carcinoma.* PLoS One, 2014. **9**(3): p. e90353.

36. Ardiani, A., et al., *Vaccine-mediated immunotherapy directed against a transcription factor driving the metastatic process.* Cancer Res, 2014. **74**(7): p. 1945-57.

37. Kwilas, A.R., et al., *A poxviral-based cancer vaccine the transcription factor twist inhibits primary tumor growth and metastases in a model of metastatic breast cancer and improves survival in a spontaneous prostate cancer model.* Oncotarget, 2015. **6**(29): p. 28194-210.

38. Malamas, A.S., et al., *Combination therapy with an OX40L fusion protein and a vaccine targeting the transcription factor twist inhibits metastasis in a murine model of breast cancer.* Oncotarget, 2017. **8**(53): p. 90825-90841.

39. Rajabi, H. and D. Kufe, *MUC1-C oncoprotein integrates a program of EMT, epigenetic reprogramming and immune evasion in human carcinomas.* Biochim Biophys Acta, 2017. **1868**(1): p. 117-122.

40. Kharbanda, A., et al., *MUC1-C confers EMT and KRAS independence in mutant KRAS lung cancer cells.* Oncotarget, 2014. **5**(19): p. 8893-905.

41. Bouillez, A., et al., *MUC1-C promotes the suppressive immune microenvironment in non-small cell lung cancer.* OncoImmunology, 2017. **6**(9): p. e1338998.

42. Zeng, Y., et al., *MUC1 predicts colorectal cancer metastasis: a systematic review and meta-analysis of case controlled studies.* PLoS One, 2015. **10**(9): p. e0138049.

43. Kharbanda, A., et al., *Oncogenic MUC1-C promotes tamoxifen resistance in human breast cancer.* Mol Cancer Res, 2013. **11**(7): p. 714-23.

44. Huang, X., et al., *MUC1 overexpression predicts worse survival in patients with non-small cell lung cancer: evidence from an updated meta-analysis.* Oncotarget, 2017. **8**(52): p. 90315-90326.

45. Khodarev, N.N., et al., *MUC1-induced transcriptional programs associated with tumorigenesis predict outcome in breast and lung cancer.* Cancer Res, 2009. **69**(7): p. 2833-7.

46. Raina, D., et al., *Dependence on the MUC1-C oncoprotein in non-small cell lung cancer cells.* Mol Cancer Ther, 2011. **10**(5): p. 806-16.

47. Maeda, T., et al., *MUC1-C induces PD-L1 and immune evasion in triple-negative breast cancer.* Cancer Res, 2018. **78**(1): p. 205-215.

48. Tsang, K.Y., et al., *Analyses of recombinant vaccinia and fowlpox vaccine vectors expressing transgenes for two human tumor antigens and three human costimulatory molecules.* Clin Cancer Res, 2005. **11**(4): p. 1597-607.

49. Kaufman, H.L., et al., *Poxvirus-based vaccine therapy for patients with advanced pancreatic cancer.* J Transl Med, 2007. **5**: p. 60.

50. Heery, C.R., et al., *Docetaxel alone or in combination with a therapeutic cancer vaccine (PANVAC) in patients with metastatic breast cancer: a randomized clinical trial.* JAMA Oncol, 2015. **1**(8): p. 1087-95.

51. Mohebtash, M., et al., *A pilot study of MUC-1/CEA/TRICOM poxviral-based vaccine in patients with metastatic breast and ovarian cancer.* Clin Cancer Res, 2011. **17**(22): p. 7164-73.

52. Morse, M.A., et al., *A randomized phase II study of immunization with dendritic cells modified with poxvectors encoding CEA and MUC1 compared with the same poxvectors plus GM-CSF for resected metastatic colorectal cancer.* Ann Surg, 2013. **258**(6): p. 879-86.

53. Gulley, J.L., et al., *Pilot study of vaccination with recombinant CEA-MUC-1-TRICOM poxviral-based vaccines in patients with metastatic carcinoma.* Clin Cancer Res, 2008. **14**(10): p. 3060-9.

54. Gatti-Mays, M. *Durable Complete Response with PANVAC and Trastuzumab in Metastatic Triple Positive Breast Cancer.* in *Society for Immunotherapy of Cancer*. 2017. National Harbor, MD.

55. Greenberg, R.N., et al., *Safety, immunogenicity, and surrogate markers of clinical efficacy for modified vaccinia Ankara as a smallpox vaccine in HIV-infected subjects.* J Infect Dis, 2013. **207**(5): p. 749-58.

56. Overton, E.T., et al., *Safety and immunogenicity of modified vaccinia Ankara-Bavarian Nordic smallpox vaccine in vaccinia-naive and experienced human immunodeficiency virus-infected individuals: an open-label, controlled clinical phase II trial.* Open Forum Infect Dis, 2015. **2**(2): p. ofv040.

57. von Sonnenburg, F., et al., *Safety and immunogenicity of modified vaccinia Ankara as a smallpox vaccine in people with atopic dermatitis.* Vaccine, 2014. **32**(43): p. 5696-702.

58. Tsang, K.Y., et al., *Generation of human cytotoxic T cells specific for human carcinoembryonic antigen epitopes from patients immunized with recombinant vaccinia-CEA vaccine.* J Natl Cancer Inst, 1995. **87**(13): p. 982-90.

59. Tsang, K.Y., et al., *A human cytotoxic T-lymphocyte epitope and its agonist epitope from the nonvariable number of tandem repeat sequence of MUC-1.* Clin Cancer Res, 2004. **10**(6): p. 2139-49.

60. Jochems, C., et al., *Identification and characterization of agonist epitopes of the MUC1-C oncoprotein.* Cancer Immunol Immunother, 2014. **63**(2): p. 161-74.

61. Gatti-Mays, M.E., et al., *A Phase 1 Dose Escalation Trial of BN-CV301, a Recombinant Poxviral Vaccine Targeting MUC1 and CEA with Costimulatory Molecules.* Clin Cancer Res, 2019. **May 20. pii: clincanres.0183.2019. doi: 10.1158/1078-0432.CCR-19-0183. [Epub ahead of print]**.

62. Horn, L.A., et al., *Simultaneous inhibition of CXCR1/2, TGF-β, and PD-L1 remodels the tumor and its microenvironment to drive antitumor immunity.* J Immunother Cancer, 2020. **8**(1).

63. Gatti-Mays, M., et al., *A Phase I Trial Using A Multi-Targeted Recombinant Ad5 (CEA/MUC/Brachyury)-based Immunotherapy Vaccine Regimen in Patients with Advanced Cancer.* 2019, The Oncologist.

64. Brenton, J.D., et al., *Molecular classification and molecular forecasting of breast cancer: Ready for clinical application?* Journal of Clinical Oncology, 2005. **23**(29): p. 7350-7360.

65. Bauer, K.R., et al., *Descriptive analysis of estrogen receptor (ER)negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype - A population-based study from the California Cancer Registry.* Cancer, 2007. **109**(9): p. 1721-1728.

66. Tutt, A., et al., *The TNT trial: A randomized phase III trial of carboplatin (C) compared with docetaxel (D) for patients with metastatic or recurrent locally advanced triple negative or BRCA1/2 breast cancer (CRUK/07/012).* Cancer Research, 2015. **75**(9): p. 2.

67. Iwamoto, T., et al., *Estrogen receptor (ER) mRNA and ER-related gene expression in breast cancers that are 1% to 10% ER-positive by immunohistochemistry.* J Clin Oncol, 2012. **30**(7): p. 729-34.

68. Landmann, A., et al., *Low Estrogen Receptor (ER)-Positive Breast Cancer and Neoadjuvant Systemic Chemotherapy: Is Response Similar to Typical ER-Positive or ER-Negative Disease?* Am J Clin Pathol, 2018. **150**(1): p. 34-42.

69. Allred, D.C., et al., *NCCN Task Force Report: Estrogen Receptor and Progesterone Receptor Testing in Breast Cancer by Immunohistochemistry.* J Natl Compr Canc Netw, 2009. **7 Suppl 6**: p. S1-S21; quiz S22-3.

70. Dirix, L.Y., et al., *Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN Solid Tumor study.* Breast Cancer Res Treat, 2017.

71. Nanda, R., et al., *Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study.* J Clin Oncol, 2016. **34**(21): p. 2460-7.

72. Rugo, H.S., et al., *Safety and Antitumor Activity of Pembrolizumab in Patients with Estrogen Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer.* Clin Cancer Res, 2018. **24**(12): p. 2804-2811.

73. Fakhry, C., et al., *Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial.* J Natl Cancer Inst, 2008. **100**(4): p. 261-9.

74. Zhang, L., et al., *Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial.* Lancet, 2016. **388**(10054): p. 1883-1892.

75. Vermorken, J.B., et al., *Platinum-based chemotherapy plus cetuximab in head and neck cancer.* N Engl J Med, 2008. **359**(11): p. 1116-27.

76. Clavel, M., et al., *Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin (C) in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group.* Ann Oncol, 1994. **5**(6): p. 521-6.

77. Baselga, J., et al., *Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck.* J Clin Oncol, 2005. **23**(24): p. 5568-77.

78. Herbst, R.S., et al., *Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck.* J Clin Oncol, 2005. **23**(24): p. 5578-87.

79. Leon, X., et al., *A retrospective analysis of the outcome of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck refractory to a platinum-based chemotherapy.* Clin Oncol (R Coll Radiol), 2005. **17**(6): p. 418-24.

80. Machiels, J.P., et al., *Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial.* Lancet Oncol, 2015. **16**(5): p. 583-94.

81. Saloura, V., et al., *An open-label single-arm, phase II trial of zalutumumab, a human monoclonal anti-EGFR antibody, in patients with platinum-refractory squamous cell carcinoma of the head and neck.* Cancer Chemother Pharmacol, 2014. **73**(6): p. 1227-39.

82. Ferris, R.L., et al., *Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck.* N Engl J Med, 2016. **375**(19): p. 1856-1867.

83. El-Naggar, A.K. and W.H. Westra, *p16 expression as a surrogate marker for HPV-related oropharyngeal carcinoma: a guide for interpretative relevance and consistency.* Head Neck, 2012. **34**(4): p. 459-61.

84. Marur, S., et al., *HPV-associated head and neck cancer: a virus-related cancer epidemic.* Lancet Oncol, 2010. **11**(8): p. 781-9.

85. Lydiatt, W.M., et al., *Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual.* CA Cancer J Clin, 2017. **67**(2): p. 122-137.

86. Chaturvedi, A.K., et al., *Human papillomavirus and rising oropharyngeal cancer incidence in the United States.* J Clin Oncol, 2011. **29**(32): p. 4294-301.

87. Seiwert, T.Y., et al., *Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial.* Lancet Oncol, 2016. **17**(7): p. 956-965.

88. Bauml, J., et al., *Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study.* J Clin Oncol, 2017. **35**(14): p. 1542-1549.

89. Wolff, A.C., et al., *Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update.* Arch Pathol Lab Med, 2014. **138**(2): p. 241-56.

90. Fakhry, C., C. Lacchetti, and B. Perez-Ordonez, *Human Papillomavirus Testing in Head and Neck Carcinomas: ASCO Clinical Practice Guideline Endorsement Summary of the CAP Guideline.* J Oncol Pract, 2018. **14**(10): p. 613-617.

91. Michot, J.M., et al., *Immune-related adverse events with immune checkpoint blockade: a comprehensive review.* Eur J Cancer, 2016. **54**: p. 139-148.

92. Strauss, J., et al., *Bintrafusp alfa, a bifunctional fusion protein targeting TGF-beta and PD-L1, in patients with human papillomavirus-associated malignancies.* J Immunother Cancer, 2020. **8**(2).

93. Eisenhauer, E.A., et al., *New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. **45**(2): p. 228-47.

94. Scher, H.I., et al., *Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group.* J Clin Oncol, 2008. **26**(7): p. 1148-59.

95. Rustin, G.J., et al., *Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer).* J Natl Cancer Inst, 2004. **96**(6): p. 487-8.

96. Bubley, G.J., et al., *Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group.* J Clin Oncol, 1999. **17**(11): p. 3461-7.

97. Vergote, I., et al., *Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup.* J Natl Cancer Inst, 2000. **92**(18): p. 1534-5.

98. Seymour, L., et al., *iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics.* Lancet Oncol, 2017. **18**(3): p. e143-e152.

99. Simon, R., *Controlled Clinical Trials*. 1989. p. 1-10.

16 APPENDICES

16.1 APPENDIX A-PERFORMANCE STATUS CRITERIA

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

16.2 APPENDIX B: DRUGS KNOWN TO SIGNIFICANTLY PROLONG THE QTC*

Generic Name*	**Brand Name***
Aclarubicin	Aclacin and others
Amiodarone	Cordarone and others
Anagrelide	Agrylin and others
Arsenic trioxide	Trisenox
Astemizole	Hismanal
Azithromycin	Zithromax and others
Bepridil	Vascor
Chloroquine	Aralen
Chlorpromazine	Thorazine and others
Cilostazol	Pletal
Ciprofloxacin	Cipro and others
Cisapride	Propulsid
Citalopram	Celexa and others
Clarithromycin	Biaxin and others
Cocaine	Cocaine
Disopyramide	Norpace
Dofetilide	Tikosyn
Domperidone	Motilium and others
Donepezil	Aricept
Dronedarone	Multaq
Droperidol	Inapsine and others
Erythromycin	E.E.S. and others
Escitalopram	Cipralex and others
Flecainide	Tambocor and others
Fluconazole	Diflucan and others
Gatifloxacin	Tequin
Grepafloxacin	Raxar
Halofantrine	Halfan
Generic Name*	**Brand Name***
Haloperidol	Haldol (US & UK) and others
Ibogaine	None
Ibutilide	Corvert
Levofloxacin	Levaquin and others
Levomepromazine (methotrimeprazine)	Nosinan and others
Levomethadyl acetate	Orlaam
Levosulpiride	Lesuride and others
Mesoridazine	Serentil
Methadone	Dolophine and others
Moxifloxacin	Avelox and others
Ondansetron	Zofran and others
Oxaliplatin	Eloxatin
Papaverine HCl (Intracoronary)	None
Pentamidine (systemic)	Pentam

Pimozide	Orap
Probucol	Lorelco
Procainamide	Pronestyl and others
Propofol	Diprivan and others
Quinidine	Quinaglute and others
Roxithromycin	Rulide and others
Sevoflurane	Ultane and others
Sotalol	Betapace and others
Sparfloxacin	Zagam
Sulpiride	Dogmatil and others
Sultopride	Barnetil and others
Terfenadine	Seldane
Terlipressin	Teripress and others
Terodiline	Micturin and others
Thioridazine	Mellaril and others
Vandetanib	Caprelsa

* CredibleMeds.org

16.3 APPENDIX C PARTICIPANT'S MEDICATION DIARY _____

16.3.1 Lead In

Participant's ID _____ Treatment LEAD IN:_____
Participant SX-682 Dose:_____ Treatment Dates:_____
INSTRUCTIONS TO THE PARTICIPANT:

1. Complete this form for two-week period on the trial.
2. You will take SX-682 twice a day for every day of two-week period. This drug should be taken in a fasting state, meaning no food 2 hours prior to taking the drug and no food 1 hour after taking the drug.
3. Record the date, the number of tablets that you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the comment's column.
5. Please bring this form and your bottles (even it is empty) when you come for your clinic visit.

Day	**Date**	**Oral SX-682 (every 12 hours)**				**Comments** *(Side effects, reason for missing dose, etc)*
		Morning Dose		**Evening Dose**		
		Time	**# Tablets**	**Time**	**# Tablets**	
-14L						
-13L						
-12L						
-11L						
-10L						
-9L						
-8L						
-7L						
-6L						
-5L						
-4L						
-3L						
-2L						
-1L						

Participant's signature: _____

16.3.2 Cycles

Participant's ID _____ Treatment Cycle:_____
Participant SX-682 Dose:_____ Treatment Dates:_____
INSTRUCTIONS TO THE PARTICIPANT:

1. Complete one form for each cycle on the trial.
2. You will take SX-682 twice a day for every day of the cycle. This drug should be taken in a fasting state, meaning no food 2 hours prior to taking the drug and no food 1 hour after taking the drug.
3. Record the date, the number of tablets that you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the comment's column.
5. Please bring this form and your bottles (even it is empty) when you come for your clinic visit.

Day	**Date**	**Oral SX-682 (every 12 hours)**				**Comments** *(Side effects, reason for missing dose, etc)*
		Morning Dose		**Evening Dose**		
		Time	**# Tablets**	**Time**	**# Tablets**	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						

Day	**Date**	**Oral SX-682 (every 12 hours)**				**Comments** *(Side effects, reason for missing dose, etc)*
		Morning Dose		**Evening Dose**		
		Time	**# Tablets**	**Time**	**# Tablets**	
25						
26						
27						
28						

Participant's signature: _____