Abbreviated Title: M7824 in HPV Malignancies

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Title: Phase II Trial of M7824 in Subjects with HPV Associated Malignancies

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Investigational Agents:

Drug Name:	M7824 (MSB0011359C)
IND Number:	136852
Sponsor:	Center for Cancer Research, NCI
Manufacturer:	EMD Serono, Inc.
Supplier	EMD Serono, Inc.

Commercial Agents: None

PRÉCIS

Background:

- Metastatic or refractory/recurrent HPV associated malignancies (cervical, anal, oropharyngeal cancers etc.) are often incurable and poorly palliated by standard therapies.
- TGFβR1 pathway signaling and overexpression are significantly associated with HPV+ cancers.
- PD-1 inhibitors have produced a 12-20% response rate for these diseases.
- M7824 is a novel bifunctional fusion protein composed of monoclonal antibodies against human PD-L1 and soluble extracellular domain of human TGF-β receptor II (TGF-βRII), which functions as a TGF-β "trap."
- Early data from a small cohort of patients with HPV associated malignancies in a phase I trial of M7824 has shown promising activity (NCT02517398). As of May 30, 2017, 4 of 9 patients (44%) with HPV associated malignancies have had preliminary evidence of clinical benefit including:
    - Patient with metastatic cervical cancer with a 25% reduction in her disease at 3 months
    - Patient with metastatic P16+ head and neck cancer with an unconfirmed partial response (PR) at 6 weeks
    - Patient with metastatic anal cancer with a durable PR ongoing 9 months after starting treatment
    - Patient with metastatic cervical cancer with a durable complete response (CR) ongoing 15 months after starting treatment.
    - Notably, the P16+ head and neck cancer patient with unconfirmed PR, anal cancer patient with durable PR and cervical cancer patient with durable CR all have HPV+ disease.
- Immune related adverse events with M7824 in the phase I trial to date have been on par with other PD-1/PD-L1 inhibitors, suggesting a manageable safety profile.
- EMD Serono has an ongoing expansion cohort evaluating M7824 in patients with HNSCC as well as in cervical cancer excluding neuroendocrine cervical cancer.

Objective:

- To determine the objective response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) in subjects with recurrent or metastatic HPV associated malignancies.

Eligibility:

- Age ≥ 18 years old
- Subjects with cytologically or histologically confirmed locally advanced or metastatic HPV associated malignancies including:

    - Non-Neuroendocrine Cervical cancers
    - P16+ Oropharyngeal cancers
    - Anal cancers
    - Vulvar, vaginal, penile, squamous cell rectal and neuroendocrine cervical cancers
    - Other locally advanced or metastatic solid tumors (e.g. lung, esophagus) that are known HPV+
- Subjects must have measurable disease.

Design:

- This is a Phase II trial of M7824 in patients with recurrent or metastatic HPV associated malignancies.
- Patients will be scheduled to receive 1,200 mg of M7824 IV every 2 weeks until off treatment criteria are met.
- There will be six cohorts: (1) Patients with anal cancer whose disease is naïve to checkpoint inhibition, (2) Patients with non-neuroendocrine cervical cancer naïve to checkpoint inhibition, (3) Patients with P16+ oropharyngeal cancers naïve to checkpoint inhibition, and (4) Patients with other rare HPV associated tumors (e.g. squamous cell rectal, vulvar, vaginal, penile cancer, neuroendocrine cervical) naïve to checkpoint inhibition, (5) Patients with any HPV associated cancers whose disease is refractory to checkpoint inhibition. Patients who are determined to be HPV negative after enrolling will be taken off of their previously assigned cohort and reassigned to cohort 6 and their slot on their previously assigned cohort will be replaced.
- Cohorts 1-5 of the trial will be conducted using a Simon two-stage phase II trial design.

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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 Objective

- To determine the objective response rate (ORR) according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) in subjects with recurrent or metastatic HPV associated malignancies.

1.1.2 Secondary Objectives

- To determine the safety and tolerability of M7824.
- To determine disease control rate (DCR) - confirmed response or stable disease (SD) lasting for at least 6 months.
- To assess progression-free survival time (PFS) according to RECIST 1.1.
- To assess overall survival (OS) time.
- To assess duration of response.
- To combine checkpoint inhibitor naïve subjects if permitted based on adequate similarity of results in cohorts 1, 2, 3, and 4.
- To determine the ratio of patients that are hospitalized because of adverse events attributed to disease progression

1.1.3 Exploratory Objectives

- To conduct exploratory immunologic studies to understand and improve the administered treatment, including:
    - peripheral immune subset analysis before and on treatment;

    - soluble factors circulation (e.g., sCD27 and sCD40 ligand) before and on treatment;
    - antigen specific T cell responses to E6/E7 oncoproteins before and on treatment;
    - tumor tissue immune infiltration before and after treatment.
- To assess circulating tumor DNA before and after treatment.
- To perform HPV typing.
- To assess responses to M7824 in patients with HPV associated tumors using (iRECIST).
- To assess responses to M7824 in patients with HPV negative tumors by RECIST 1.1 and iRECIST.
- To assess response rate to M7824 by RESIST 1.1 and iRESIST in two sub populations: (1) patients who have previously received lymphodepleting chemotherapy regimens (e.g. fludarabine/ cyclophosphamide) and (2) patients who have not previously received lymphodepleting chemotherapy regimens.

1.2 BACKGROUND AND RATIONALE

1.2.1 HPV Associated Malignancies

In the United States, there are more than 30,000 cases of HPV associated cancer annually[1] (**Table 1**). Metastatic HPV associated malignancies (cervical, anal, oropharyngeal cancers etc.) are often incurable and poorly palliated by standard therapies. Responses to chemotherapy are variable but generally short-lived with median PFS around 3 to 7 months[2-5]. In a Gynecologic Oncology Group randomized trial comparing four cisplatin-based doublets as first line therapy for cervical cancer the response rates were 22-29% and median PFS was 4 to 6 months with median OS 10 to 13 months [6]. The addition of bevacizumab to combination chemotherapy has been reported to increase OS by 3.7 months, but virtually all patients die of their disease within 2 years [7]. Randomized trials of second line therapy are lacking but response rates for single agents are generally reported to be less than 20% [8]. Early evidence suggests that immune checkpoint therapy also has a low response rate in this disease with a phase 1b trial (KEYSTONE 028) showing a 12.5% response rate (3/24 patients) to pembrolizumab in patients with recurrent or metastatic cervical cancer [9].

For oropharyngeal cancer, the best estimates of the chemotherapy responsiveness are inferred from looking at the oropharyngeal site in subset analyses from clinical trials for head and neck cancers. In a pivotal clinical trial that established platinum, 5-fluorouracil (5-FU), plus cetuximab as first line therapy in head and neck cancer, patients with oropharyngeal tumors experienced PFS of 4 to 6 months and OS of 8 to 11 months [3]. Immune checkpoint therapy has become the standard second line therapy for metastatic oropharyngeal cancer but response rates are still low with this therapy. As an example, the phase 1b trial (KEYNOTE-012) of pembrolizumab which led to its FDA approval for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) as second line therapy had a 17.7% response rate (34/192 patients). Response rates were slightly better in HPV positive HNSCC (21.9%) [10], but still occurred in only a minority of the patients.

In regards to metastatic anal cancer, only a handful of randomized trials have been performed in the last 30 years. In the metastatic setting, most of the evidence is limited to small phase II trials,

retrospective series, and case reports. A recent retrospective series looking at 77 patients, 44 (55%) of whom received 5-FU in combination with cisplatin, 24 (31%) of whom received carboplatin + paclitaxel, and 11 (14%) of whom received another regimen showed a median PFS of 7 months and median OS of 22 months [5]. As with HNSCC, recent early phase trials evaluating immune checkpoint therapy in this disease have shown that responses here too are limited to around 20% of patients treated. A recent phase II trial of nivolumab for metastatic squamous cell anal cancer showed a 21% response rate (7/33 patients) and a recent phase IB trial (KEYNOTE-028) of pembrolizumab showed a 20% response rate (5/25 patients) [11].

Unfortunately, little data exists evaluating immunotherapy for rarer HPV associated malignancies including metastatic vulvar, vaginal, penile, squamous cell rectal or neuroendocrine cervical cancer.

Table 1: Estimated annual incidence of HPV associated cancers in the US

Site	Incidence of HPV associated cancers	Cases attributed to HPV (%)
Oropharyngeal	15,738	11,000 (70.1%)
Cervix	11,771	10,700 (90.6%)
Vulvar	3554	2400 (68.8%)
Vaginal	802	600 (75%)
Penis	1168	700 (63.3%)
Rectal (squamous cell)	750	700 (91.1%)
Anus	5,010	4,600 (91.1%)
Total	38,793	30,700 (79.1%)

1.2.2 M7824

Transforming growth factor β (TGF-β) is a pleiotropic cytokine. In the premalignant state, it has tumor-suppressive effects and suppresses tumorigenic inflammation. However, in patients with cancer, TGF-β is associated with malignant progression, evasion of immune surveillance, invasion, and metastasis [12, 13]. TGF-β Receptor 1 (TGFβR1*)* pathway signaling and overexpression have also been found to be significantly associated with HPV+ cancers [14]. Based on two genome wide association studies (GWAS) which compared patients with upper aero-digestive (n= 2091) and cervical cancers (n=617) to cancer free patients (8,334 and 512 respectively), an integrative computational analysis (including single-gene, gene-interconnectivity, protein–protein interaction, gene expression, and pathway analysis) looked to identify immune genes and pathways significantly associated with cervical and oropharyngeal cancer. They found that TGFβR1 was significantly overexpressed in cervical cancer and HPV+ head and neck cancers. In addition, they observed that *TGFβR1* pathway signaling was significantly associated with HPV+ head and neck cancer as well as cervical cancer [14].

The direct effects of TGF-β on T cells include decreases in perforin, granzymes, interferon gamma, FAS ligand, and natural killer group 2D (NKG2D). It can also decrease NKG2D and major histocompatibility complex (MHC) class I polypeptide sequence A (MICA) in natural killer (NK) cells [15]. Elevated levels of TGF-β have been found to correlate with poor

outcomes in many different human cancers [16, 17] [18, 19] . Prompted by these observations, antibodies (e.g., fresolimumab) and small-molecule inhibitors (e.g., galunisertib) targeting the TGF-β pathway have entered clinical development, where they have demonstrated initial signs of efficacy in hepatocellular carcinoma, pancreatic cancer, and melanoma [20].

Programmed death ligand 1 (PD-L1) expression on tumor cells has also been associated strongly with poor prognosis in a variety of human cancers [21-24]. In recent years, a number of agents targeting the programmed death 1 (PD-1)/PD-L1 pathway have received regulatory approval, demonstrating impressive durations of response for multiple tumor types, including melanoma, non-small cell lung cancer, renal cell cancer, and head and neck cancer [25-33]. Notably, atezolizumab, durvalumab and avelumab are all anti–PD-L1 antibodies with proven efficacy and regulatory approval [34-36]. Unfortunately, not all cancer types seem to respond to these agents, and, even among susceptible cancer types, the percentage of responding patients is usually < 20% [37].

In an effort to increase the rate of response to these therapies, many ongoing trials are evaluating anti–PD-1/PD-L1 agents in combination with other immunotherapies [38]. Importantly, combined inhibition of PD-L1 and TGF-β is a promising therapeutic strategy because these key pathways have independent and complementary immunosuppressive functions; therefore, their dual inhibition may result in synergistic antitumor activity.

M7824 is a novel bifunctional fusion protein composed of a fully human IgG1 monoclonal antibody against human PD-L1 fused, via a flexible glycine-serine linker, to the soluble extracellular domain of human TGF-β receptor II (TGF-βRII), which functions as a TGF-β "trap." The anti-D-L1 moiety of M7824 is based on avelumab (MSB0010718C), which is currently in Phase III clinical trials in multiple tumor types and was recently FDA approved for metastatic Merkel cell carcinoma and urothelial carcinoma [35, 36]. Preclinical studies have shown its ability to simultaneously bind PD-L1 and TGF-β, as well as appropriately block PD-L1 signaling and TGF-β signaling in vitro. M7824 was shown to have better antitumor efficacy than anti-PD-L1 or TGF-β trap control (a mutated antibody that doesn't bind to PD-L1, linked with the TGF-β trap) in both MC38 and EMT-6 tumor models in both wild-type mice and B cell deficient mice Because M7824 is very immunogenic in mice, due to the fully human antibody and its immune stimulatory mechanism of action, host anti-drug antibodies preclude continued dosing. In an orthotopic EMT-6 breast cancer model using B cell-deficient Jh mice M7824 showed much better activity than either anti-PD-L1 antibody alone or TGF-β trap control (**Figure 1**). At tumor re-challenge, 13/13 mice previously cured with M7824 treatment had complete protection (resistance to tumor; **Figure 2**). Furthermore, M7824 therapy extended survival in a dose dependent manner. Similar results were also observed in the MC38 colorectal carcinoma model. Furthermore, depletion studies in MC38 model demonstrated that both CD8+ cytotoxic T cells and NK cells are required for tumor rejection (**Figure 3**).

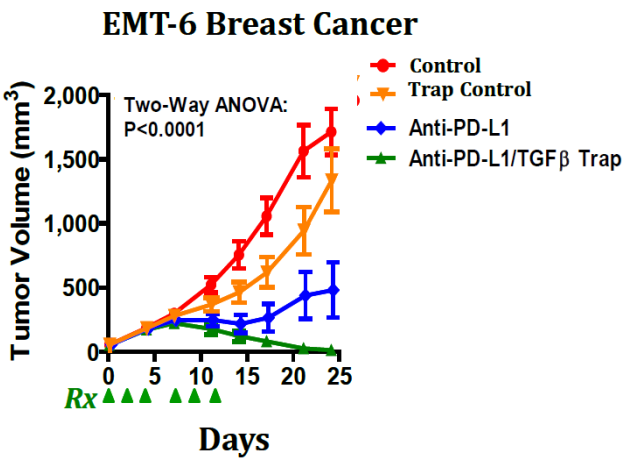

Figure 1: Preclinical studies using B cell-deficient Jh mice with subcutaneous EMT-6 breast cancer tumors showing significantly reduced tumor volume with M7824 (anti-PD-L1/TGFβ) compared with either anti-PDL1 antibody or TGF-β trap alone.

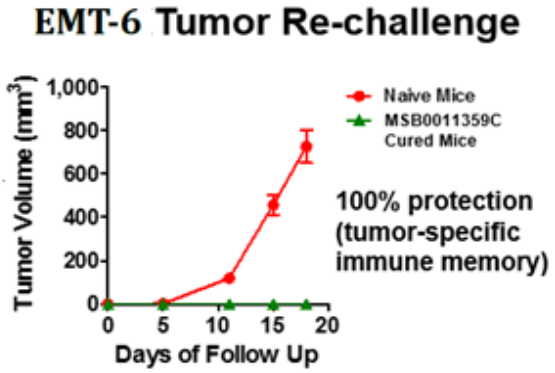

Figure 2: Mice previously cleared of their EMT-6 breast cancer tumors after treatment with M7824 were resistant to tumor re-challenge with EMT-6 cells.

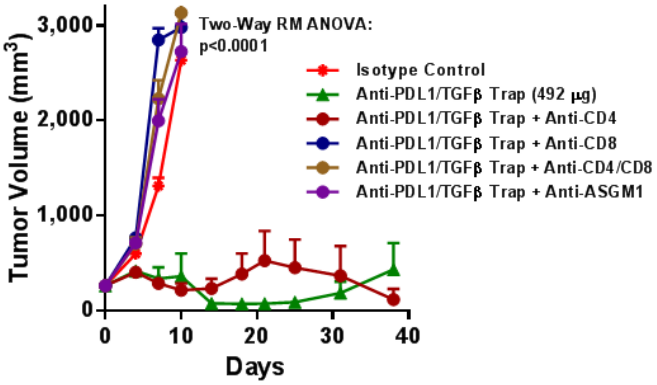

Figure 3: **Antibody-based, selective depletion of immune effector cell subsets showed that both CD8+ cytotoxic T cells and NK cells are required for tumor rejection with M7824 (Anti-PD-L1/TGFβ Trap) in MC38 model.**

In in vivo studies, not only did M7824 decrease TGF-β in the serum and bind PDL1 within the tumor, it also substantially increased CD8+ T-cell and NK cell infiltration within the tumor, while decreasing myeloid-derived suppressor cell (MDSC) infiltration, compared with an anti–PD-L1 antibody control.

Based on these preclinical data, a Phase I 3+3 dose-escalation study was completed to evaluate the pharmacokinetics (PK), safety, tolerability, and biological and clinical activity of M7824 in patients with advanced solid tumors (NCT02517398).

Sixteen heavily pretreated patients received M7824 at 1, 3, 10, or 20 mg/kg once-every-2-weeks. M7824 was shown to saturate peripheral PD-L1 at doses ≥ 3 mg/kg (**Figure 4**) and sequester plasma TGF-β1, -β2, and -β3 (**Figure 5**) throughout the dosing period at ≥1 mg/kg. The only DLT observed was colitis with associated anemia (20 mg/kg). No MTD was reached. Grade 3 treatment-related adverse events occurred in 3 patients (skin infection secondary to localized bullous pemphigoid (3 mg/kg), asymptomatic lipase increase (20 mg/kg), and colitis (20 mg/kg) with associated anemia). These toxicities are on par with other PD-1/PD-L1 inhibitors. The only added toxicity seen over traditional PD-1/PD-L1 inhibitors was the occurrence of keratoacanthomas which have been described previously with TGFβ inhibitors [39]. There were no treatment-related grade 4–5 events.

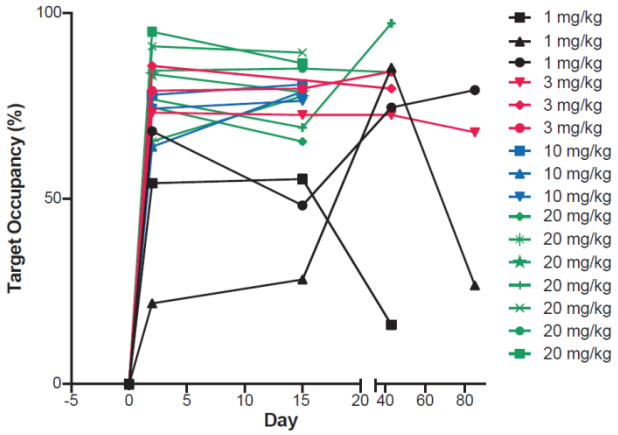

Figure 4: **PD-L1 target occupancy following intravenous administration of M7824**

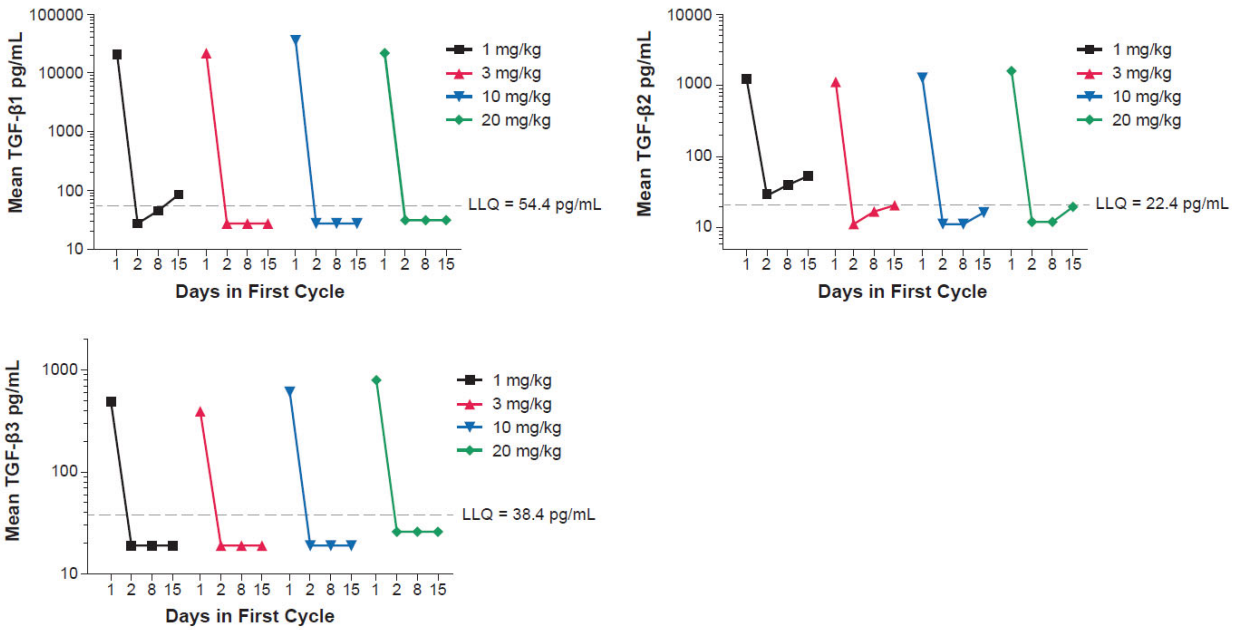

Figure 5: **Total TGF-β1, -β2, and -β3 plasma concentrations following intravenous administration of M7824.**
LLQ, lower limit of quantification.

In addition, in the ongoing Phase I study of M7824 (NCT02517398), substantial clinical evidence has been seen in 4 of 9 patients (44%) with HPV associated malignancies, including 2 of 5 patients (40%) with metastatic cervical cancer, 1 of 2 patients (50%) with metastatic anal cancer and 1 of 2 patients (50%) with metastatic P16+ head and neck cancer have had substantial clinical benefit. This includes a patient with metastatic cervical cancer with a 25% reduction (by long axis measurement) in her disease at 3 months (**Figure 6**), a patient with metastatic P16+ head and neck cancer with an unconfirmed partial response 6 weeks after starting treatment (**Figure 7**), a patient with metastatic anal cancer with normalization of tumor markers (**Figure 8**) and an ongoing durable partial response 9 months after starting treatment (**Figure 9**) and a patient with metastatic cervical cancer with normalization of tumor markers (**Figure 10**) and an ongoing durable complete response for more than a year (**Figure 11**).

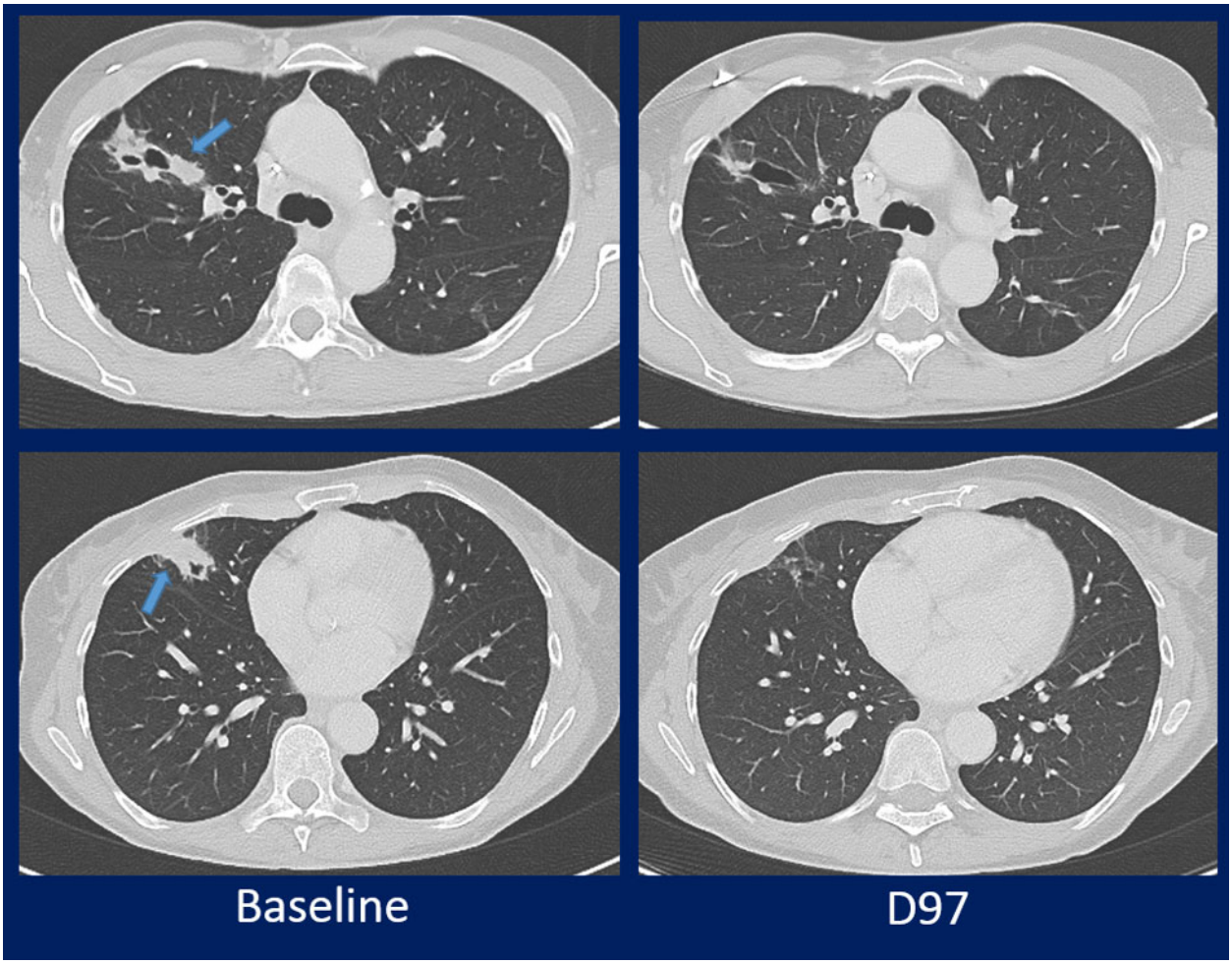

Figure 6: **This 56-year-old woman with initially locally advanced cervical cancer status post (s/p) cisplatin/RT developed metastases to lung within 3 months of initial treatment. Then went on to receive topotecan/taxol plus bevacizumab and was enrolled on phase I of M7824 with enlarging right-sided lung masses (arrows in left side of figure). She received 2 doses of M7824 at 20 mg/kg but then developed colitis necessitating drug discontinuation. Despite this her restaging scan at 12 weeks showed marked reduction in disease volume (right side of figure).**

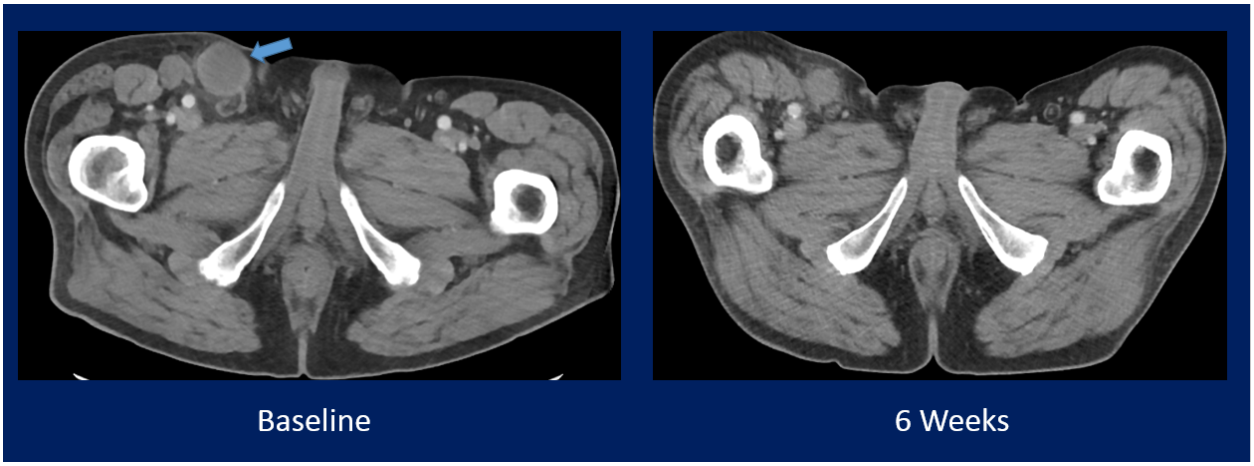

Figure 7: **This 72-year-old man with metastatic HPV+ head and neck cancer s/p cisplatin/RT for initially local disease with multiple disease recurrences in neck s/p modified radical neck dissection and Erbitux/RT (to neck) who developed mets to lungs, back and knee s/p multiple rounds of surgery + Erbitux/RT (to knee) with metastatic right groin mass (arrow in left side of figure) who received M7824 at 20 mg/kg every other week. Restaging scan at 6 weeks showed an unconfirmed PR (right side of figure).**

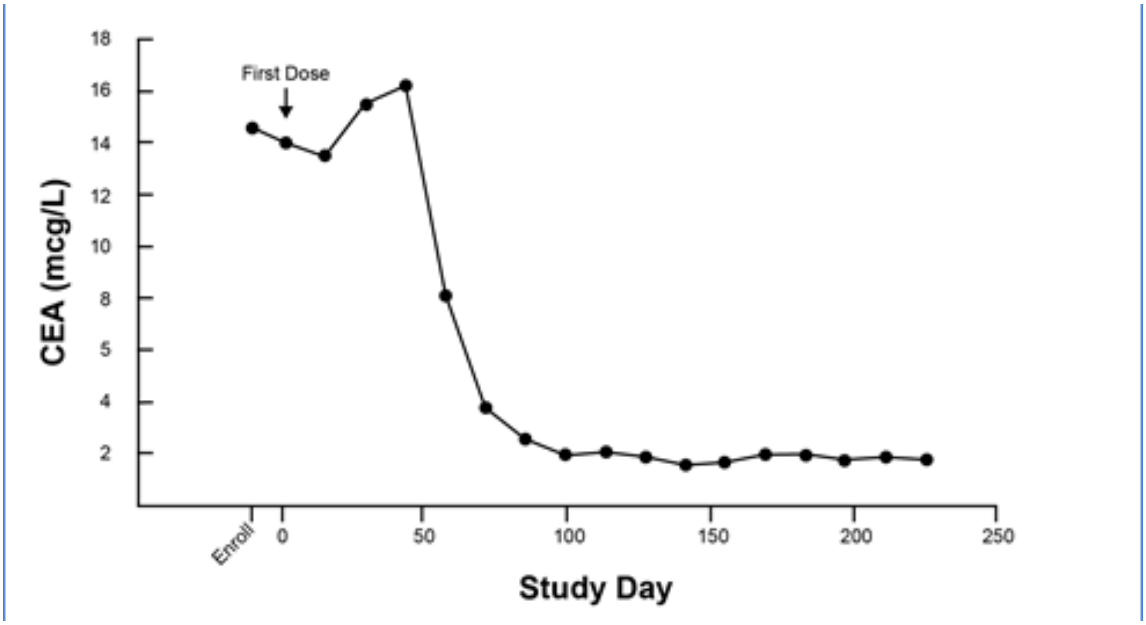

Figure 8: **Carcinoembryonic antigen (CEA) curve for anal cancer patient with ongoing PR.**

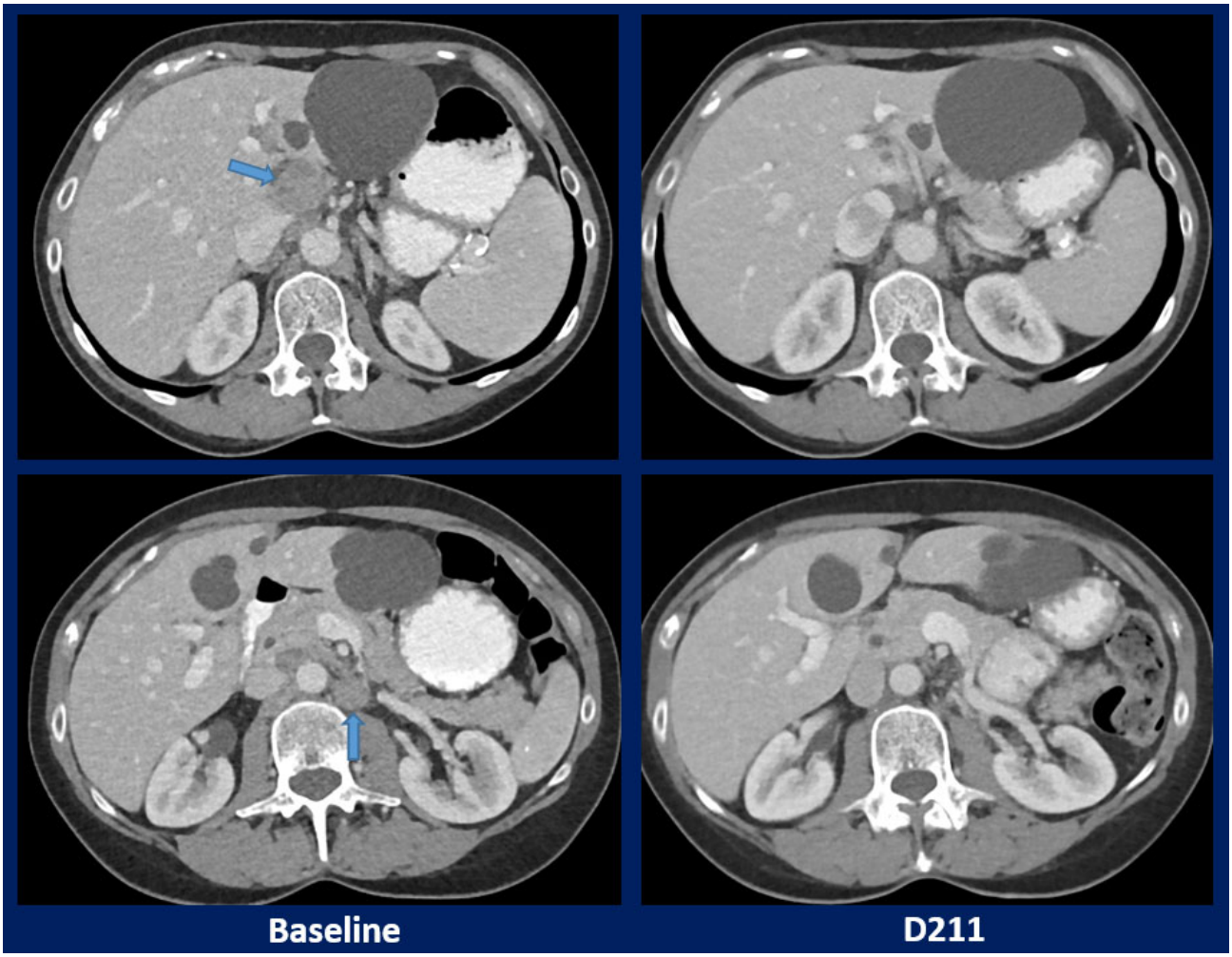

Figure 9: **This 57-year-old female with metastatic HPV+ anal cancer to liver, retroperitoneal and periportal nodes s/p definitive chemoradiation with 5-FU + mitomycin in the locally advanced setting followed by cisplatin + xeloda for recurrent metastatic disease had progressive disease at enrollment (arrows in left side of figure). She received a single dose of M7824 at 0.3 mg/kg followed by M7824 at 10 mg/kg every other week. Restaging scans at 3 months showed a PR which has been durable as of her 7.5 month restaging visit (right side of figure).**

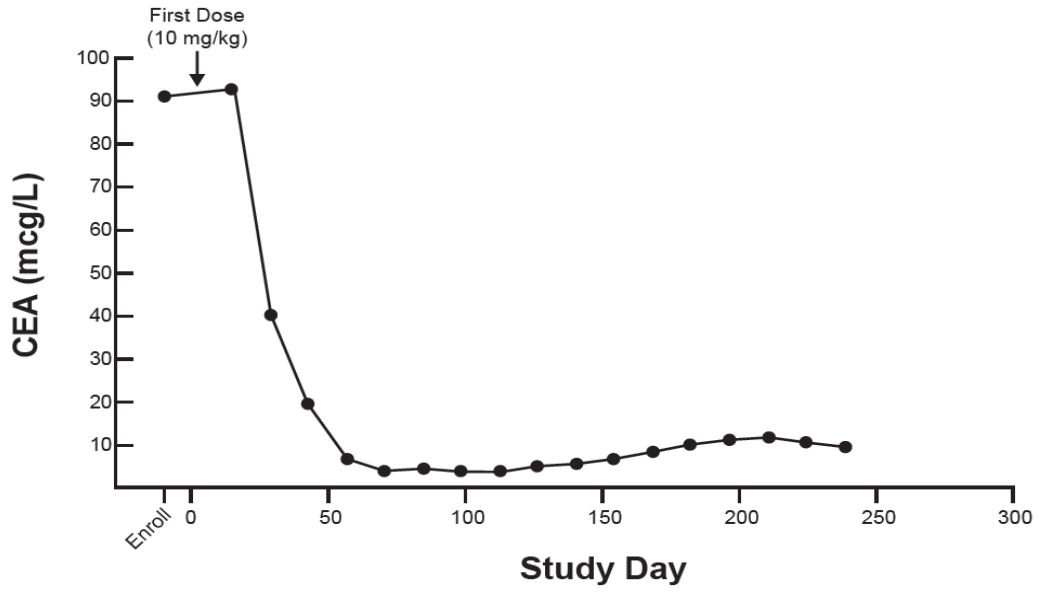

Figure 10: **CEA curve for cervical cancer patient with ongoing CR.**

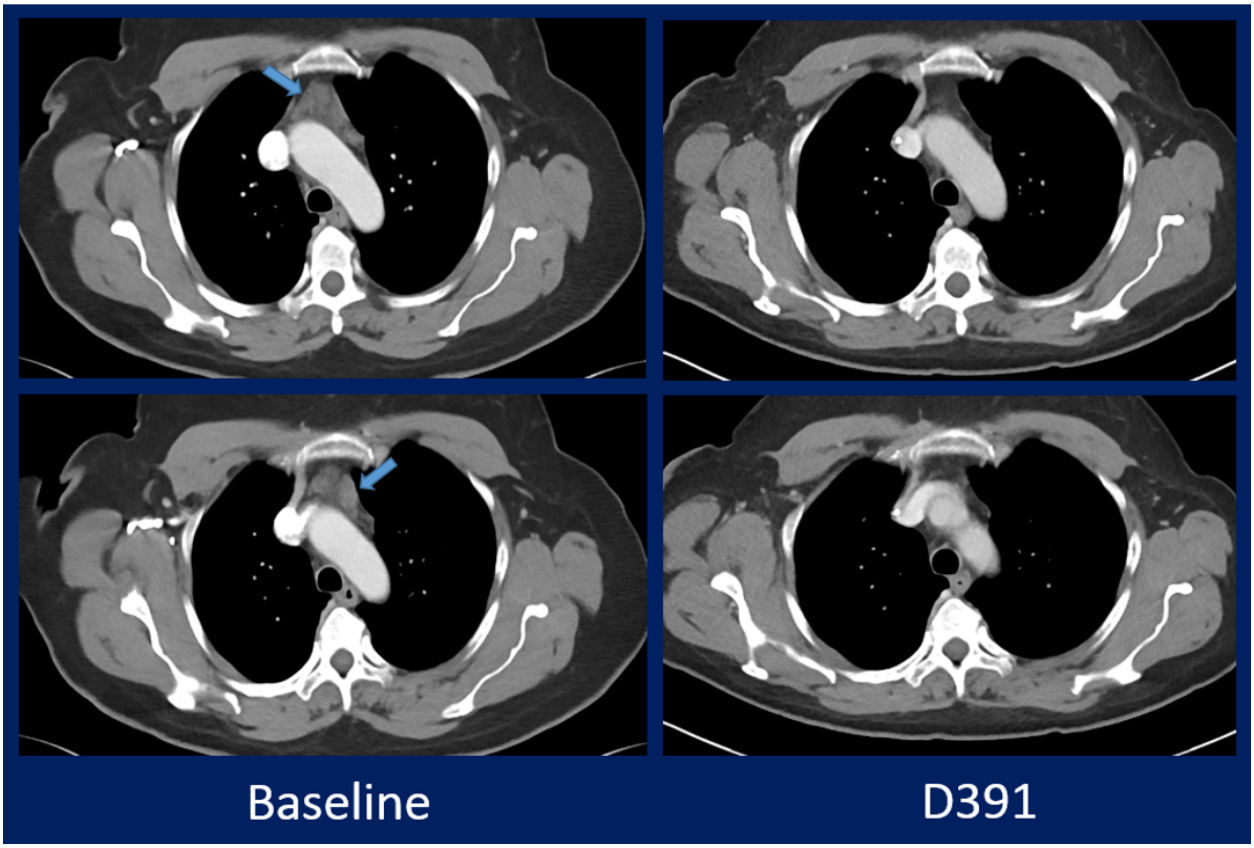

Figure 11: **This 49-year-old woman with metastatic HPV + cervical cancer s/p cisplatin/taxol followed by carboplatin/taxol plus bevacizumab was enrolled with 2 pathologically enlarging mediastinal lymph nodes (arrows in left side of figure). She received M7824 at 10 mg/kg every other**

week. Restaging scan 7.5 months after enrollment showed reduction in lymph nodes to < 1 cm by short-axis measurement meeting RECIST v1.1 criteria for a CR. CR was durable as of her 13-month restaging scan (right side of figure).

This early data from a small cohort of patients with HPV associated malignancies in this phase 1 trial of M7824 suggests that this agent, which targets both PD-L1 and TGFβ pathways, may produce responses at a higher rate as compared with other single agent PD-1/PD-L1 inhibitors in this patient population. Of note the above P16+ head and neck cancer patient with unconfirmed PR, anal cancer patient with durable PR and cervical cancer patient with durable CR all have HPV+ disease.

EMD Serono has several tumor specific expansion cohorts ongoing evaluating M7824 including expansion cohorts in patients with HNSCC as well as cervical cancer excluding neuroendocrine cervical cancer. There are no trials evaluating M7824 in patients with rarer HPV associated malignancies including anal, vulvar, vaginal, penile, neuroendocrine cervical or squamous cell rectal cancer. Therefore, we propose this phase II trial which will include the evaluation of M7824 efficacy in these rarer tumor types.

Clinical benefit was observed in a small cohort of patients with HPV associated malignancies in a Phase I trial of M7824. This Phase II study will further investigate the clinical efficacy of M7824 in HPV associated tumors.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

- Age ≥ 18 years.
- Ability of subject to understand and the willingness to sign a written informed consent document.
- Subjects with cytologically or histologically confirmed locally advanced or metastatic HPV associated malignancies including:
  - Non-Neuroendocrine Cervical cancers
  - P16+ Oropharyngeal cancers
  - Anal cancers
  - Vulvar, vaginal, penile, squamous cell rectal and neuroendocrine cervical cancers
  - Other locally advanced or metastatic solid tumors (e.g. lung, esophagus) that are known HPV+
- Patients must have disease that is not amenable to potentially curative resection
- Subjects must have measurable disease (Section **6.3.3**).
- ECOG performance status ≤ 2 (**Appendix A**).
- Adequate hematologic function at screening, as follows:
  - Absolute neutrophil count (ANC) ≥1 x 109/L

- Hemoglobin ≥ 9 g/dL
- Platelets ≥ 75,000/microliter.

- Adequate renal and hepatic function at screening, as follows:
  - Serum creatinine ≤ 1.5 x upper limit of normal (ULN) OR creatinine clearance (CrCl) ≥ 40 mL/min per institutional standard.
  - Bilirubin ≤ 1.5 x ULN OR in subjects with Gilbert's syndrome, a total bilirubin ≤ 3.0 x ULN
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN, unless liver metastases are present, then values must be ≤ 3 x ULN)
- The effects of M7824 on the developing human fetus are unknown; thus, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation and up to 60 days after the last dose of the drug. 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.
- Patients serologically positive for HIV, Hep B, Hep C are eligible as long as the viral loads are undetectable by quantitative PCR. HIV positive patients must have CD4 count ≥ 300 cells per cubic millimeter at enrollment, be on stable antiretroviral therapy and have no reported opportunistic infections within 12 months prior to enrollment.

2.1.2 Exclusion Criteria

- Pregnant women are excluded from this study because this drug has not been tested in pregnant women and there is potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with M7824, breastfeeding should be discontinued if the mother is treated with M7824.
- Patients with prior investigational drug, chemotherapy, immunotherapy or any prior radiotherapy (except for palliative bone directed therapy) within the past 28 days prior to the first drug administration except if the investigator has assessed that all residual treatment-related toxicities have resolved or are minimal and feel the patient is otherwise suitable for enrollment. Patients may continue adjuvant hormonal therapy in the setting of a definitively treated cancer (e.g., breast).
- Major surgery within 28 days prior to the first drug administration(minimally invasive procedures such as diagnostic biopsies are permitted).
- Known intolerance to or life threatening side effects resulting from prior checkpoint inhibitor therapy.
- Known active brain or central nervous system metastasis (less than 1 month out from definitive radiotherapy or surgery), seizures requiring anticonvulsant treatment (<3 months) or clinically significant cerebrovascular accident (<3 months). In order to be eligible patients must have repeat CNS imaging at least one month after definitive treatment showing stable CNS disease. Patients with evidence of intratumoral or

peritumoral hemorrhage on baseline imaging are also excluded unless the hemorrhage is grade ≤ 1 and has been shown to be stable on two consecutive imaging scans.

- Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent with exception of:
  - diabetes type I, eczema, vitiligo, alopecia, psoriasis, hypo- or hyperthyroid disease or other mild autoimmune disorders not requiring immunosuppressive treatment;
  - Subjects requiring hormone replacement with corticosteroids are eligible if the steroids are administered only for the purpose of hormonal replacement and at doses ≤ 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;
  - Subjects on systemic intravenous or oral corticosteroid therapy with the exception of physiologic doses of corticosteroids (≤ the equivalent of prednisone 10 mg/day) or other immunosuppressives such as azathioprine or cyclosporin A are excluded on the basis of potential immune suppression. For these subjects these excluded treatments 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). In addition, the use of corticosteroids as premedication for contrast-enhanced studies is allowed prior to enrollment and on study.
- Subjects 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 non-HPV associated second malignancy within 3 years of enrollment except localized malignancy which has been adequately treated or malignancy which does not require active systemic treatment (e.g., low risk CLL).
- Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥ 3 NCI-CTCAE v5.0)
- Receipt of any organ transplantation requiring ongoing immunosuppression.
- Patients with vulvar cancer originating from differentiated vulvar intraepithelial neoplasia (d-VIN), as opposed to vulvar intraepithelial neoplasia of usual type, are excluded. Vulvar squamous cell carcinoma originating from differentiated VIN (d-VIN) is HPV negative; however, rare cases of HPV positive d-VIN can occur. Patients are not excluded if their tumor has tested positive for HPV or there is no documentation of prior VIN type.
- Patients with known HPV negative malignancies based on comprehensive laboratory testing (e.g. PCR based assay evaluating for HPV 16, 18, 31, 33, 35, 39, 51, 52, 56, 58, 59, 66, 68). Patients with HPV associated malignancies and unknown HPV status prior to enrollment are eligible.

2.1.3 Recruitment Strategies

This study will be listed on available websites (www.clinicaltrials.gov) and participants will be recruited from the current patient population at NIH.

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 videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes

A waiver of consent for these activities has been requested in section **12.6.2**.

For Patients not-requiring HPV testing:

Note: Screening evaluation testing/procedures are conducted under the separate screening protocol, 01-C-0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols).

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

For Patients requiring HPV testing:

The following activities will be performed only after the subject has signed the consent for this study for screening. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

For Patients not-requiring HPV testing:

The following activities will be performed only after the subject has signed the consent for study # 01C0129 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 patient has signed the consent.

All screening tests and procedures must be performed within 28 days prior to the first drug administration:

- Complete medical history and physical examination (including height, weight, vital signs, and ECOG performance status).
- CT of chest, abdomen and pelvis or MRI
- A brain CT / MRI scan if clinically indicated
- Nuclear bone scan if clinically indicated

- Clinical laboratory tests (within 16 days prior to enrollment)
  - Chemistry: sodium, potassium, chloride, 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)
- Serum pregnancy test (β-HCG) for females of childbearing-potential and women < 12 months since the onset of menopause (within 16 days prior to enrollment).
- HBV, HCV, HIV testing including viral load if clinically indicated (within 3 months prior to enrollment).
- Histologic confirmation (at any time point prior to enrollment). If there is no available tumor sample or pathology report, a biopsy will be performed to confirm the diagnosis.

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 here.

2.3.1 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Cohort 1	Subjects with anal cancer whose disease is naïve to checkpoint inhibition
2	Cohort 2	Subjects with non -neuroendocrine cervical cancer naïve to checkpoint inhibition
3	Cohort 3	Subjects with P16+ oropharyngeal cancer naïve to checkpoint inhibition
4	Cohort 4	Subjects with other rare HPV associated tumors (e.g. squamous cell rectal, vulvar, vaginal, penile cancer, neuroendocrine cervical) whose disease is naïve to checkpoint inhibition
5	Cohort 5	Subjects with any HPV associated cancer whose disease is refractory to checkpoint inhibition
6	Cohort 6	Patients who are determined to be HPV negative after enrolling will be taken off of their previously assigned cohort and

		reassigned to cohort 6 and their slot on their previously assigned cohort will be replaced.

Arms

Number	Name	Description
1	Arm 1	M7824 at a flat dose of 1,200 mg IV once every 2 weeks

Arm Assignment

Patients in Cohort 1-6 will be directly assigned to treatment Arm 1.

2.4 BASELINE EVALUATION

All subjects are required to complete baseline evaluations within one week prior to the first planned dosing of the study drug (any screening evaluation done within this time period can also serve for the baseline evaluation):

- Physical exam including 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 menopause.
- Chemistry: sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, and total and direct bilirubin.
- ACTH, TSH, free T4, lipase, amylase
- Hematology: CBC with differential and platelets
- Coagulation panel: PT, INR, and PTT
- Sedimentation Rate (ESR), CRP
- Urinalysis

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a Phase II trial of M7824 in patients with recurrent or metastatic HPV associated malignancies.

Subjects will be treated with 26 doses of M7824 and at this point the drug will be withheld. These subjects will be followed with surveillance scans every 6-12 weeks. Patients with evidence of disease progression will be allowed retreatment with M7824 using the same dosing regimen.

Retreatment will restart after repeat of baseline evaluation. Participants will not be re-treated unless willing to accept blood products as medically indicated as there is a risk of severe bleeding with this study drug. Participants must be willing to receive blood transfusions if medically necessary for their own safety in order to minimize the risks of receiving M7824.

The second course of treatment will continue for 26 doses of M7824 and at this point the drug will be withheld. These subjects will be followed with surveillance scans every 6-12 weeks. Patients with evidence of disease progression will be allowed additional treatment courses with M7824 using the same dosing regimen. These additional treatment courses will restart after repeat of baseline evaluations.

Patents might be taken off treatment for disease progression during 26 doses period, but where clinically appropriate, treatment beyond radiographic progression is allowed if in the opinion of the investigator the subject is benefiting from treatment.

Subjects will be taken off treatment for unacceptable toxicity.

Although positive HPV testing will not be required prior to enrolling, HPV testing will be offered as an exploratory endpoint and patients testing negative for HPV after enrolling or whose HPV status cannot be confirmed may be replaced with other patients for the primary efficacy analysis. Patients testing negative for HPV after enrolling or whose HPV status cannot be confirmed may continue to receive treatment on study. The response rate of M7824 in patients who are HPV negative will be assessed as an exploratory endpoint.

In addition, early data from the phase I trial suggests that patients with HPV associated malignancies who have previously received lymphodepleting chemotherapy regimens (i.e. fludarabine/cyclophosphamide) may not respond as well to M7824 as standard patients. Of the initial 9 patients with HPV associated malignancy enrolled three had received prior lymphodepleting chemotherapy regimens and all three had no evidence of clinical benefit whereas six patients did not receive prior lymphodepleting chemotherapy and of these four had evidence of clinical benefit. Therefore given this early data and the possibility that patients receiving prior lymphodepleting chemotherapy may not respond as well to M7824 as standard patients, patients previously receiving lymphodepleting chemotherapy regimens may be replaced with other patients for the first stage of the Simon two -stage assessment as well as the primary efficacy analysis. The response rate of M7824 in patients previously receiving lymphodepleting chemotherapy regimens will be assessed as an exploratory endpoint.

In addition, early data from the phase I/II trial suggest that older patients with HPV associated malignancies may respond more frequently to M7824. The observation that older patients may respond more often to checkpoint therapy has also been described in the literature with other checkpoint inhibitors and malignancies[40]. Of the initial 10 patients over the age of 65 with HPV associated malignancies enrolled who received M7824, 5 patients responded per RECIST 1.1 including 3/6 patients with checkpoint naïve disease and 2/4 patients with checkpoint refractory disease. A 4th patient with checkpoint naïve disease had 27% reduction in her disease. No patients with checkpoint refractory disease less than 65 years of age have responded to date. As clinical trial options for patients > 65 years of age are limited due to their general exclusion from adoptive T cell protocols it is worth evaluating the efficacy signal of M7824 specifically in this older patient population. Therefore given this data and rationale patients < 65 years of age may be replaced with patients ≥ 65 years of age for the first stage of the Simon two -stage assessment as well as the primary efficacy analysis.

All Cohorts 1-5 of the trial (see section **2.3.1**) will be conducted using a Simon two-stage Phase II trial design.

- For Cohorts 1, 2, 3, and 4: 8 evaluable patients will be enrolled on each cohort in the first stage and if 2 or more of the 8 on an individual cohort have an objective response (see section **6.3**) within 1 year of starting treatment, then accrual would continue on that individual cohort until a total of 13 evaluable patients have been treated. If there are 4 or more of 13 (30.8%) who experience a response on an individual cohort, this would be sufficiently interesting to warrant further study in later trials.
- For Cohort 5: 13 evaluable patients will be enrolled in the first stage, and if 1 or more of the 13 have an objective response (see section **6.3**) within 1 year of starting treatment, then accrual would continue until a total of 20 evaluable patients have been treated. If there are 3 or more of 20 (15.0%) who experience a response, this would be sufficiently interesting to warrant further study in later trials. To assure a mixture of tumor types in Cohort 3: no more than 8 evaluable patients with cervical cancer, 8 evaluable patients with anal cancer and 8 evaluable patients with head and neck cancer will enroll on this cohort.
- A total of 45 evaluable subjects (8, 8, 8, 8, 13 in Cohorts 1, 2, 3, 4, 5 respectively) will be enrolled in the first stage of the trial. Depending upon the number of objective responses seen in the first stage of the trial up to another 27 evaluable subjects may be enrolled in the second stage for up to a total of 72 evaluable subjects.
- In the event that a patient develops a response (>30% decrease in target lesions as compared with baseline scan) following initial progression of disease attributed to pseudo-progression, this response will be considered as an objective response in the determination to expand a given cohort.

3.2 DRUG ADMINISTRATION

Bintrafusp alfa should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Subjects will be scheduled to receive M7824 at a flat dose of 1,200 mg IV once every 2 weeks. M7824 may be administered through a peripherally inserted intravenous catheter including a peripherally inserted central catheter. It may also be administered through an implanted access device (i.e. port) when the reservoir of the device is made of titanium.

In the phase I trial, M7824 was evaluated at a dose of 1, 3, 10 and 20 mg/kg IV once every 2 weeks and only one DLT was observed (colitis) at a dose of 20 mg/kg. No MTD was found. Based upon this safety data the decision was made to continue with a flat dose of 1,200 mg IV once every 2 weeks in nearly all phase Ib expansion cohorts. To align with these cohorts this phase II trial will also evaluate M7824 at a flat dose of 1,200 mg IV once every 2 weeks.

Subjects will receive IV infusion of M7824 over 1 hour (-10 minutes / +20 minutes, that is, 50 to 80 minutes). As a routine precaution, subjects enrolled in this trial must be observed for 60 minutes' post end of infusion, in an area with resuscitation equipment and emergency agents.

3.2.1 Premedication

Current experience revealed that infusion related reactions (IRRs) to M7824 seldom occur and are generally mild to moderate in severity. Therefore, administration of a premedication is generally not required.

If an Investigator deems it necessary to administer a premedication, an antihistamine (for example, 25-50 mg diphenhydramine) and acetaminophen 500-650 mg intravenously or equivalent oral dose is recommended approximately 30 to 60 minutes prior to each dose of M7824. If Grade ≥ 2 infusion reactions are seen during the first two infusions, premedication should not be stopped. Steroids as premedication are not permitted.

Management of symptoms should follow the guidelines shown in **Table 2**.

3.2.1.1 Immediate Hypersensitivity Reaction

Hypersensitivity reactions may require immediate intensive care. M7824 should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1: 1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council United Kingdom and can be found at https://www.resus.org.uk/pages/reaction.pdf

3.2.1.2 Flu-Like Symptoms

For prophylaxis of flu like symptoms, a nonsteroidal anti-inflammatory drug (NSAID), e.g., ibuprofen 400 mg or comparable NSAID dose, may be administered 2 hours before and 8 hours after the start of each IV infusion.

3.3 DOSE MODIFICATIONS

3.3.1 Discontinuation

M7824 treatment will be discontinued in case of:

- Any Grade 4 adverse drug reactions (ADRs), as defined by CTCAE v5.0 and assessed as related to M7824 by the Investigator, 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.
- Any Grade 3 ADRs except 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 which is controlled with 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
- 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 patient (e.g. placement of a pleural catheter for recurrent inflammatory pleural effusions)

3.3.2 Dose Delay

M7824 should be withheld for any Grade 2 or 3 ADR until resolution to Grade ≤ 1 unless the ADR in the opinion of the investigator is not clinically relevant or can be medically managed with minimal risk to the patient. Should a clinically relevant grade 2 or 3 ADR persist for more than 4 weeks, consideration should be given to discontinuing treatment with M7824 at the discretion of the investigator.

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

3.3.3 Dose Modifications

In the Phase I dose escalation trial of M7824, durable responses were seen at doses of 3 mg/kg and 10 mg/kg as well as clinical benefit (prolonged stable disease) at 1 mg/kg. With these data in mind, the dose of M7824 may be either held or reduced from 1200 mg flat dose to 1-10 mg/kg when in the opinion of the investigator doing so will minimize the risks to the patient and maximize clinical benefit (e.g. in the event of observed tumor reduction but also intolerable ADRs at the full 1200 mg flat dose).

3.3.4 Toxicity Management

Table 2: Treatment Modification Guidance for Symptoms of Infusion-Related Reactions including Immediate Hypersensitivity

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

Infusion-Related Reactions (IRR) are an important risk for M7824.

NCI-CTCAE Grade	Treatment Modification for M7824
Grade 1 – mild Mild transient reaction; in general, infusion interruption not indicated; intervention not indicated.	• Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. • Hold infusion if deemed necessary by the investigator.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, nonsteroidal anti inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h.	• Stop the infusion of the study intervention. • Increase monitoring of vital signs as medically indicated as participants are deemed medically stable by the attending Investigator. • If symptoms resolve quickly, resume infusion at 50% of original rate with close monitoring of any worsening signs and symptoms, otherwise dosing held until resolution of symptoms with mandated premedication for the next scheduled visit. • If not improving, consider administration of glucocorticoids and stop the infusion for that day. • If the participant has a second IRR Grade ≥ 2 on the slower infusion rate despite premedication, the infusion should be stopped, and the investigator may consider withdrawal of this participant from the study.
Grade 3 or Grade 4 – severe or life-threatening Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the infusion of study intervention immediately and disconnect infusion tubing from the participant with additional appropriate medical measures and closely monitor until deemed medically stable by the attending Investigator. Hospitalization and/or close monitoring is recommended. • Administration of glucocorticoids may be required. • For Grade 3 or 4 IRRs, permanent discontinuation of study intervention is mandated.
Once the infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded. Participants should be instructed to report any delayed reaction immediately.	

NCI-CTCAE Grade	Treatment Modification for M7824
Once the infusion is interrupted or rate reduced to 50% of previous infusion rate, it must remain decreased for all subsequent infusions. For all types and grades of infusion reactions, details about drug physical constitution, method of preparation, and infusion must be recorded. Participants should be instructed to report any delayed reaction immediately.	

Table 3 Immune-related adverse events (irAEs)

Immune-related AEs are specific to immunotherapies and vary by organ system.
The following immune-related AEs are important identified risks for M7824:

- Immune-related pneumonitis
- Immune-related hepatitis
- Immune-related colitis
- Immune-related nephritis and renal dysfunction
- Immune-related endocrinopathies
- (thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders)
- Immune related rash
- Other immune-related events (myositis, myocarditis, encephalitis)

The following immune-related AEs are important potential risks for M7824:

- Guillain-Barré syndrome
- Uveitis
- Pancreatitis
- Myasthenia gravis/myasthenic syndrome

Recommended guidance and management for specific irAEs are provided in the current NCCN (guideline available at http://www.nccn.org).

Requirements in addition to NCCN guidelines:

- 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 ≤ 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: in case of 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.

Table 4 Management of M7824 mediated Skin Reactions

Skin reactions are considered important identified risk for M7824. • Hyperkeratosis • Keratoacanthoma • Cutaneous squamous cell carcinoma (cSCC) • Basal cell carcinoma • Actinic keratosis
Management

• Discontinuation or termination not required in most cases. Continuation of treatment should be evaluated by the Investigator.
• Emollients may be used
• Develop diagnostic and treatment plan in collaboration with Investigator and dermatologist
• Treatment follow-up will depend on number and localization of lesions.
  ○ Single lesion: full excision may be recommended
  ○ Multiple lesion or location not suitable for full excision: Mohrs surgery, cryotherapy or other standard treatment options depending on pathology. Retinoids may be used after discussion with Investigator.
• Close clinical follow-up for re-evaluation, resolution and potential recurrence should be implemented
• In general, treatment of skin lesions should be based on local guidelines/standard of care.

Additional consideration: Keratoacanthoma lesions may resolve spontaneously without surgical intervention within weeks after discontinuing M7824. Consult with Medical Monitor as needed for management of skin lesions.

Table 5 Management of Treatment-Related Anemia

Anemia is considered an important identified risk for M7824. • All relevant hematological testing for treatment-related anemias should be done prior to a blood transfusion, if clinically feasible
Basic Anemia Evaluation

• CBC with emphasis on red cell indices
• If indicated and at clinical discretion, the following should be considered:
  ○ Iron studies
  ○ Serum Folate and Vit B12 values
  ○ Coagulation factors
  ○ Fecal occult blood
  ○ Urinalysis
  ○ Hormone panel: TSH, Erythropoietin
  ○ Peripheral blood smear

Further Recommendation Based on Suspected Etiology (in Addition to Basic Anemia Testing)

• Suspected Hemolysis
  ○ bilirubin, LDH, Coombs test, haptoglobin
• Suspected bleeding:
  ○ Consider imaging/interventional radiology consultation as indicated
  ○ Consider imaging and/or endoscopy as clinically indicated
• Suspected aplastic anemia:
  ○ Hematology consultation
  ○ Consider bone marrow aspiration/morphologic evaluation

Additional consideration: In general, blood transfusions and erythroid growth factors are permitted as clinically indicated.

Table 6 Management of Bleeding Adverse Events

Bleeding Adverse Events	

• Bleeding adverse events are considered important identified risk for M7824.
• In general, mild and moderate mucosal bleedings resolve without discontinuation of treatment.
• These events may include, but are not limited to the following:
  ○ Epistaxis
  ○ Hemoptysis
  ○ Gingival bleeding
  ○ Hematuria	

Non-tumor Bleeding	
Grading	Management
Grade 2	• If resolves to Grade ≤ 1 by the day before the next infusion, study intervention may be continued • If not resolved to Grade ≤ 1 by the day before the next infusion, but is manageable and /or not clinically relevant, assessment if clinically reasonable to administer the following infusion will be per PI discretion.
Grade 3	• Permanently discontinue treatment unless an alternative explanation can be identified (such as concomitant use of antithrombotic agents, traumatic events, etc.) • In case of alternative explanations, hold study treatment until the event recovers to Grade ≤ 1
Grade 4	• Treatment must be permanently discontinued if no alternative explanation is identified.
Tumor Bleeding	
Grade ≥ 2	• Study treatment must be held till the event recovers to Grade ≤ 1 • Permanently discontinue treatment if the Investigator considers the participant to be at risk for additional severe bleeding.

Table 7 Impaired Wound Healing

• Impaired wound healing is considered important potential risk for M7824.

- Elective surgery on study will be allowed per PI discretion.
- It is recommended to hold study intervention for approximately 4 weeks post major surgery for observation.

Post-operative wound healing should be closely monitored.

3.4 ASSESSMENTS ON TREATMENT

For assessments on treatment, please, see Study Calendar **3.5**

3.5 STUDY CALENDAR

Procedure	Screening[1]	Baseline / Week 1[2]	Week (2N+1)[3]	EOT[4]	Safety follow up[5]	Long Term follow up[6]
M7824[7]		X	X			
NIH Advance Directives Form[8]		X				
Medical History	X					
Height	X					
Physical exam, weight, vital signs, ECOG	X	X	X	X	X	
HIV, HCV, HepB	X					
EKG		X		X	X	
CBC with differential, platelets	X	X	X	X	X	
Biochemical profile[9]	X	X	X	X	X	
CD4 [12]	X					
ESR, CRP		X	X			
ACTH, TSH, Free T4, lipase, amylase		X	X[10]			
Urinalysis		X				
Serum pregnancy testing in women of childbearing potential (2.2)	X	X	X			
PT, INR, aPTT		X				
Tumor evaluation (CT Scan / MRI) [11]	X		X			X
Brain CT/MRI [12]	X					
Nuclear bone scan [12]	X					
Concomitant Medications		X	X	X	X	
Adverse events		X	X	X	X	
Optional biopsy for immune analysis and HPV testing [13]		X	X			
Research Blood (PBMCs/serum/plasma) [14]		X	X	X		
Telephone Follow Up					X	X

1. Screening evaluations performed within 28 days prior to the first drug administration, unless specified in Section **2.2.**
2. Baseline evaluations performed within 1 week of first drug administration.
3. Every odd numbered week for up to 51 weeks. M7824 administration and indicated evaluations can be done up to 3 days earlier or delayed up to 14 days due to holidays, inclement weather, conflicts, or similar reasons. The timing of subsequent administrations is then adjusted to maintain a 2 week-interval. In the event of a durable PR or CR after one year on trial further treatment may be held (even if a total of 26 doses have not been given) and scheduled assessments may be performed at every 3 months (+/- 2 weeks) intervals at the discretion of the investigator.
4. EOT – End of treatment visit: Where feasible, on the day of or within 7 days of the decision to discontinue treatment prematurely before completion of 26 doses. Does not need to be completed if drug is withheld after 26 doses.
5. 28 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.
6. Patients who have come off treatment for disease progression will be followed by phone annually for survival. Patients who have not progressed on treatment will continue to be followed and scanned per investigator discretion until progression. Those that completed one year of treatment will be invited for an additional year of treatment at the time of progression. Initial and follow up courses of treatment may extend beyond a year per investigator discretion.
7. M7824 administered IV at flat dose of 1,200 mg.
8. As indicated in Section **12.3**, all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required
9. Biochemical profile: sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, and total and direct bilirubin
10. Every 6 weeks
11. Every six 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 patients who have not experienced PD until they experience PD in order to assess PFS.
12. If clinically indicated
13. Optional biopsies at baseline and within one week of first imaging restaging.
14. Where feasible, research blood (PBMCs, serum, plasma) for all study assessments (see Section **Error! Reference source not found.**) will be collected at weeks 1, 3, 7 and every 6 weeks thereafter in selected patients per PI discretion.

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 generally be provided or paid for by the NIH Clinical Center.

3.6.2 Compensation

Participants will not be compensated on 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

Regardless of reason for removal from study therapy, patients will be asked to have a 28 day follow up safety visit. Patients who refuse to return for this visit will be asked to review any safety concerns by phone within this time period.

3.7.1 Criteria for Removal from Protocol Therapy

- Clinical or radiographic progression of disease except when the investigator feels the subject is still benefiting from treatment. (It is generally preferable for patients to remain on treatment past initial radiographic progression in case there is pseudo - progression, except when the investigator feels that the clinical picture warrants changing therapy at initial progression).
- Unacceptable Toxicity (as defined in **3.3.1**)
- Participant requests to be withdrawn from active therapy
- Start of another systemic anticancer treatment or participation in another investigational therapeutic trial. Focal palliative radiotherapy, ablation, or surgery to a site of disease will not necessitate removal from protocol therapy.
- Investigator discretion
- Positive pregnancy test

3.7.2 Off-Study Criteria

- Screen failure
- PI decision to end the study
- Participant requests to be withdrawn from study.
- Participant lost to follow up
- Investigator discretion

- Death

3.7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 4 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 within the next two weeks 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 MEDICATIONS / MEASURES

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 medication 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
- Any live vaccine therapies for the prevention of infectious disease. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccines or locally approved COVID vaccines).
- Systemic anticancer treatment.

4.2 OTHER MEDICATIONS

Subjects must be instructed to inform the investigators of the current or planned use or all other medications during the study (including prescription medications, over-the-counter medications, vitamins and herbal and nutritional supplements). Bisphosphonates started prior to screening

activities or initiated during the course of the study to control bone pain may be used with caution.

5 CORRELATIVE STUDIES FOR RESEARCH / PHARMACOKINETICS STUDIES

5.1 BIOSPECIMEN COLLECTION

5.1.1 Immune Assessments

Exploratory immunologic studies will be conducted to evaluate the study drug's effect on the immune response before and after treatment and help improve the administered therapy. This will include functional and quantitative analyses of immune cell types (CD4 and CD8 T cells, natural killer [NK] cells, regulatory T cells [Tregs], myeloid-derived suppressor cells [MDSCs], and dendritic cells) pre and post therapy as well as soluble factors which have been both positively and negatively associated with T cell activation and anti-tumor immunity (e.g., sCD27 and sCD40 ligand). In addition, T cell clonality and antigen specific T cell responses to E6/E7 oncoproteins before and after treatment will also be assessed. These assessments will help us evaluate the effect of treatment on the peripheral immune system. In addition to evaluate the effect of treatment on the tumor microenvironment, tumor immune infiltration as well as PD-L1 expression will be evaluated on optional biopsies pre and post treatment. Finally, TGF beta levels pre and post treatment will also be assessed to evaluate any correlation between changes in these values and response to treatment.

5.1.2 HPV status

As the primary efficacy analysis, we will try to focus on HPV positive malignancies, it will be important to determine the HPV status of patients' tumors. Therefore, where at all possible HPV testing will be done on archived tissue or optional biopsies. In addition to evaluate the correlation between peripheral HPV DNA testing and HPV testing on tumor tissue, circulating tumor DNA (e.g., HPV DNA) will also be assessed in the peripheral blood.

5.1.3 RNA Analysis

Where possible, RNA analysis will be done on the peripheral blood as well as archived tumor tissue or optional biopsies to help further evaluate changes in immune pathways with treatment as well as to determine tumor 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 in combination with M7824.

Test/assay	**Volume (approx.)**	**Type of tube**	**Collection point**	**Location of specimen analysis**
Standard and 123 immune cell subsets by FACS	PBMC	Sodium heparin (green top) tubes	See study calendar **3.5**	LTIB

Test/assay	Volume (approx.)	Type of tube	Collection point	Location of specimen analysis
Functional Analysis of immune cell subsets by FACS	PBMC	Sodium heparin (green top) tubes	See study calendar **3.5**	LTIB
Antigen Specific Immune Response by cytokine staining assay	PBMC	Sodium heparin (green top) tubes	See study calendar **3.5**	LTIB
sCD27 and sCD40 ligand by ELISA	Serum	SST	See study calendar **3.5**	LTIB
TGFβR1 levels by ELISA or bead based multiplex assays	Plasma	EDTA (lavender top)	See study calendar **3.5**	LTIB or Dr. Liang Cao's Lab
Immune Markers by IHC	Tumor samples	N/A	See study calendar **3.5**	GMB TIME Lab
RNA expression level of 770 genes	Whole blood	Sodium heparin (green top) tubes	See study calendar **3.5**	LTIB and NCI Frederick Genomic Core Facility
RNA expression level of 770 genes	Tumor samples	N/A	See study calendar **3.5**	LTIB and NCI Frederick Genomic Core Facility
HPV status by PCR of DNA	Tumor samples	N/A	See study calendar **3.5**	Dr. Hinrich's Lab
Circulating free tumor DNA (cftDNA) by PCR system	Plasma	EDTA (lavender top)	See study calendar **3.5**	Dr. Liang Cao Lab
T cell clonality by immunseq platform	Tumor samples	N/A	See study calendar **3.5**	LTIB and NCI Frederick Genomic Core Facility
T cell clonality by immunseq platform	PBMC	Sodium heparin (green top) tubes;	See study calendar **3.5**	LTIB and NCI Frederick Genomic Core Facility

Patients will undergo blood and tissue sampling for research purposes on the time points outlined in the Study Calendar **3.5**.

Tissue samples will be sent to Laboratory of Pathology for disease evaluation first, leftover samples will be used for research.

5.2 SAMPLE COLLECTION

5.2.1 Peripheral Blood Collection

Subjects will have approximately 100 mL of peripheral blood drawn at each time point specified in Study Calendar **3.5** (five to six, 10-mL green top sodium heparin tubes for PBMC samples, two 8-mL serum-separating tube for serum samples, two 10-mL lavender EDTA tubes.

5.2.2 Tissue Samples

Where available archival tumor samples will be requested. For patients with lesions amenable to biopsy, two optional biopsies may be performed at baseline and at first restaging. CT or other imaging guidance will be used as appropriate. Tumor samples will be sent to the Laboratory of Pathology for disease evaluation and storage.

5.3 RESEARCH ANALYSIS PERFORMED AT NIH

Unless otherwise specified, assessments will be performed at the Laboratory of Tumor Immunology and Biology at the NCI's Center for Cancer Research (CCR) and include:

5.3.1 Standard and 123 immune cell subsets PBMC analysis

Per PI discrection, PBMCs, separated by Ficoll-Hypaque density gradient centrifugation, will 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 [41] .

5.3.2 Functional Analysis of immune cell subsets from blood

This analysis may include phenotypic and functional analysis of immune-cell subsets (such as CD4 and CD8 T cells, NK cells, Tregs, and MDSCs) including proliferation, cytokine production, lysis, and suppression using flow based assays.

5.3.3 PBMC Antigen Specific Immune Response

Per PI discretion, PBMCs may be analyzed for antigen-specific immune responses to the oncoproteins E6 and E7 using an intracellular cytokine staining assay. PBMCs will be stimulated in vitro with overlapping 15-mer peptide pools encoding E6 and E7. Control peptide pools will include evaluation of the use of human leukocyte antigens (HLA) 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, tumor necrosis factor, and CD107a. If sufficient PBMCs are available, assays may also be performed for the development of T cells to other tumor-associated antigens.

5.3.4 Serum analyses of soluble factors

Per PI discrection, sera will be analyzed pre- and post-therapy for the following soluble factors: sCD27 and sCD40 ligand using commercial ELISAs.

5.3.5 Plasma analysis for TGFβR1 levels

Per PI discrection, plasma will be analyzed pre- and post-therapy for TGFβR1 levels (using ELISA or bead based multiplex assays in the LTIB or Dr. Liang Cao's Lab).

5.3.6 Analyses of Tumor Tissue for Immune Markers by IHC:

Study of immune infiltration as well as PD-L1 status by IHC within the tumor microenvironment pre vs. post treatment may be performed (collaboration with the GMB TIME Lab).

5.3.7 RNA analysis of blood and tumor tissue

Peripheral blood samples and tumor samples may be analyzed to evaluate immune related pathways related to cancer or a protocol therapy mechanism of action.
RNA expression level of 770 genes will be done using nanostring platform (LTIB and NCI Frederick Genomic Core Facility).

Fredrick genomic core facility:
Leidos Biomedical Research, Inc:
Dr. Xiaolin Wu
ATRF, Rm C3016
8560 Progress Drive
Frederick, MD 21701
Ph. 301-846-7677

5.4 SAMPLE STORAGE, TRACKING AND DISPOSITION

5.4.1 Sample 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.

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

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

Blood samples will be processed at:

Leidos Biomedical Research
Attn: Theresa Burks
1050 Boyles Street
Bldg. 496/Room 121
Frederick, MD 21702

On days samples are drawn, Jen Bangh at CSP (part of NCI Frederick Central Repositories) should be notified (phone: [301] 846-5893; fax [301] 846-6222). She will arrange same-day courier delivery of the specimens.

All data associated with the patient samples is protected by using a secure database. All Clinical Support Laboratory Staff receive annual training in maintaining records' confidentiality. 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 patient 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 coded, linked 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 patient-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.

5.4.3 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

5.4.3.1 BPC contact information

Please e-mail NCIBloodcore@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.4.3.2 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the Labmatrix utilized by the BPC. This is a secure program, with access to Labmatrix limited to defined Figg lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen.

Labmatrix creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without Labmatrix access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient 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.).

5.4.3.3 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°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 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 IRB approval.

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 tissues are stored 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 patient was enrolled.

5.4.5 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 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. Reporting will be per the requirements of section **7.2.1**.

5.5 SAMPLES FOR GENETIC/GENOMIC ANALYSIS

5.5.1 Assessment of HPV status

In patients with available tumor tissue (either archival or by optional biopsy), HPV testing will be performed using the Roche Cobas or Becton Dickinson HPV PCR based DNA assay, if no prior HPV testing of the tumor has been performed. This will be done through collaboration with Dr. Hinrich's Lab.

5.5.2 Circulating tumor DNA

If sufficient plasma is available, select patient samples may be analyzed for circulating tumor DNA (Collaboration with Dr. Liang Cao). Plasma DNA will be isolated with an automated purification system by Promega Corp using a system-attached bar-code reader to track samples and DNA products. The circulating tumor/HPV DNA will be quantified with a digital droplet PCR system from Bio-Rad to obtain precise quantification. This is just quantification by PCR. There is no DNA sequencing.

5.5.3 T cell clonality at NIH

Tumor tissue and blood from selected patients may be tested for T cell clonality using immunseq platform of adaptive biotechnologies (LTIB lab and Fredrick genomic core facility). V, D, and J genes of T cell receptors will be sequenced.

5.5.4 Management of Results

All samples will be coded as described in Section **7.2.1.** None of the assays are expected to generate incidental findings as they're not broad enough in scope and we are not returning research results.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) 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 first study intervention, Study Day 1 through 28 days after removal from study treatment or until off-study, whichever comes first. Adverse events that are serious need to be recorded through 28 days after the last intervention. Beyond 28 days after the last intervention and through long term follow up (survival of subject), 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 patient's outcome.

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 breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in Section **7.2.1**.

6.1.1 Exceptions to Data Collection and/or Reporting

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (e.g., an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)
- Coded, linked or identified data with approved outside collaborators under appropriate agreements.

Data will be shared through:

- An NIH-funded or approved public repository: clinicaltrials.gov.
- BTRIS (automatic for activities in the Clinical Center)
- Approved outside collaborators under appropriate individual agreements.
- Publication and/or public presentations.

Data will be shared:

- Before publication.

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

6.3.1 Antitumor Response

Tumor assessments may include the following evaluations: physical examination (with photograph and measurement of skin lesions, as applicable); cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis (pelvis scan is optional unless known pelvic disease is present at baseline); 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). 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.

At baseline, tumor lesions will be selected and categorized as target or non-target lesions. Target lesions include those lesions that are measureable per Section **6.3.2**. Malignant lymph nodes with a short axis diameter ≥ 15 mm can be considered target lesions. Up to a maximum of 2 target lesions per organ and 5 target lesions in total will be identified at baseline. These lesions should be representative of all involved organs and selected based on their size (those with the longest diameter) and their suitability for accurate repeated measurements. A sum of the longest lesion diameter (LLD) for all target lesions will be calculated and reported as the baseline sum LLD. For malignant lymph nodes identified as target lesions, the short axis diameter will be used in the sum of LLD calculation. All other lesions (or sites of disease) should be identified as non-target lesions (including bone lesions).

All post-baseline response assessments should follow the same lesions identified at baseline. The same mode of assessment (e.g., CT) used to identify/evaluate lesions at baseline should be used throughout the course of the study unless subject safety necessitates a change (e.g., allergic reaction to contrast media).

For the primary endpoint antitumor activity will be evaluated with target and/or non-target lesions according to RECIST Version 1.1

6.3.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded):

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

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

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

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

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

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

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

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

6.3.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

6.3.4 Response Criteria

All the scans performed at Baseline and other imaging performed as clinically required (other supportive imaging) need to be repeated at subsequent visits. In general, lesions detected at Baseline need to be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

Brain CT / MRI scan should be performed, if clinically indicated by development of new specific symptoms or on the discretion of the Prinicpal 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. The tumor response assessment will be assessed and listed according to the Study Calendar **3.5**.

The foreseen treatment duration is until disease progression verified by a scan subsequent to the initial documentation of PD, unacceptable toxicity, or any criterion for withdrawal from the trial occurs (see Section **3.6**). Before stopping the treatment, progressive disease should be confirmed

by imaging 4 to 6 weeks (preferably 6 weeks, but not later) after progression has been diagnosed according to RECIST 1.1 [42, 43]. If progression is based on the occurrence of a new lesion in an area not scanned at Baseline, a further on-study scan 6 weeks later should be considered before performing the 28-Day Safety Follow-up visit. 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.

The treatment should be stopped immediately, if the subject does not tolerate M7824 or if therapeutic failure occurs, which requires urgent treatment with an additional drug or results in clinically significant progression / deterioration.

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.

Any CR or PR should be confirmed according to RECIST 1.1 (**Table 8**). In the case of a PR or CR, a confirmatory CT or MRI scan should be done no sooner than 4 weeks (preferably at the scheduled 6-week interval).

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

Table 8. Response Criteria for Patients with Measurable Disease (i.e., Target Disease)

Target LesionsNon-Target Lesions New Lesions Overall Response Best Overall Response when Confirmation is Required*

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

	PD/not evaluated			
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
*	See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.			
**	Only for non-randomized trials with response as primary endpoint.			
***	In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			
Note:	Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.			

As an exploratory endpoint antitumor activity will also be evaluated according to iRECIST [44]:

Using iRECIST criteria the following will be incorporated into assessment:

1. An increase in the sum of target lesions of more than 20%, unequivocal increase in non-target lesions or new lesions result in iUPD (unconfirmed progressive disease); iUPD can be assigned multiple times as long as iCPD (confirmed progressive disease) is not confirmed at the next assessment.
2. 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 5 mm. Progression is confirmed in the non-target lesion category if subsequent imaging, done 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 size of previously seen new lesions is seen (≥5 mm for sum of new lesion target).
3. 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.

6.3.5 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.

6.3.6 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.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5. (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm)

7 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

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 here. 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 here.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.
In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.
To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis (approximately weekly) when patients are being actively treated on the trial to discuss each patient, enrollment and data management issues. Decisions about dose level enrollment and dose escalation will be made based on the toxicity data from prior patients.

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 patient 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.

7.4.2 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 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 SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with 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 Adverse Event of Special Interest (AESI)

Mucosal bleeding events which are at least possibly related to study drug (M7824) will be captured as AESIs. These events will not require expedited reporting to the study sponsor unless they also meet SAE criteria.

8.1.3 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 **8.1.4**)
- 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 patient or subject 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.

8.1.4 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)

8.1.5 Severity

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

8.1.6 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.

8.2 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 **7.2.1**. 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 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 Section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

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 overall survival, which includes death due to disease progression and hospitalization due to disease progression are part of the study objectives, and captured as an endpoint in this study, death/hospitalization 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 **7.2.1**.

8.5 Safety Reporting Criteria to the Pharmaceutical Collaborators

8.5.1 Reporting to EMD Serono Research

To be sent by Office of Sponsor and Regulatory Oversight, CCR, NCI/NIH:
The following reportable events must be submitted to EMD Serono within 2 business days or 3 calendar days (whichever comes first) using the applicable safety report form provided. The

Sponsor will assume responsibility for submitting the reportable event(s) to EMD Serono as well as ensuring that any local reporting requirements are completed in parallel.

- Serious Adverse Events
- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.
- In addition, all aggregated AEs including periodicity will be collected in tabulated form and reported to EMD Serono as outlined in the Collaborative Agreement.

To be sent by study team:
Reporting of Overdose of M7824

- An overdose is defined as any dose twice the recommended single dose. Any overdose must be recorded in the trial medication section of the eCRF.
- For monitoring purposes, any case of overdose, whether or not associated with an AE (serious or non-serious), must be reported to the sponsor.

There are no known symptoms of M7824 overdose to date. The Investigator should monitor closely for AEs should an overdose occur and use his or her clinical judgment in providing symptomatic / supportive care as medically indicated. There is no known antidote for M7824.

Contact information for submission of reportable events to EMD Serono:

Fax: +49 6151 72 6914

OR

E-mail: GlobalDrugSafety@merckgroup.com

Specifying:

PROTOCOL Number and/or Title

EMD Serono assigned Study Number

SUBJECT Number

SITE Number/PI Name

SAE/ONSET DATE

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here:
https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 Maternal exposure

If a patient 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 becomes 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 (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.6.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 2 months after the last dose of M7824.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 2 months after the last dose should, if possible, be followed up and documented.

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.

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESIS

This is a Phase II trial of M7824 in patients with recurrent or metastatic HPV associated malignancies. Patients will receive 1200 mg flat dose of M7824 IV every 2 weeks until PD or toxicity.

The primary objective of this trial is to determine the objective response rate to a combined anti PD-L1/TGF beta inhibitor in patients with HPV associated cancers. Patients will be enrolled into five cohorts: (1) Patients with anal cancer whose disease is naïve to checkpoint inhibition, (2) Patients with non-neuroendocrine cervical cancer naïve to checkpoint inhibition, (3) Patients with P16+ oropharyngeal cancer naïve to checkpoint inhibition, (4) Patients with rare HPV associated tumors (e.g., squamous cell rectal, vulvar, vaginal, penile cancer, neuroendocrine cervical) naïve to checkpoint inhibition, and (5) Patients with any HPV associated cancer whose disease is refractory to checkpoint inhibition. A secondary hypothesis (objective) will be to obtain preliminary data on DCR, duration of response, PFS, and OS in treated subjects. An exploratory hypothesis (objective) will be to evaluate exploratory immunologic studies to understand and improve the administered treatment.

10.2 SAMPLE SIZE DETERMINATION

10.2.1 Checkpoint Naïve Cohorts (Cohorts 1-4)

Data from the literature suggest that a response rate for HPV associated cancers including anal, cervical and oropharyngeal cancers receiving PD-1/PD-L1 treatment may be approximately 15%. This trial will try to demonstrate if the proposed therapy may be associated with an improved response rate.

In order to establish the efficacy of this treatment in patients naïve to therapy, the primary objective in cohorts 1-4 would be to determine if using the proposed agent would rule out a 15% response rate and result in a response rate consistent with 40%. As such, cohort 1-4 will be conducted using a Simon minimax two-stage phase II trial design (Simon R, Controlled Clinical Trials 10:1-10, 1989) in order to rule out an unacceptably low PR+CR rate of 15% (p0=0.15) in favor of an improved response rate of 40% (p1=0.40). Aiming to keep the cohorts deliberately small, with alpha=0.15 (probability of accepting a poor treatment=0.15) and beta = 0.20 (probability of rejecting a good treatment=0.20), the first stage of each cohort will enroll 8 evaluable patients, and if 0 to 1 of the 8 have a clinical response, then no further patients will be accrued. If 2 or more of the first 8 patients have a response in an individual cohort, then accrual would continue until a total of 13 evaluable patients have been treated in that cohort. As it may take up to several months to determine if a patient has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. Only HPV positive patients will be included in the first stage when determining if adequate responses have occurred. If any patients in the first stage are determined to be HPV negative, they will be replaced by additional patients until the first stage contains the intended number of HPV positive patients. If there are 2 to 3 patients with a response out of 13 patients, this would be an uninterestingly low response rate. If there were 4 or more of 13 (30.8%) 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 of each cohort is 65.7%.

10.2.2 Checkpoint Refractory Cohort (Cohort 5)

There is limited information in the published literature regarding potential response rates in this population, but it is expected to be low. A response rate clearly exceeding 5% would be of interest to obtain.

In order to establish the efficacy of this treatment in patients who are refractory to immune checkpoint therapy, the primary objective in this cohort would be to determine if using the proposed agent would rule out a 5% response rate and result in a response rate consistent with 25%. As such, this cohort of the trial will be conducted using a Simon minimax two-stage phase II trial design (Simon R, Controlled Clinical Trials 10:1-10, 1989) in order to rule out an unacceptably low PR+CR rate of 5% (p0=0.05) in favor of an improved response rate of 25% (p1=0.25). With alpha=0.10 (probability of accepting a poor treatment=0.10) and beta = 0.10 (probability of rejecting a good treatment=0.10), the first stage will enroll 13 evaluable patients, and if 0 of the 13 have a clinical response, then no further patients will be accrued in this cohort. If 1 or more of the first 13 patients have a response, then accrual would continue until a total of 20 evaluable patients who are refractory to therapy have been treated. As it may take up to several months to determine if a patient has experienced a response, a temporary pause in the accrual may be necessary to ensure that enrollment to the second stage is warranted. Only HPV positive patients will be included in the first stage when determining if adequate responses have occurred. If any patients in the first stage are determined to be HPV negative, they will be replaced by additional patients until the first stage contains the intended number of HPV positive patients. If there are 1 to 2 patients with a response out of 20 patients, this would be an uninterestingly low response rate. If there were 3 or more of 20 (15.0%) 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 51.3%.

It is expected that approximately 3 patients per month may enroll onto this trial. Thus, it is expected that 2 years may be required in order to enroll up to 72 evaluable patients. In order to allow for replacement of patients with HPV negative tumors or patients whom have previously received lymphodepleting chemotherapy as well as a small number of inevaluable patients in addition to screen failures the accrual ceiling will be set at 120 patients.

10.3 POPULATION FOR ANALYSES

A Modified Intention-to-Treat Analysis Dataset will be used. Only those patients who have measurable disease present at baseline and have had their disease re-evaluated at first restaging will be considered evaluable for response. (Note: Patients who exhibit objective disease progression prior to first restaging will also be considered evaluable.)

Evaluable participants will be evaluable for the primary efficacy analysis unless they are replaced due to negative HPV testing, inability to confirm HPV status, or prior lymphodepleting chemotherapy. (Efficacy of the study drug in patients who test negative for HPV as well as in patients whom previously received lymphodepleting chemotherapy will be assessed as correlative exploratory endpoints.)

Evaluable patients for objective response will have their response classified according to the definitions stated below.

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with M7824.

10.4 STATISTICAL ANALYSES

10.4.1 General Approach

The planned analyses for each objective is described in the subsections below.

10.4.2 Analysis of Primary Efficacy Endpoint(s)

The percentage of subjects that achieve an objective confirmed complete or partial overall tumor response using RECIST Version 1.1 will be evaluated per cohort (Cohort 1-5). If anti-tumor responses are observed, the 95% confidence interval of the response rate will be evaluated.

10.4.3 Analyses of Secondary Efficacy Endpoints

Disease control (confirmed response or SD lasting for at least 6 months) will be analyzed in a similar manner as the primary endpoint.

Data will be obtained on duration of response, PFS and OS.

At the conclusion of the trial, the response rates from cohorts 1-4 will be compared with a non-parametric two-sided test, Mehta's modification to Fisher's exact test. If the response rates are sufficiently similar ($p>0.20$ by Fisher's exact test), in addition to reporting their results individually by cohort, a secondary analysis will be to report a combined response rate based on total responses in cohorts 1-4 out of the total number of evaluable subjects in cohorts 1-4. This response fraction will be reported along with a 95% two-sided confidence interval.

10.4.3.1 Duration of Response

The duration of overall response will be evaluated by cohort. 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 PD is objectively documented, and is evaluated using the Kaplan-Meier method.

10.4.3.2 Progression-Free Survival

PFS will be evaluated by cohort and overall using Kaplan-Meier methods. PFS will be defined as the time from the date of first treatment to the date of disease progression or death (any cause) whichever occurs first. Subjects who do not have disease progression or have not died at the end of follow up will be censored at the last known date the subject was progression free.

10.4.3.3 Objective response

Objective response is a complete or partial radiographic response as defined by RECIST 1.1.

10.4.3.4 Disease control rate (DCR)

DCR is the percentage of patients who achieve a complete response, partial response and stable disease as defined by RECIST 1.1.

10.4.3.5 Overall Survival

OS will be evaluated by cohort and overall using Kaplan-Meier methods. OS will be defined as the time from the date of first treatment to the date of death (any cause). Subjects who are alive at the end of follow up will be censored at the last known date alive.

10.4.4 Safety Analysis

Safety endpoints will be analyzed as summary statistics during treatment and/or as change scores from baseline assessments. AEs will be coded as defined in the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be recorded and tabulated following each treatment. AEs will be recorded by severity, frequency, and relationship to the study intervention and will be presented by System Organ Class (SOC) designations and preferred term groupings. Information on each AE will include start date, stop date, severity, relationship, expectedness, outcome, and duration. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented either in a Table or a Listing.

In addition, overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 5.0 within dose cohorts and for the overall study population in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, and vital signs.

10.4.5 Baseline Descriptive Statistics

Baseline Characteristics will be described.

10.4.6 Planned Interim Analyses

Interim assessment of efficacy will be made according to the Simon two stage phase II designs of each cohort described in Section **10.2**.

10.4.7 Sub-Group Analyses

Each of the five cohorts will be evaluated independently. If feasible outcomes will be evaluated based upon specific tumor type and/or HPV type. Outcomes may also be evaluated with respect to treatment with prior lymphodepleting chemotherapy regimens or HIV status. Finally outcomes may be evaluated with respect to histologic subtypes (adenocarcinoma, squamous, poorly differentiated etc).

10.4.8 Tabulation of Individual Participant Data

Individual responses in a cohort may be depicted within a larger group using a waterfall plot or spider diagram.

10.4.9 Exploratory Analyses (Immune Responses)

Exploratory immune analyses will be conducted to evaluate anti-tumor immune responses induced by M7824. Immune response will be assessed among all subjects treated in each cohort. The magnitude of immune responses will be described. A subject will be considered evaluable for immune response if they receive at least one dose of treatment. The percentage of subjects with a positive immune response will be evaluated by cohort. For flow cytometry analyses on PBMC samples, Student T tests or Kruskal-Wallis and Wilcoxon rank sum tests as appropriate will be performed on percentages of TNF-α and/or IFN-γ expressing cells among the different cohorts to determine any significant differences in cell populations. For antigen specific T cell responses a positive immune response is defined by CMI reactivity in *ex vivo* stimulation using a flow cytometric readout (cytokine production or CD107 expression). Antigen-specific peptide challenge assays require a readout of >250 reactive T-cells/million cells above the background [45].

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

A CRADA (02666) is in place between the Laboratory of Tumor Immunology and Biology (LTIB), CCR NCI and EMD Serono, the manufacturer of M7824.

11.2 PATENT

The provisional patent application # 62/503,405 is for a method of inhibiting a malignancy associated with human papilloma virus (HPV) comprising administering to a subject an agent (specifically M7824) that blocks PD-L1 and TGF-beta pathways.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

Subjects from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. Efforts will be made to extend accrual to a representative population. Due to impaired cellular immunity which may affect the efficacy of treatment, patients with poorly controlled HIV as well as patents with detectable viral loads of hepatitis B and C will be excluded.

12.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because of unknown toxicities in pediatric patients.

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**). All subjects ≥ age 18 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 **12.6.1** for consent procedure.

12.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

Patients will receive evaluation of their disease at the National Cancer Institute's Clinical Center. The potential benefit to a patient that goes onto study is a reduction in the bulk of their tumor which may or may not have 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 Section **13**. All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. Patients will be examined and evaluated prior to enrollment. All evaluations to monitor the treatment of patients will be recorded in the patient chart. If

patients suffer any physical injury as a result of the participation in this study, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland.

The potential benefits to patients may include improvement of their condition or temporary relief of symptoms.

Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations. In all publications and presentations resulting from this trial, patients' anonymity will be protected to the maximum extent possible. Authorized personnel from the National Cancer Institute (NCI) and Food and Drug Administration (FDA) or other regulatory authorities may have access to research files in order to verify that patients' rights have been safeguarded. In addition, patient names will be given to the Central Registration to register and verify patients' eligibility.

12.5 RISK/BENEFIT ANALYSIS

12.5.1 Risks

12.5.1.1 Known Potential Risks

Some of the procedures performed on this study are not known to be associated with risk. These include urine tests and EKGs. Below are a list of procedures and study interventions that are associated with risk.

12.5.1.2 Potential Risks Associated with M7824

Participants may be harmed from being in this study by toxicity due to the drug or combination of drugs given during this study. M7824 is similar to immune check point inhibitors. There are preliminary data to suggest that not all patients benefit from immune check point inhibitors nor M7824. Additionally, there are preliminary data to suggest that an unexpectedly rapid progression of disease occurs in some patients receiving immunotherapy such as immune checkpoint inhibitors.

12.5.1.3 Risk of Optional Biopsies

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.

12.5.1.4 Risks of exposure to ionizing radiation

This research study involves the possibility of 8 CT CAP scans and 2 CT guided biopsies collected for research purposes.

The amount of radiation exposure you will receive from these procedures is equal to approximately 10.4 rem. The CT scans and CT guided biopsies in this study will expose the research participant to 34.7 years' worth of background radiation. This level of exposure results in an increased risk of cancer.

Subjects undergoing two optional biopsies collections will be exposed to 1.6 rem.

12.5.1.5 Risks Due to Contrast Agents for CT

Contrast agents can cause allergic reactions and kidney damage. Allergic reactions can include mild itching associated with hives but can also result in a serious life-threatening emergency from difficulty breathing. If this occurs, it is treatable.

12.5.1.6 Risk of MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. 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.

12.5.1.7 Risk of Gadolinium Enhanced MRI

The gadolinium infusion may cause mild symptoms such as coldness in the arm during the injection, a metallic taste, headache, and nausea. There are risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Procedure-related risks from MRI and gadolinium enhanced MRI will be explained fully during informed consent.

12.5.1.8 Research Blood Collection Risks

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

12.5.1.9 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.

12.5.2 Benefits

The potential benefit to a patient that goes onto study is a reduction in the bulk of their tumor which may or may not have favorable impact on symptoms and/or survival.

12.6 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable 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 here.

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

For participants addressed in Section **Error! Reference source not found.**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **Error! Reference source not found.**.

12.6.2 Request for Waiver of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in Section **2.2.1** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether or not they are eligible to sign a consent for additional screening.

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, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor 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 as applicable, Food and Drug Administration (FDA).

13.2 Quality Assurance and Quality Control

The 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 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 National Cancer Institute 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 the 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 the 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 the clinical site 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 DESCRIPTION OF M7824

M7824 will be supplied by EMD Serono as a sterile liquid formulation. Each vial of Powder for Concentrate for Solution for Infusion (freeze-dried formulation) is packaged in United States Pharmacopeia (USP) and European Pharmacopeia (Ph Eur) type I glass vials. Each vial is filled with 45 mg of M7824 (45 mg/vial) as preservative-free powder containing histidine, trehalose dihydrate, sodium chloride, L-methionine and polysorbate 20 (Tween 20). The vials are closed with a rubber stopper in lyophilization format complying with USP and Ph Eur and sealed with an aluminum plastic crimping cap. Only excipients that conform to the current USP and / or Ph Eur are used for M7824 drug product.

The Concentrate for Solution for Infusion (liquid formulation) is packaged at a 10 mg/mL concentration in USP / Ph Eur type I 50R vials that are filled with drug product solution to allowan extractable volume of 60 mL (600 mg/60 mL). The liquid formulation contains histidine, trehalose dihydrate, sodium chloride, L-methionine and polysorbate 20 (Tween 20). The vials are closed with rubber stoppers within serum format complying with USP and Ph Eur with an aluminum crimp seal closure.

For applications in clinical studies, the liquid formulation is diluted directly with 0.9% NaCl solution (sodium chloride injection) supplied in an infusion bag.

The estimated volumes of delivery are anticipated to be no more than 250 mL, which are clinically acceptable.

14.2 TOXICITY

The immunoglobulin portion of M7824 molecule is identical to avelumab (Bavencio). Respective warnings and precautions for grade 2 or higher immune-mediated pneumonitis, immune-mediated colitis, immune-mediated endocrinopathies, immune-mediated hepatitis) and infusion reactions are included in the prescribing for Bavencio (bavencio.com). Participants will be pre-medicated to prophylax against infusions reactions. The following additionally significant immune-mediated adverse reactions have occurred in less than 1% of 1738 participants treated with BAVENCIO: myocarditis with fatal cases, myositis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barré syndrome, and systemic inflammatory response. The above irAEs are all considered an anticipated risk of treatment with M7824 and thus will not be considered DLTs.

In a phase 1, open-label 3+3 dose-escalation study of M7824 in 16 participants, 3 participants experienced grade 3 drug-related adverse events including skin infection secondary to grade 2 bullous pemphigoid, lipase increased, and colitis with associated anemia. There were no grade 4 – 5 treatment related adverse events. Please see table below for details.

Treatment-related adverse events

	3 mg/kg (n = 3)		*10 mg/kg (n = 3)*		*20 mg/kg (n = 7)*		*Total (n = 16)*	
	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3	Any Grade	Grade 3
Participants with any event**	**2 (66.7)**	**1 (33.3)**	**1 (33.3)**	**0 (0.0)**	**4 (57.1)**	**2 (28.6)**	**7 (43.8)**	**3 (18.8)**
Anemia					1 (14.3)	1 (14.3)	1 (6.3)	1 (6.3)
Bullous pemphigoid	1 (33.3)						1 (6.3)	
Colitis					1 (14.3)	1 (14.3)	1 (6.3)	1 (6.3)
Dermatitis acneiform			1 (33.3)				1 (6.3)	
Dyspnea exertional***					1 (14.3)		1 (6.3)	
Hyperthyroidism					1 (14.3)		1 (6.3)	
Hypophosphatemia					1 (14.3)		1 (6.3)	
Hypothyroidism			1 (33.3)		1 (14.3)		2 (12.5)	
Infusion-related reaction					1 (14.3)		1 (6.3)	
Keratoacanthoma					1 (14.3)		1 (6.3)	

	3 mg/kg (n = 3)		*10 mg/kg (n = 3)*		*20 mg/kg (n = 7)*		*Total (n = 16)*	
Lipase increase					1 (14.3)	1 (14.3)	1 (6.3)	1 (6.3)
Nausea	1 (33.3)						1 (6.3)	
Pruritus	1 (33.3)						1 (6.3)	
Rash maculo-papular	1 (33.3)		1 (33.3)				2 (12.5)	
Skin infection	1 (33.3)	1 (33.3)					1 (6.3)	1 (6.3)
Vomiting	1 (33.3)						1 (6.3)	

**There were no treatment-related AEs in the 3 participants treated with 1 mg/kg M7824.

***The differential for this dyspnea was pneumonitis vs. lymphangitic spread of disease (disease progression).

As of August 2017, > 500 participants have been treated with M7824 across multiple solid tumor expansion cohorts. The safety profile is consistent with other monotherapy checkpoint inhibitors, with the exception of keratoacanthomas and cutaneous squamous cell carcinomas which have occurred in approximately 3-5% of participants, and are well managed with surgical excision. These lesions have not been a criterion for treatment discontinuation, but thus far have all spontaneously regressed following treatment discontinuation.

In addition, after discussion among NCI investigators on multiple protocols using M7824, multiple 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 colitis or cystitis 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. It is hypothesized that this possible increased bleeding risk may be due to TGF beta inhibition which has an effect on angiogenesis; bleeding has also been observed in participants receiving M7824 and may be drug-related (e.g., gum bleeding, nose bleeds, coughing up blood, blood in their urine, or blood in the stool). Accordingly, participants will be notified of the same possible risk in the informed consent document for this study (e.g., gum bleeding, nose bleeds, coughing up blood, blood in their urine, or blood in the stool).

At least 2 instances of nodular regenerative hyperplasia have been observed with the use of this agent.

14.3 PREPARATION, HANDLING, AND STORAGE

M7824 drug product must be stored at 2°C to 8°C until use. The storage condition is based on data from ongoing long term 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. M7824 must not be frozen. Rough shaking of the reconstituted solution must be avoided.

M7824 must not be used for any purpose other than the study.

The contents of the M7824 vials are sterile and nonpyrogenic, and do not contain bacteriostatic preservatives. Any spills that occur should be cleaned up using the facility's standard cleanup procedures for biologic products.

Any unused portion of the solution should be discarded in biohazard waste disposal with final disposal by accepted local and national standards of incineration.

14.4 DOSAGE AND ADMINISTRATION

See Section **3.2**

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16 APPENDICES

16.1 APPENDIX A PERFORMANCE STATUS CRITERIA

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