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Title: A Phase I/II Study of Immunotherapy Combination BN-Brachyury vaccine, M7824, N-803 and Epacadostat (QuEST1)

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Drug Name:	BN-Brachyury	MSB001359C (M7824, Bintrafusp alfa)	ALT-803 (N-803)	INCB024360 (Epacadostat)
IND Number:	BB-IND 17851			
IND Sponsor	CCR, NCI			
Manufacturer:	Bavarian Nordic, Inc.	EMD Serono	Immunity Bio	Incyte
Supplier:	Bavarian Nordic, Inc.	EMD Serono	Immunity Bio	Incyte

Commercial Agents: None

PRÉCIS

Background:

- PD-1/PD-L1 signaling appears to be a major inhibitor of activated T cell anti-tumor immune responses. The rapid, deep and durable responses seen in various malignancies with PD-1/PD-L1 targeted agents demonstrate that blockade of this axis is key to facilitating immune responses within the tumor microenvironment (TME).
- Prostate cancer is poorly recognized by T cells. Lack of an immune response is one explanation for the lower response rates (<15%) observed with anti-PD-1/PD-L1 therapies for prostate cancer.
- Increasing response rates will likely require therapeutic nullification of multiple immune deficits by combining immunotherapies that generate tumor-specific T cells (vaccine), dampen the inhibitory milieu of the TME, and enhance T and NK cell activity within the TME.
- A quick efficacy seeking trial, utilizing sequential arms offers a means to identify signals of activity for combinations of immunotherapy, added sequentially, in castration-resistant prostate cancer (CRPC) participants.
- BN-Brachyury is a novel recombinant vector-based therapeutic cancer vaccine designed to induce an enhanced immune response against brachyury, which is overexpressed in many solid tumor types, including prostate adenocarcinoma. BN-Brachyury collectively refers to the priming doses (MVA-BN-Brachyury) and the boost doses (FPV-Brachyury) of the vaccine platform.
- M7824 is a bifunctional fusion protein consisting of an anti-programmed death ligand 1 (PD-L1) antibody and the extracellular domain of transforming growth factor beta (TGF-β) receptor type 2, a TGF-β trap. M7824 can also mediate antibody-dependent cellular cytotoxicity in vitro.
- N-803 is an IL-15/IL-15Rα superagonist complex that can enhance NK cell mediated ADCC and T-cell cytotoxicity.
- Synergistic anti-tumor effects have been observed *in vitro* when combining M7824 and N-803, and in vivo when combining these agents with tumor vaccine in animal models.
- IDO1 is overexpressed in many solid tumors and can contribute to immune escape by tumor cells. INCB024360 (Epacadostat) is an IDO1 inhibitor under investigation in combination with different immunotherapies in treatment of various malignancies.
- In treating of CRPC, we hypothesize that these agents and their effects will be complementary. Tumor-specific T cells generated by vaccine may become more functional in a TME following treatment with M7824 and Epacadostat. N-803 can further enhance the activity of antigen-specific T cells as well as NK cells.

Objective:

- To determine if there is clinical benefit to any of a set of 3 possible treatments for participants with CRPC:
    - BN-Brachyury + M7824

- BN-Brachyury + M7824 + N-803
- BN-Brachyury + M7824 + N-803 + Epacadostat

Eligibility:

- Adults with histologically proven CRPC, or metastatic solid tumor of any type for which there is no standard treatment or standard treatment has failed.
- Adequate organ function as defined by liver, kidney, and hematologic laboratory testing.
- Participants with acquired immune defects, active systemic autoimmune disease, history of organ transplant, history of chronic infections, or history of active inflammatory bowel disease are excluded.

Design:

Open label Phase I/II trial with following randomization during the expansion.

Phase I: Cohort 1, Arm 1.1

- Up to 18 participants with any solid tumor will be enrolled in dose escalation Cohort 1 for treatment in Arm 1.1 (flat dose of M7824 + different dose levels of N-803).

Phase IIA: expansion with sequential enrollment into Cohort 2A, Arms 2.1A, 2.2A and 2.3 A

- Concurrently with the enrollment to Arm 1.1, 13 participants with CRPC will start enrollment in Cohort 2A for treatment in Arm 2.1A (M7824 + BN-Brachyury).
- When safe dosing of N-803 is identified during Phase I, 13 participants have enrolled in arm 2.1A and the first 6 participants, treated in Arm 2.1A, have met safety requirements, 13 participants with CRPC will start enrollment in Cohort 2A for treatment in Arm 2.2A (M7824 + BN-Brachyury + N-803).
- When 13 participants have enrolled in Arm 2.2A and the first 6 participants, treated in Arm 2.2A, have met safety requirements, 13 participants with CRPC will start enrollment in Cohort 2A for treatment in Arm 2.3A (M7824 + BN-Brachyury + N-803 + Epacadostat).

Phase IIB: expansion with randomized enrollment into Cohorts 2D and 2R, Arms 2.1B, 2.2B. and 2.3B

- Each Arm in Cohorts 2D and 2R: 2.1B, 2.2B and 2.3B will be open for additional enrollment (25 evaluable participants total) when the initial 13 participants have accrued, safety requirements are meet and a positive signal (defined as Objective Response by RECIST 1.1 or sustained PSA decrease ≥ 30% sustained for > 21 days) in ≥ 2 participants is shown.
- If only one arm is open for additional enrollment, participants will be directly assigned to this arm. If 2 arms are open for additional enrollment, participants will be randomized between these 2 open arms. If 3 arms are open for additional enrollment, participants will be randomized among these 3 open arms.

If there are ≥ 6 of 25 participants with a positive signal of activity in any expansion arm, that arm will be considered of interest for future studies.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference for 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 if there is clinical benefit to any of a set of 3 possible treatments for participants with castration-resistant Prostate Cancer (CRPC):
    - BN-Brachyury + M7824
    - BN-Brachyury + M7824 + N-803
    - BN-Brachyury + M7824 + N-803 + Epacadostat

1.1.2 Secondary Objectives

- Evaluate PFS in CRPC participants treated with:
    - BN-Brachyury + M7824
    - BN-Brachyury + M7824 + N-803
    - BN-Brachyury + M7824 + N-803 + Epacadostat
- To characterize the safety profile of the above combinations and M7824 + N-803

1.1.3 Exploratory Objectives:

- To study M7824 pharmacokinetics;
- To study anti-drug antibody levels (ADA);
- To study tryptophan and kynurenine levels in participants treated with Epacadostat;
- To analyze Immunologic Parameters before and after combined treatment;
- To analyze Prostate-specific Membrane Antigen (PSMA) positive extracellular vesicles (EV) and immune EVs;

- Correlate immunologic outcomes with clinical data and outcomes.

1.2 BACKGROUND AND RATIONALE

Treatment with immune checkpoint modulators can produce dramatic and sometimes durable responses in patients with several types of advanced cancers. Such responses demonstrate the power of an appropriately manipulated immune system. Unfortunately, this is only seen in 15-25% of unselected patients in many cancers, and even fewer in cancers such as prostate, which lack a robust tumor immune cell infiltrate. Data presented at ESMO 2016 from a phase I trial of pembrolizumab for PD-L1 positive advanced prostate cancer showed an ORR of 13%, with no CRs. There were no ORs observed in 17 unselected prostate cancer patients treated with nivolumab in a phase I trial in solid tumors[1] and no ORs in 17 unselected mCRPC patients treated with avelumab (anti-PD-L1) in a phase I trial in solid tumors.[2]

Three key components of a successful anti-tumor immune response are:

1) presence of effector cells in the form of antigen specific T lymphocytes and/or natural killer cells

2) the ability of those cells to traffic to tumor

3) effective cytotoxicity of those cells within the tumor microenvironment (TME)

In cases of success, a given immunotherapy compensates for a deficient component of anti-tumor immune activity. For example, it is hypothesized that in clinical responders, anti-PD-1/PD-L1 agents overcome PD-1 axis mediated suppression of T cell cytotoxicity within the TME. Alternatively, adoptive cellular therapies can introduce tumor antigen-specific T cells. The limited frequency of objective responses seen across the board with these strategies indicate that in most patients, correcting only one deficiency in the anti-tumor response is not sufficient. It is currently impossible to know which critical immune function(s) needs enhancement in each individual patient and therefore impossible to know which monotherapy will be effective in each patient. A multi-pronged pharmacologic approach utilizing multiple immune therapies is warranted as we aim to improve clinical outcomes in tumors such as prostate cancer that lack an inflamed phenotype. A recent report highlighted the potential for improvements in outcomes with combination of immunotherapy in prostate cancer. Men with mCRPC and ARV-7+ circulating tumors cells were treated with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 3 weeks for 4 doses, followed by maintenance nivolumab 3 mg/kg every 2 weeks. The PSA 50% response rate was 1/15 (7%). Furthermore, ORR was 2/8 (25%) and durable PFS rate was 3/15 (20%).[3] This minimal clinical signal was associated with significant immune related adverse events with grade 3-4 adverse events occurring in 7/15 (46%) men with (no grade 5 irAE).

The use of novel combination approaches is in keeping with the Cancer Moonshot Taskforce's mandate which called for the use of innovative strategies to rapidly translate new agents from bench to bedside. Rational combination of immune therapies is a plausible strategy to achieve this aim and is especially warranted in treating patients who have exhausted most, if not all, therapeutic options. A quick efficacy seeking trial will add an immunotherapy to each sequential cohort until a signal of activity is identified. Enhancing immunity via several different mechanisms is a promising means to produce objective responses in a substantially increased portion of patients. Below we describe four treatment agents that possess potential to enhance anti-tumor immunity in CRPC patients.

1.2.1 BN-Brachyury

Epithelial-to-mesenchymal transition (EMT) is a reversible process during which cells switch from a polarized, epithelial phenotype into a highly mobile, mesenchymal phenotype.[4] Numerous observations support the concept that the EMT process plays a role in the progression of human carcinomas [5] and data demonstrate that the transcription factor brachyury confers upon cells a mesenchymal phenotype as well as migratory and invasive capabilities and enhances tumor cell progression.[6] Investigators in the LTIB identified the overexpression of brachyury mRNA in cell lines of lung, colon and prostate cancers, but not in the majority of normal tissues tested, with the exception of expression in the testis and low levels of expression in B cells pooled from multiple normal donors. However, it is likely that this expression of brachyury in B-cells is from EBV infected cells. Preclinical studies suggest that brachyury expression by CD19+ B cells does not select them for lysis by brachyury-specific CD8+ T cells [7] and clinical studies of brachyury specific vaccines have shown no decrease in B-cells despite good brachyury specific immune responses.[8] Furthermore, other studies quantified brachyury expression in normal tissue and demonstrated low level or no expression in normal tissue except for testis.[6, 9-11]

Analyses of prostate tumor samples have shown higher levels of brachyury expression to be associated the presence of poor prognostic factors, including higher Gleason score, perineural invasion and capsular invasion. [12] Additionally, it is a highly immunogenic target. Brachyury-specific T cells have been observed following vaccine targeting other antigens, a phenomenon referred to as antigen cascade.

It is important to note that, as a manifestation of tumor plasticity, brachyury expression is thought to take place in a transient fashion along the course of tumor progression. Therefore, tumor samples may be negative for brachyury expression, while disseminated tumor cells might still be positive for expression of the target brachyury. For this reason, expression of brachyury on the primary tumor is not thought relevant as an inclusion criterion for patients receiving brachyury-targeted vaccine.[13, 14]

MVA-BN-Brachyury and FPV-Brachyury are the components of a novel recombinant vector-based therapeutic cancer vaccine platform developed by the LTIB in collaboration with our CRADA partner Bavarian Nordic, Inc. The vaccine is designed to enhance the immune response against brachyury. This vector-based vaccine regimen consists of two priming doses of MVA-BN-Brachyury, followed by FPV-Brachyury booster doses. These vaccines encode the transgenes for brachyury as well as a triad of human T-cell costimulatory molecules (TRICOM: B7.1, LFA3, and ICAM-1). TRICOM has previously been evaluated in several clinical trials.[13, 15-20] These vaccines differ from the previous generation of TRICOM-based vaccines in that the priming vector is not vaccinia virus, but a replication-incompetent form of vaccinia designated Modified Vaccinia Ankara (MVA) or fowlpox based.

MVA has an improved safety profile when compared with vaccinia and its inability to replicate in human cells also allows MVA to be administered more than once without significant host neutralizing immune response.[21-26] Similarly, several studies have shown recombinant fowlpox vectors to have an excellent safety profile. [27] They are unable to replicate in mammalian cells, minimizing production of host vector neutralizing immunity and enabling administration of multiple booster vaccinations.

Experiments conducted at the LTIB demonstrated that MVA-BN-Brachyury is able to efficiently infect and direct the expression of the encoded transgenes, brachyury, B7-1, ICAM-1 and LFA-3

in human DCs. DC's infected with MVA-BN-Brachyury were able to induce IFN-γ production by brachyury-specific CD8 and CD4 T cells in vitro (**Figure 1**).

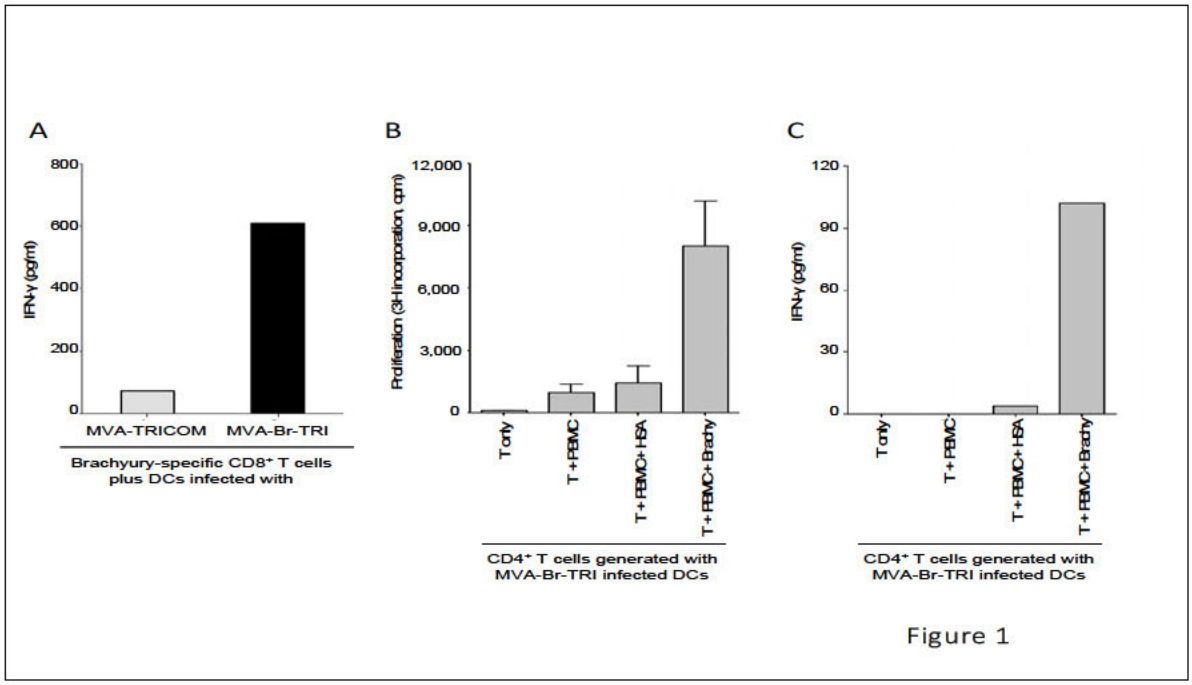


Figure 1: IFN-γ production by brachyury-specific CD8 and CD4 T cells *in vitro*

Data from a phase I dose-escalation study of MVA-BN-Brachyury in patients with advanced solid tumors demonstrated it to be safe and well tolerated (NCT02179515). Maximum tolerated dose was not reached and not dose limiting toxicities were observed. Of the 34 patients with samples sufficient for evaluation, 28 (82%) developed $CD4^+$ and/or $CD8^+$ T cell brachyury-specific immune responses evidenced by production of interferon gamma by s following incubation with peptide encoding brachyury.[28] The background signal (obtained with the HLA peptide pool) and any value obtained prior to vaccination, was subtracted from those obtained after vaccination ([post-brachyury − post-HLA] − [pre-brachyury − pre-HLA]). An antigen-specific immune response to brachyury was scored as positive if a patient had more than 250 CD4+ or CD8+ T cells that produced IFN-γ, TNF, IL-2, or were positive for CD107a at the end of the stimulation assay per 1x106 cells that were plated at the start of the assay.

Of the 28 patients with brachyury-specific immune responses, 20 (71%) exhibited CD107a+ T cells, a degranulation marker associated with tumor lytic cells.[29] Polyfunctional brachyury specific T cells were detected at all dose levels, with 2/3 (66%) patients developing brachyury specific T cells post vaccination at dose level one, 12/15 (80%) patients at dose level two, and 14/16 (88%) patients at dose level three. One concern is the observation that most patients did not maintain brachyury-specific immune responses during the course of the trial. Aiming to prolong immune responses, we will employ MVA-BN-Brachyury followed by FPV-Brachyury boosters.

Bavarian Nordic is a CRADA partner and will supply the BN-brachyury vaccines.

1.2.2 Anti-PD-L1 TGF-β trap (M7824)

M7824 (MSB0011359C) is a bifunctional fusion protein combining an anti-programmed death ligand 1 (PD-L1) antibody and the extracellular domain of transforming growth factor beta (TGF-β) receptor type 2, a TGF-β trap.

Transforming growth factor beta (TGF-β) has tumor-suppressor effects in the pre-malignant state. However, elevated levels of TGF-β have been found to correlate with poor outcomes in prostate cancer.[30] TGF-β has been associated with malignant progression, evasion of immune surveillance, invasion, and metastasis.[31-33] Its direct effects on T cells include decreases in perforin, granzymes, interferon gamma (IFN-γ), Fas ligand (FasL), and natural killer (NK) group 2D (NKG2D). It can also decrease NKG2D and major histocompatibility complex (MHC) class I polypeptide sequence A (MICA) in NK cells.[34] TGF-β is also implicated in the expansion of Tregs [35].

Expression of PD-L1 has been linked to immune evasion by tumor cells and poor prognosis in several malignancies.[36] Initial data from clinical trials of anti-PD-1 therapies in mCRPC did not yield many clinical responses, suggesting that PD-L1 expression may not be present in CRPC.[1, 37] However, more recent studies have observed PD-L1 expression in enzalutamide-resistant prostate cancer.[38, 39] Suggesting a role for anti-PD-1/PD-L1 therapy in enzalutamide resistant patients, a small cohort study in men with metastatic prostate cancer on enzalutamide linked increased numbers of circulating PD-L1/2+ DC with enzalutamide refractoriness.[38] The frequency of PD-L1/2 positive DCs in circulating blood was significantly lower in enzalutamide naïve (n=3) and enzalutamide responders (n=4), compared to non-responders(n=8). There was also a trend toward increasing PD-L1/2+ DC's in patients who had been on enzalutamide longer.

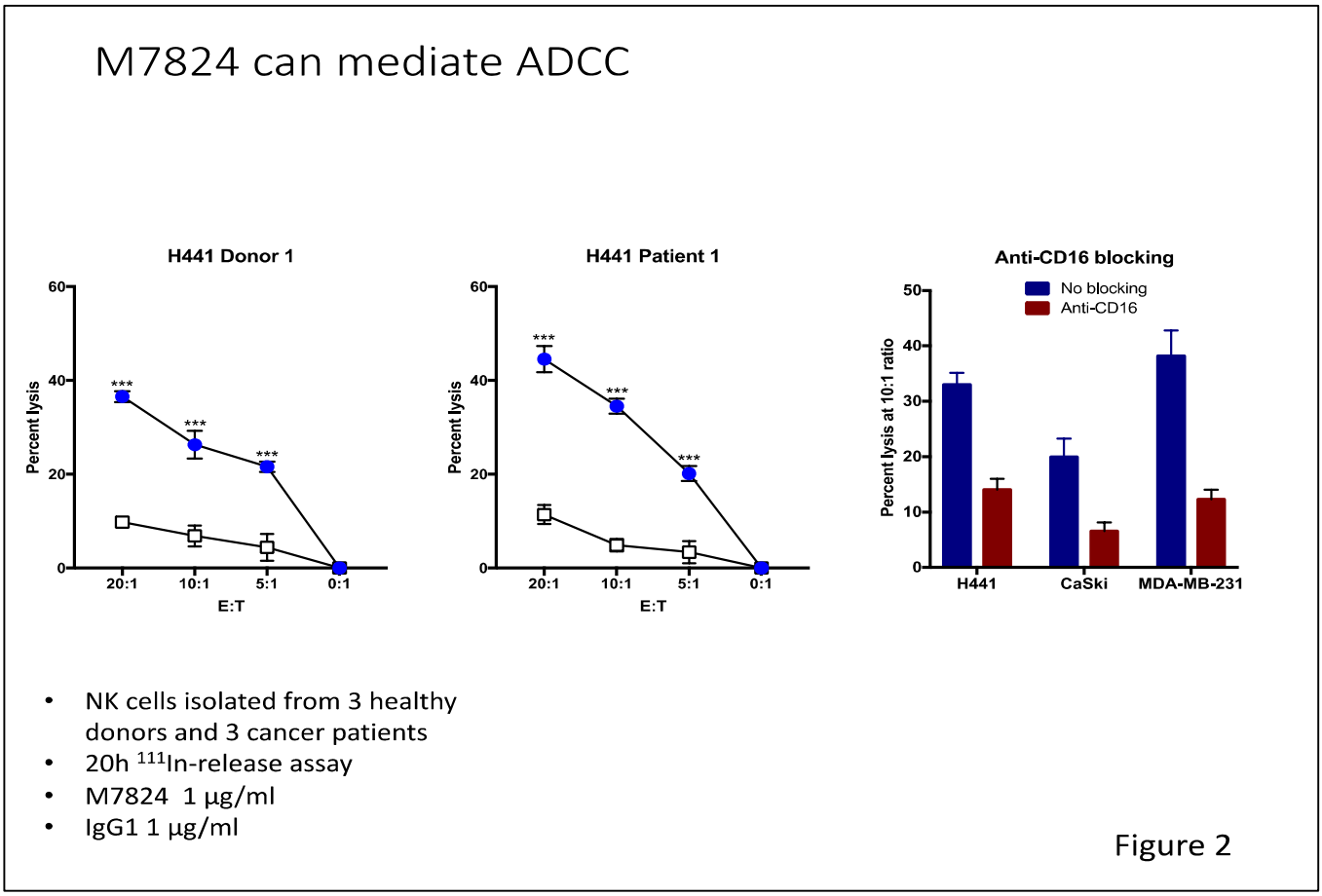
Unpublished data from the LTIB suggest that vaccinating with a pox viral vector containing a tumor associated antigen (which is also a self-antigen) leads to upregulation of PDL1 in T-cell poor murine tumor models, likely due to trafficking of activated T-cells to the tumor and subsequent release of IFG-gamma. This may explain why therapeutic vaccines alone rarely lead to objective responses and provides the rational for combination with agents targeting PD-1 or PD-L1.

Nonetheless, the utility of anti-PD-L1 therapy in combination approaches, especially ones that directly cause an anti-tumor immune response, is unknown. Another study at the NCI showed that PARP inhibition with durvalumab (anti-PD-L1) in patients that had progressed on either abiraterone or enzalutamide was associated with PSA declines in the majority of patients on treatment (7/16). PARP inhibition is associated with double stranded DNA breaks which are a potent activator of the STING pathway which leads to interferon upregulation.[40] Work aimed at further understanding these findings is ongoing. Taken together, the lack of signal in anti-PD-1 trials as monotherapy in prostate cancer and activity seen with strategies designed to increase T-cell inflammation or activation, we believe that strategies aimed at focusing an immune response on the tumor (e.g. vaccine) while also providing for optimal activity of anti-tumor effector cells within the tumor microenvironment (e.g. M7824, ALT-803, epacadostat) will be required for enhancing efficacy of immunotherapeutic approaches in prostate cancer.

M7824 is a multifunctional agent. It has been shown to simultaneously bind PD-L1 and TGF-β, as well as block PD-L1 signaling and TGF-β signaling in vitro. Furthermore, in a murine model (EMT-6 breast cancer), M7824 demonstrated superior anti-tumor activity compared to treatment with anti-PD-L1 monoclonal antibody or control antibody attached to TGF-β trap alone. All 13

mice in the breast cancer model had complete responses and this treatment extended survival in a dose-dependent manner. Depletion studies demonstrated that anti-tumor efficacy of M7824 was CD8 cytotoxic T-cell and NK-cell dependent, whereas M7824 decreased TGF-β in the serum, bound PD-L1 within the tumor, and increased CD8+ T-cell infiltration of tumor. Treatment of NSCLC cells with M7824 *in vitro* and *in vivo* attenuated features of TGF-β1-mediated mesenchymalization, including mesenchymal marker expression, proliferation suppression, and chemoresistance. Furthermore, M7824 can mediate ADCC in vitro. Cytotoxicity assays conducted at the

Figure 2: M7824 can mediate ADCC



LTIB demonstrated that mixing normal donor or cancer patient NK cells with M7824 induces ADCC of human tumor cells. This effect was abrogated by addition of anti-CD16 blocking antibodies (**Figure 2**).

Murine studies performed at the LTIB combined M7824 with a vaccine targeted to Twist1, a transcription factor involved in murine EMT.[5] The combination resulted in prolonged survival following tumor implantation, compared to either treatment alone (**Figure 3**). Although the EMT processes in human and mouse are distinct, these data suggest that combining EMT targeted vaccine with M7824 may be synergistic.

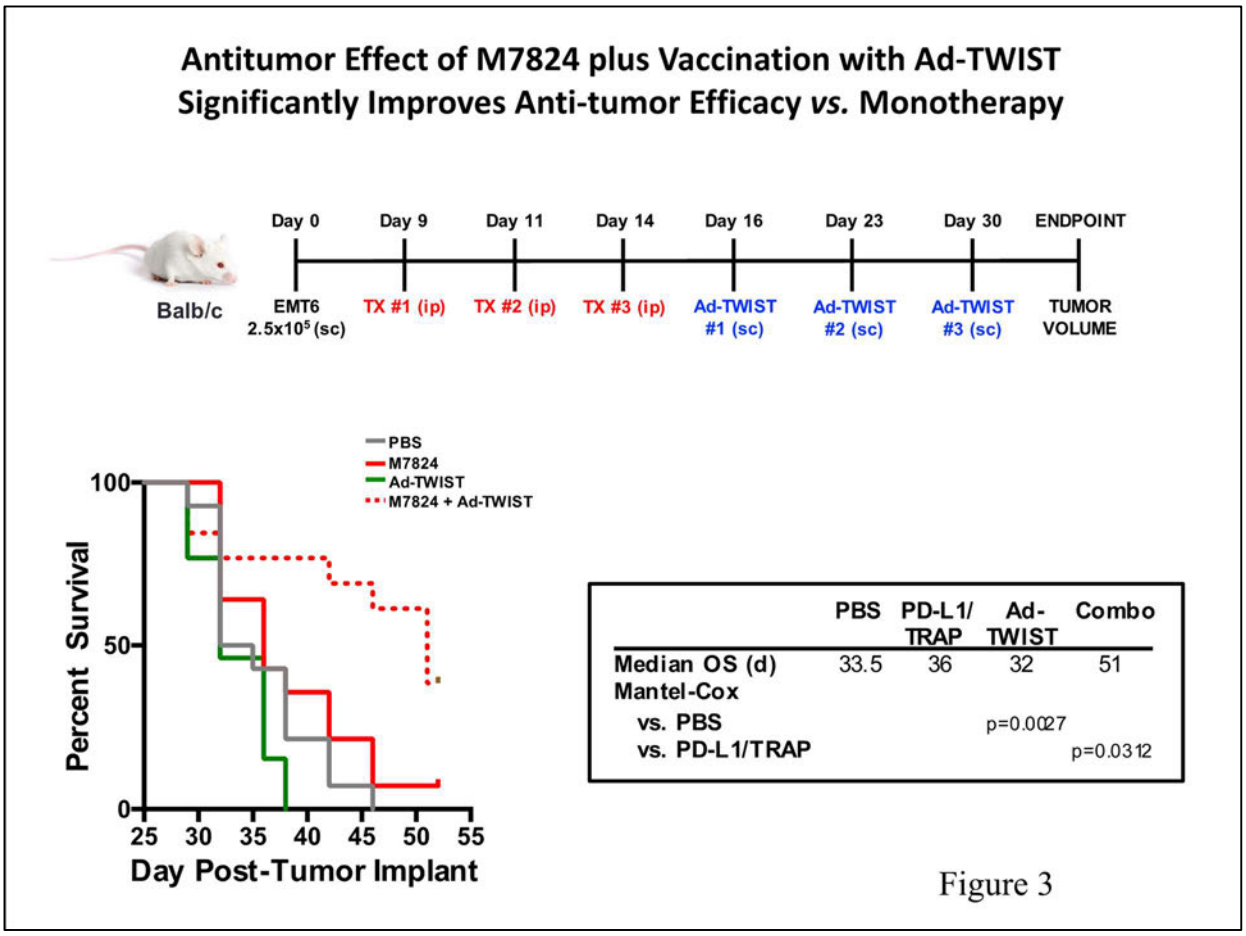


Figure 3: Antitumor effect of M7824 plus vaccination with Ad-TWIST significantly improves anti-tumor efficacy vs. monotherapy

Taken together, these data provide rational for combination of M7824 with BN-Brachyury.

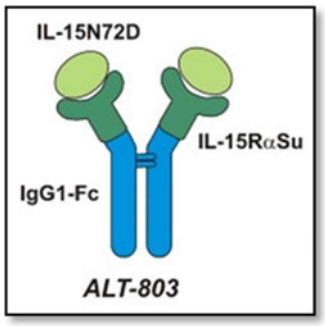
Preliminary results from a phase 1, open label, 3+3 dose escalation trial of M7824 conducted by the Genitourinary Malignancies Branch demonstrated efficacy in subjects with advanced solid tumors (NCT02517398).[41] Although no patients with prostate cancer enrolled, M7824 was observed to have a manageable safety profile. Data from 16 subjects with advanced cancer (three, three, three, and seven subjects treated with M7824 at 1, 3, 10, and 20 mg/kg, respectively, every 2 weeks) were presented at the ASCO Annual Meeting in 2017. PK data showed a dose-linear increase in exposure starting at a dose of 3 mg/kg; furthermore, M7824 saturates peripheral PD-L1 and sequesters any released plasma TGF-β1, -β2, and -β3 throughout the dosing period in a dose-dependent manner. Grade 3 drug-related treatment-emergent adverse events (TEAEs) occurred in 3 pts (skin infection secondary to grade 2 bullous pemphigoid [BP], lipase increased, and anemia caused by underlying colitis); there were no grade 4-5 drug-related TEAEs. BP and colitis responded well to steroids. Colitis and its secondary events of anemia and rectal hemorrhage (in a previously radiated area) were considered dose limiting in 1 pt. There was preliminary evidence of efficacy across all dose levels, including 1 ongoing confirmed complete response (cervical), 1 durable partial response (pancreatic), a 25% reduction in the sum of diameters of target lesions after 2 doses of M7824 (cervical), and 2 cases of prolonged stable disease

(pancreatic; carcinoid).[41] This agent is now in multiple expansion cohorts in 120 centers internationally, given at a flat dose of 1,200 mg. The entire dose escalation study was completed at the NCI.

EMD Serono is a CRADA partner and will supply M7824.

1.2.3 ALT-803 (IL-15 Superagonist Complex)

ALT-803 is an IL-15 superagonist complex that has an increased ability to bind IL-2/15Rβγ and enhance immunostimulatory activity compared to native IL-15. In several rodent tumor models, ALT-803 has increased NK cell and CD8 T-cell numbers, decreased tumor size, and increased survival in the absence of significant toxicity.[42-44] [45, 46] ALT-803 leads to about a 20-fold upregulation in the number of circulating NK cells but also about a 2 log increase in the high effector (CD 111b, $CD27^{hi}$) NK cells. This was associated with about a 3-fold increase in cytotoxic activity and with substantial antitumor activity in a tumor treatment model.[44] Purified NK cells from a normal human donor showed much greater lytic activity when treated with ALT-803. Unpublished experiments conducted by the LTIB demonstrate an increase NK-mediated lysis in vitro with the combination of ALT-803 plus the anti-PD-L1 TGF-β trap (M7824), compared to either treatment alone (**Figure 4**). Other LTIB experiments also demonstrate improved survival in tumor bearing mice with ALT-803 plus a CEA vaccine, compared to either treatment alone **Figure 5**. Other reports from preclinical studies have suggested synergy with ALT-803 and anti-PD-L1.[47] Taken together, this provides rationale for a trial of ALT-803 in combination with M7824.



ALT-803

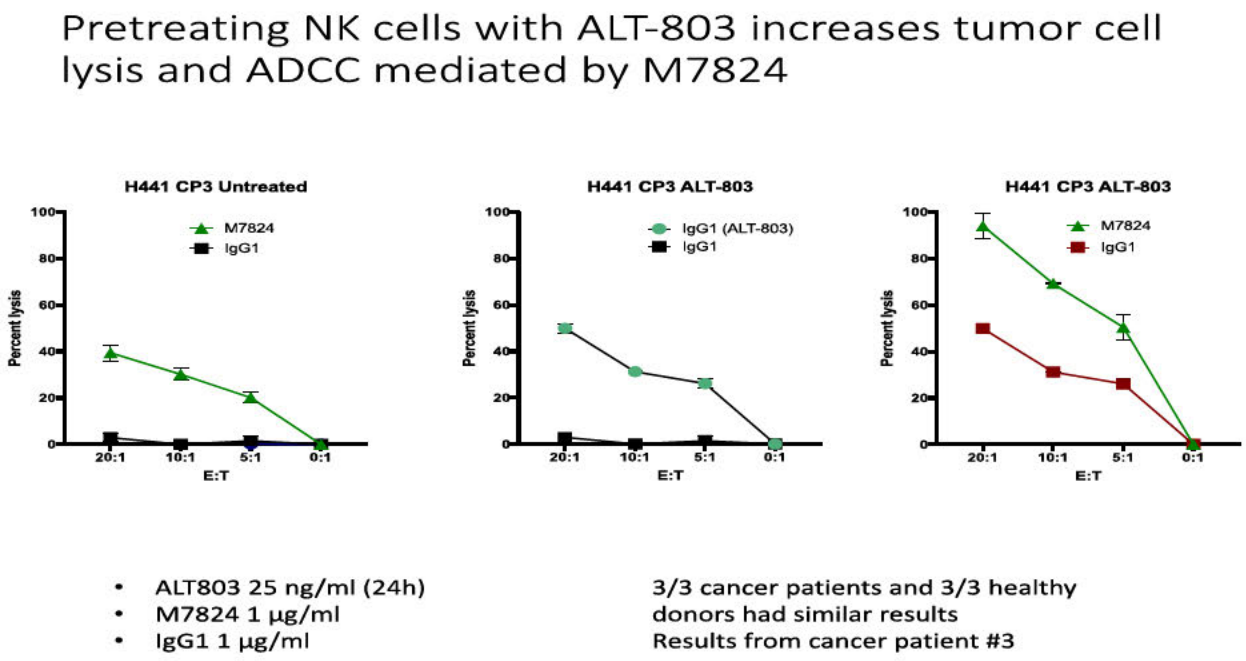


Figure 4: Pretreating NK cells with ALT-803 increases tumor cell lysis and ADCC mediated by M7824

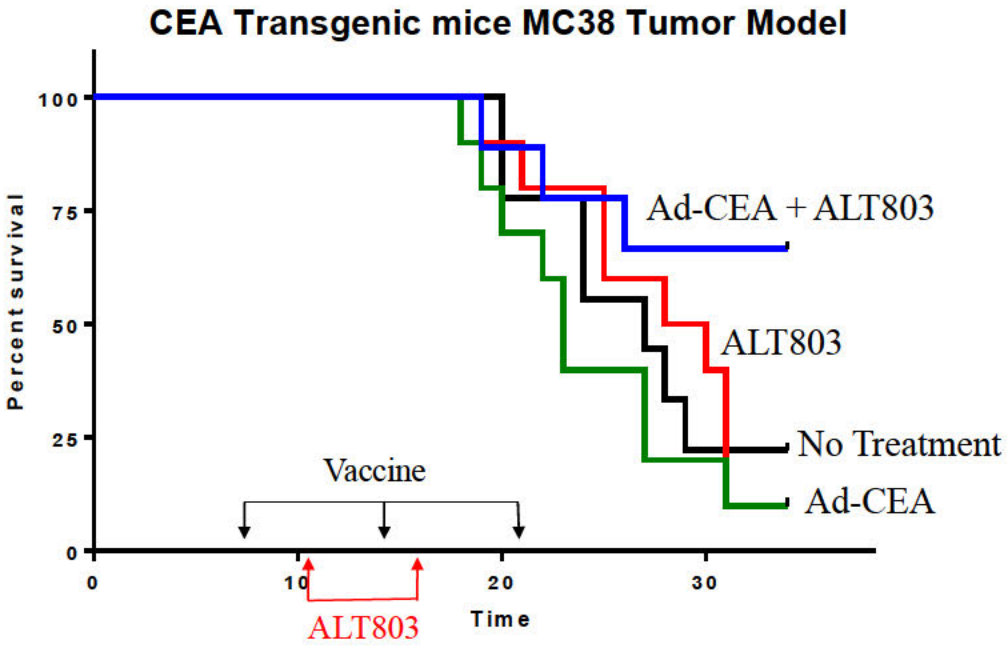


Figure 5

Figure 5: CEA Transgenic mice MC 38 Tumor model

A phase I dose escalation of ALT-803 plus Nivolumab is complete and preliminary data supported 20 µg/kg ALT-803 weekly as an appropriate and safe dose for combination with biweekly nivolumab for phase II expansion. However, Altor has evidence that T cell exhaustion occurs at the 20 µg/kg dosing. Based on this, Altor recommends that we start at 10 µg/kg every two weeks then increase to 15 µg/kg during dosing for ALT-803 in combination with M7824. It is felt that there will be good activity at this dose and schedule (with expansion of T cells and NK cells) while decreasing the chance of T cell exhaustion.

Although preclinical data indicate that the combination is safe in mice, ALT-803 and M7824 have never been tested in combination in humans. However, ALT-803 has been tested in combination with the anti-PD-1 agent, nivolumab 240 mg i.v. every 4 weeks, in a phase 1 dose expansion study (n=21) with ALT-803 given weekly for 5 weeks on, 1 week off, for up to 5-6 months for pre-treated, advanced/metastatic NSCLC (NCT02523469). Fifteen patients received higher ALT-803 dosing: 15 mcg/kg (n=6) and 20 mcg/kg (n=9). While a peer-reviewed report detailing the activity and favorable safety profile of this combination is forthcoming, the clinical investigators of this trial have discussed promising data with the LTIB/GMB Cancer Immunotherapy Program. Zero dose limiting toxicities and zero grade 4 or higher adverse events were observed with this combination. Grade 3 adverse events were fever (n=1), flu-like illness (n=2), lymphopenia (n=2), fatigue (n=2), back pain (n=1), and dizziness (n=1). Grade 1 or 2 large injection site reactions were observed in 14 patients. These effects tended to exhibit tachyphylaxis, with symptoms decreasing in intensity with subsequent dosing. Average follow up thus far has been 7.7 months and average time on treatment has been 4.4 months. Three of the treated patients had PD-L1^{hi} tumor (> 50% PD-L1 positivity), and all three of those patients responded to treatment. For PD-L1+ patients, the

response rate was ~50%. The response rate for PD-L1- patients was ~30%. Interestingly, one patient who achieved a CR exhibited pseudoprogression, with an increase of tumor size 4 times that of baseline, prior to shrinking. Peripheral blood analyses suggest that this combination increases NK cell activity with a dose of 6 mcg/kg of ALT-803. CD8 T cell activity is increased with the combination as well. However increased activity was only seen at 15 or 20 mcg/kg dosing of ALT-803. The recommended phase 2 dose of ALT-803 in combination with nivolumab is 20 mcg/kg.

Given the phase I safety data for the combination of anti-PD-1 with ALT-803, we do not expect severe toxicity from the anti-PD-L1 portion of M7824 when combined with ALT-803. However, since both of these agents can have multi-pronged effects on the immune system including the TGF-beta sequestration by M7824, a safety dose finding cohort of the combination will recruit up to 18 patients, prior to accrual of Cohort 2. This safety cohort will be open to any solid tumor type.

Altor is a CRADA partner and will supply ALT-803.

1.2.4 IDO1 and Epacadostat

Indoleamine 2,3-dioxygenase-1 (IDO1) is an enzyme overexpressed many solid malignancies. IDO1 catalyzes the conversion of tryptophan to N-formyl-kynurenine and enhances immune escape.[48, 49] Kynurenine and other metabolites of tryptophan produced by IDO1 can cause T cell G1 arrest, T cell and dendritic cell apoptosis, dampening of NK cell activity, and enhancement of regulatory T cells.[50-53] Impeding immune escape with IDO1 inhibitors is a promising candidate for combination with other immune therapies such as checkpoint inhibitors or other immunomodulators. Many trials are underway combining IDO1 inhibitors with other immunotherapies.

IDO1 appears to be particularly relevant in prostate cancer patients treated with checkpoint inhibitors and tumor-targeted vaccine. Compared to pre-treatment biopsies, Zahm et al detected increased IDO1 expression in tumor from 8 patients treated with prostatatic acid phosphatase-targeted vaccine and/or anti-PD-1. [54] Patients who experienced PSA declines following vaccine and/or anti-PD-1 were observed to have stable plasma kynurenine levels. In contrast, an increase in serum kynurenine, compared to baseline, was associated with lack of response to treatment and suggests that IDO1 production of kynurenine is a key obstacle to be overcome in some patients receiving checkpoint inhibitors and/or vaccine.

Epacadostat (INCB024360) is a selective inhibitor of IDO1. In a phase I dose escalation trial at doses of 50, 100, 300, 400, 500, 600 or 700 mg twice daily, epacadostat was shown to decrease plasma levels of kynurenine in a dose dependent fashion.[55] Dose limiting toxicities of grade 3 radiation pneumonitis and grade 3 fatigue occurred at the 300 mg and 400 mg dose levels, respectively. Seven out of 52 patients had stable disease lasting ≥ 16 weeks. Maximal inhibition of IDO1 was achieved at doses ≥ 100 mg twice daily. Moreover, immune mediated adverse events associated with checkpoint inhibitor therapies e.g. anti-PD-L1 monoclonals were not common with epacadostat, suggesting that toxicities of epacadostat and the anti-PD-L1 TGF-β trap are unlikely to overlap.

Data from a phase 1 study of Epacadostat in combination with pembrolizumab (anti-PD-1) in advanced melanoma patients presented at ESMO 2016 demonstrated objective responses in 5 out of 6 patients who received Epacadostat at a dose ≥ 100mg orally twice daily.[56]

Additionally, 241 patients with advanced cancer were treated in a phase I/II dose escalation combining epacadostat with nivolumab 3 mg/kg every 2 weeks. As with the combination of epacadostat and pembrolizumab, epacadostat plus nivolumab appears to be well tolerated and active. Patients treated in the phase II portion (n=205) received epacadostat 100 mg or 300 mg orally daily. In these patients, the most common treatment-related adverse events (defined as occurring in ≥15% of patients) were rash (33% for 300 mg and 22% for 100 mg,), fatigue (26% and 31%, respectively), and nausea (24% and 19%, respectively). Rash was the most common grade ≥3 adverse event in the 100 mg and 300 mg subgroups (10% and 12%). There were no treatment-related deaths. For example, head and neck cancer patients treated at the 300 mg dose had a preliminary disease control rate (DCR) of 70% (n = 16). Of 30 melanoma patients, 8 were treated at the 100 mg dose and 22 were treated with 300 mg. ORR and DCR in melanoma patients treated with 100 mg were 75% (n = 6; all PR) and 100% (n = 8; 2 SD), respectively.

Despite promising early phase clinical trial results, Incyte announced in 2018 that a phase III study combining nivolumab and epacadostat in metastatic melanoma did not meet its co-primary endpoint of improved PFS. [57] Subsequent exploratory correlative analyses conducted by Incyte provide some insight into this clinical trial failure. Epacadostat 100 mg BID as monotherapy achieves an exposure that exceeds the IC50 at steady state and epacadostat 400 mg BID and greater (as monotherapy) achieve exposures that exceed the IC90 at steady state in peripheral blood. In clinical studies combining epacadostat (primarily at 100 mg or 300 mg twice daily) with PD-1 inhibition, durable reductions in plasma kynurenine were not observed. The 100 mg dose produced only minor reductions in plasma kynurenine. While the 300 mg dose produced greater reductions in kynurenine, reductions down to the levels observed in healthy volunteers were not durable over time in most patients. Preliminary clinical data from cancer patients treated with epacadostat 600 mg twice daily in combination with checkpoint inhibitors demonstrate reductions in kynurenine that are durable for several cycles of treatment.

Since IDO1 expression is induced by IFN-γ [58], it is expected that IFN-γ induced IDO1 expression will be increased in the setting of immune activity (i.e. BN-brachyury, vaccine, M7824, and ALT-803 administration). As suggested by the report from Zahm and colleagues [54], adequate control of the IDO1 metabolite kynurenine may be a crucial component in the facilitation of anti-tumor immune activity in these patients. Therefore, the potential for epacadostat to increase the activity of M7824, ALT-803, and BN-brachyury will be optimized at a dose that durably reduces serum kynurenine (600 mg orally twice daily). As discussed below in section **1.2.4.1**, safety data from clinical trials combining checkpoint inhibitors with higher doses of epacadostat suggest the regimen is well tolerated. Incyte is a CRADA partner and will provide Epacadostat.

1.2.4.1 Expanded safety data combining higher dose of epacadostat with checkpoint inhibitors

INCMGA0012-102 (ClinicalTrials.gov Identifier: NCT03589651) is a Phase 1b study to evaluate the safety and tolerability of combination of epacadostat and INCMGA0012, an anti-PD-1 antibody, in participants with advanced solid tumors. Thirty-one participants received INCMGA00012 500 mg Q4W plus epacadostat. Four dose levels of epacadostat were studied (100 mg BID, 400 mg BID, 600 mg BID and 900 mg BID).

All participants experienced an adverse event (AE). Sixteen participants (52%) experienced an AE that was considered related to epacadostat. The dose of 600 mg BID was established as the maximum tolerated dose of epacadostat in combination with INCMGA00012. Two of the 3 participants who received INCMGA00012 in combination with epacadostat 900 mg BID experienced diffuse maculopapular erythematous rash, which was determined to be the dose limiting toxicity.

Twelve participants received INCMGA00012 in combination with epacadostat at the MTD of 600 mg BID. Six of these participants (50%) experienced an AE related to epacadostat. One of these participants experienced a Grade 3 (CTCAE v.5.0) AE which was maculopapular rash and fever. Other AEs related to epacadostat at this dose were nausea, fatigue, dyspepsia, hypothyroidism, rash, pruritus, and diarrhea.

Nine participants received INCMGA00012 in combination with epacadostat 400 mg BID. Four of these participants (44%) experienced an AE related to epacadostat. One of these was a Grade 3 maculopapular rash. Other AEs related to epacadostat reported at this dose included nausea, fatigue, fever, diarrhea, and dyspepsia.

Three participants received INCMGA00012 in combination with epacadostat 100 mg BID. One of them experienced an AE of Grade 1 anorexia that was noted as related to epacadostat.

No significant drug related laboratory abnormalities have been reported at any dose level.

Serious AEs have been reported in 6 of the 31 participants (19%). Only 1 participant had an SAE noted as related to epacadostat, which was the event of fever and maculopapular rash.

This appears to be higher than what is expected with bintrafusp alfa alone. In conclusion, the combination of epacadostat plus immune checkpoint inhibitor (INCMGA00012) has been studied in the phase 1 setting and informs the dosing with the anti-PD-L1 agent in this study (M7824). Common toxicities of BN-brachyury and N-803 (fever, flu-like symptoms, and injection site reactions are not expected to overlap.

1.2.4.2 Isolated Adrenocorticotropin Deficiency (IAD)

As of July, 17th 2020, 4 of 25 patients treated on arm 2 had developed central adrenal insufficiency (1/13 in Arm 2.1A and 3/12 in Arm 2.2A).

1.2.5 Rationale Summary

- Brachyury has a tumor-restricted pattern of expression and a relevant role in several aspects of tumor progression, including EMT, making brachyury an ideal vaccine target for CRPC.
- Preclinical data suggests that M7824 may have synergistic anti-tumor activity with EMT-targeted vaccines and ALT-803.
- IDO1 inhibition can dampen the inhibitory milieu within the TME, further augmenting anti-tumor activity of BN-Brachyury, M7824 and ALT-803, and is unlikely to add significant toxicity.
- National initiatives such as the Cancer Moonshot Taskforce dictate initiation of trials that pursue innovative approaches aimed at translating novel cancer treatments from bench to bedside. This quick efficacy seeking trial aimed at identifying a signal of activity in multiple combination regimens offers a means to enhance response rates in CRPC on a potentially shorter timeline than with that of traditional trial designs.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Participants must have histologically or cytologically confirmed any solid tumor (Cohort 1) or castration-resistant prostate cancer (CRPC, Cohorts 2A, 2D and 2R).

2.1.1.2 For the Cohort 1, eligible participants must have a histologically, cytologically or radiographically proven metastatic or locally advanced solid tumor of any type, for which there is no curative standard therapy or standard therapy has failed.

2.1.1.3 Castrate testosterone level (<50ng/dl or 1.7nmol /L). (Participants with a malignancy other than prostate cancer are excluded from this criterion).

2.1.1.4 Radiological confirmation of metastatic disease, **or**

Progressive disease at study entry defined as one or more of the following criteria occurring in the setting of castrate levels of testosterone:

- Radiographic progression defined as **any new** or enlarging bone lesions or growing lymph node disease, consistent with prostate cancer

OR

- PSA progression defined by sequence of rising values separated by >1 week (2 separate increasing values over a minimum of 1 ng/ml (PCWG3 PSA eligibility criteria). If participants had been on flutamide, PSA progression is documented 4 weeks or more after withdrawal. For participants on bicalutamide or nilutamide disease progression is documented 6 or more weeks after withdrawal. The requirement for a 4-6 week withdrawal period following discontinuation of flutamide, nilutamide or bicalutamide only applies to participants who have been on these drugs for at least the prior 6 months. For all other participants they must stop bicalutamide, nilutamide or flutamide the day prior to enrollment.

2.1.1.5 Asymptomatic or mildly symptomatic form prostate cancer; no use of regularly scheduled opiate analgesics for prostate cancer-related pain. (Participants with a malignancy other than prostate cancer are excluded from this criterion).

2.1.1.6 Participants must agree to continuation of androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone analogue/antagonist or bilateral orchiectomy. (Participants with a malignancy other than prostate cancer are excluded from this criterion). Participants may also continue oral androgen receptor antagonist/anti-androgen therapy (e.g. enzalutamide or abiraterone) unless enrolling to Arm 2.3A or 2.3B due to concerns regarding CYP-mediated drug-drug interactions epacadostat.

2.1.1.7 Participants must have had the following prior therapy:

2.1.1.7.1 Testosterone lowering therapy for CRPC

2.1.1.7.2 In addition to continuation of ADT (unless status post bilateral orchiectomy) eligible patients must have received and had PSA or radiographic progression on enzalutamide

(or other oral androgen receptor antagonist e.g. darolutamide or apalutamdide) or abiraterone acetate.

2.1.1.7.3 Participants who have tumors known to be microsatellite instability high/mismatch repair deficient or tumor mutational burden high must have received prior pembrolizumab.

2.1.1.7.4 Participants with known pathogenic homologous recombination repair mutations for which there is evidence of benefit with PARP inhibitors (e.g. BRCA1. BRCA2, ATM,) must have received prior PARP inhibitor.

2.1.1.8 Age ≥18 years.

2.1.1.9 ECOG performance status ≤ 1 (see **Appendix A**).

2.1.1.10 Participants must have adequate organ and marrow function as defined below:

- Absolute neutrophil count ≥ 1000/mcL
- Platelets ≥ 100,000/mcL
- Hemoglobin ≥ 9.0 g/dL
- Total bilirubin within normal institutional limits; in participants with Gilbert's, ≤ 3.0 mg/dL
- AST (AGOT)/ALT (AGPT) ≤ 2.5X upper limit of normal. For subjects with liver involvement in their tumor, AST ≤ 3.5. × ULN, ALT ≤ 3.5 × ULN, and bilirubin ≤ 3.0 is acceptable
- Creatinine within 1.5X upper limit of normal institutional limits

2.1.1.11 The effects of BN-Brachyury, M7824, N-803, and Epacadostat on the developing human fetus are unknown. For this reason, men and women must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, during the study and maintain such contraception until 4 months following the last dose of any study agent. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her partner's treating physician immediately.

2.1.1.12 Ability of subject to understand and the willingness to sign a written informed consent document

2.1.1.13 Participants with successfully treated HCV are eligible if HCV viral load is undetectable.

2.1.2 Exclusion Criteria

2.1.2.1 Participants who are immunocompromised as follows:

- Human immunodeficiency virus positivity due to the potential for decreased tolerance, and potential to be at risk for severe side effects with immunotherapies. These concerns are relevant to all drugs, as drug-drug interactions among anti-retrovirals and immunotherapies are yet uncharacterized.
- Chronic administration (defined as daily or every other day for continued use >14 days) of systemic corticosteroids or other immune suppressive drugs, within 28

days before treatment on study. Nasal, or inhaled steroid, topical steroid creams and eye drops for small body areas are allowed. Physiologic doses of steroids are permitted, e.g. a participant taking hydrocortisone for adrenal insufficiency or a patient recently on abiraterone (administered with 10 mg of prednisone daily) who is tapering off of prednisone is allowed to continue that taper.

- Participants who have undergone allogeneic peripheral stem cell transplantation, or solid organ transplantation requiring immunosuppression.
  - Active autoimmune disease, except participants with type 1 diabetes mellitus, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring current immunosuppression, or with other endocrine disorders on replacement hormones or are not excluded if the condition is well controlled.

2.1.2.2 Prostate cancer participants with a history of brain/leptomeningeal metastasis, since these participants have a very poor prognosis and immunotherapy may take time to lead to beneficial clinical effects. Participants with brain or CNS metastases enrolling to arm 1.1 are eligible if they are status post definitive radiotherapy or surgery and are asymptomatic.

2.1.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to study agents to be used in the cohort the subject will be enrolled into.

2.1.2.4 Known allergy to eggs, egg products, aminoglycoside antibiotics (for example, gentamicin or tobramycin).

2.1.2.5 Any condition which, in the opinion of the investigator, would prevent full participation in this trial (including the long-term follow-up), or would interfere with the evaluation of the trial endpoints.

2.1.2.6 Participants with prior investigational drug, chemotherapy, immunotherapy or any prior radiotherapy (except for palliative bone directed therapy) within the past 28 days prior to enrollment except if the investigator has assessed that all residual treatment-related toxicities have resolved or are minimal and feel the participant is otherwise suitable for enrollment.

2.1.2.7 Uncontrolled intercurrent acute or chronic illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure (>New York Heart Association Class I), hepatic disease, unstable angina pectoris, serious cardiac arrhythmia, requiring medication, uncontrolled hypertension (SBP>170/ DBP>105) or psychiatric illness/social situations within 12 months that would limit compliance with study requirements.

2.1.2.8 Use of herbal products that may decrease PSA levels (e.g. saw palmetto).

2.1.2.9 Participants who have had cytotoxic chemotherapy for metastatic castration-resistant prostate cancer within the past 3 months. (Participants who have had docetaxel for metastatic castration sensitive per CHAARTED data may enroll as long as they did not have progressive disease while on docetaxel and are 3 months removed from treatment, with all treatment related toxicities resolving to at least grade 1.)

2.1.2.10 Participants who have undergone major surgery within 4 weeks of enrollment. A biopsy will not preclude a participant from starting study.

2.1.2.11 Participants with a history of hepatitis B (HBV) are excluded due to potential risk for viral reactivation and resulting liver injury in persons with latent HBV.

2.1.2.12 Subjects unwilling to accept blood products or blood transfusions as medically indicated. As there is a risk of severe bleeding with M7824, participants must be willing to receive blood transfusions if medically necessary for their own safety

2.1.2.13 For Participants enrolling in Arm 2.3A and for participants who may be randomized to Arm 2.3B, the following additional exclusion criteria will apply:

2.1.2.13.1 Subjects receiving Monoamine Oxidase Inhibitors (MAOIs) or a drug which has significant MAOI activity (meperidine, linezolid, methylene blue) within the 21 days before initiation of study therapy are excluded.

2.1.2.13.2 Since epacadostat's metabolism may be altered by drugs that inhibit UDP-glucuronosyltransferase UGT1A9 (see **Appendix D**), Participants receiving such drugs within 21 days of initiation of study therapy are excluded.

2.1.2.13.3 Participants receiving agents that are substrates of CYP1A2, CYP2C8, and CYP2C19 or affected by OATP1B1 or OATP1B3 (see **Appendix E**) within 21 days of initiation of study therapy or 5 half lives of the agent (whichever is shorter) are excluded. Participants receiving medications that are substrates of these enzymes/transporters but are not listed in the appendix or participants receiving substrates of CYP2B6 and CYP3A will be evaluated on a case-by-case basis prior to enrollment. Patients who consume caffeine are eligible but must agree to moderate consumption as specified in Appendix E.

2.1.2.13.4 Subjects receiving coumarin-based anticoagulants (e.g. Coumadin) are excluded.

2.1.2.13.5 Subjects having any history of Serotonin Syndrome (SS) after receiving serotonergic drugs are excluded.

2.1.2.13.6 Participants with a QTcF interval > 480 milliseconds at the screening are excluded. In the event that a single QTc F is > 480 milliseconds, the subject may enroll if the average QTcF for 3 ECGs is < 480 milliseconds. For subjects with an intraventricular conduction delay (QRS interval > 120 milliseconds), the JTc interval may be used in place of the QTc. The JTc must be < 340 milliseconds if JTc is used in place of the QTc. QTc prolongation due to pacemaker may enroll if the JTc is normal.

2.1.2.13.7 Subjects with left bundle branch block are excluded.

2.1.2.13.8 Pregnant women are excluded from this study because investigational agents used in this study (BN-Brachyury, M7824, N-803, and/or Epacadostat) could have 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 these investigational agents, breastfeeding should be discontinued if the mother is treated with either of them.

2.1.3 Recruitment Strategies

This study will be listed on available websites (www.clinicaltrials.gov, https://ccr.cancer.gov/clinical-trials) and participants will be recruited from the current participant population at NIH and participating sites. This study could be posted on NIH social media forums.

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**

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

The following activities will be performed only after the subject has signed the study consent OR the consent for study 01-C-0129 (provided the procedure is permitted on that study) on which screening activities may also be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

Screening tests and procedures must be performed within 28 days prior to drug administration, unless otherwise specified:

1. Complete medical history and physical examination (including height, weight, vital signs, and ECOG performance status).
2. CT of chest, abdomen and pelvis *
3. Clinical laboratory tests*

- Chemistry: sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, and total and direct bilirubin, PT/PTT
- Hematology: complete blood count (CBC) with differential and platelets
- Serum PSA (participants with a malignancy other than prostate cancer do not need this test)
- Testosterone level (participants with a malignancy other than prostate cancer do not need this test)
- Urinalysis

- Serum pregnancy test (β-HCG) for females of childbearing-potential and women < 12 months since the onset of menopause (within 16 days prior to initiation of study therapy).
- HBV, HCV, HIV testing including viral load for HCV and HBV (within 3 months prior to enrollment).

4. Histologic confirmation* (at any time point prior to initiation of study therapy).
5. Electrocardiogram (EKG) for participants enrolling in arm 2.3 A and for participants who may be randomized to arm 2.3 B

* Outside test results are acceptable if performed in designated time frame.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g. **w**hen 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: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

2.3.1 Screen Failures

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

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

2.3.2 Treatment Assignment and Randomization Procedures

Cohorts

Number	Name	Description
1	Cohort 1	Participants with any solid tumor
2	Cohort 2A	Participants with CRPC during Phase IIA
3	Cohort 2D	Participants with CRPC requiring direct assignment in phase IIB
4	Cohort 2R	Participants with CRPC requiring randomization in phase IIB

Arms

Number	Name	Description

1	Arm 1.1	M7824 + N-803 (accrual closed)
2	Arm 2.1A	M7824 + BN-Brachyury during phase IIA (accrual closed)
3	Arm 2.2A	M7824 + BN-Brachyury + N-803 during phase IIA
4	Arm 2.3A	M7824 + BN-Brachyury + N-803 + Epacadostat during phase IIA
5	Arm 2.1B	M7824 + BN-Brachyury during phase IIB
6	Arm 2.2B	M7824 + BN-Brachyury + N-803 during phase IIB
7	Arm 2.3B	M7824 + BN-Brachyury + N-803 + Epacadostat during phase IIB

Arm Assignment

During Phase I Participants in Cohort 1 will be directly assigned to Arm 1.1.

During Phase IIA participants in Cohort 2A, will be first assigned to Arms 2.1A (13 participants total) until filled, then to Arm 2.2A (13 participants total), and finally to Arm 2.3A (13 participants total).

Arm 2.1B will not be used, as inadequate responses were noted in 2.1A.

During phase IIB, participants in cohort 2D will be directly assigned to the appropriate arm (either Arms 2.2B or 2.3B) if direct assignment to an arm is required; participants in cohort 2R will be randomized among the open arms (among Arms, 2.2B and 2.3B) if randomization is required

Randomization

As safety and efficacy information about the treatments in Arms 2.1A, 2.2A and 2.3A becomes available, Arms 2.1B, 2.2B and 2.3B may become open for enrollment. During this expansion (Phase IIB portion) of this trial, more than one arm e.g. Arms 2.1B (up to 25 participants), 2.2B (up to 25 participants, 2.3B (up to 25 participants) may be open for accrual simultaneously. In order to avoid any selection bias, if more than one expansion arm is open for accrual, participants will be randomized among all open arms. Hence, if 2 arms are open simultaneously, randomization will occur between two arms. If 3 arms are open simultaneously, randomization will occur among three arms. If an arm completes accrual, assignment to the remaining open arms will be randomized between the 2 remaining open arms, or by direct assignment, if only 1 arm remains open. For logistical reasons involved in randomization, a cohort is not permitted to be heterogeneous, in terms of participants who have been randomized or directly assigned. For this reason, cohorts 2D and 2R are added. See Section **10.2** for further details.

Note: Randomization will be performed by the CRO. Since the expansion phase can start with only one arm open, participants will be assigned directly to the first expansion arm that may open.

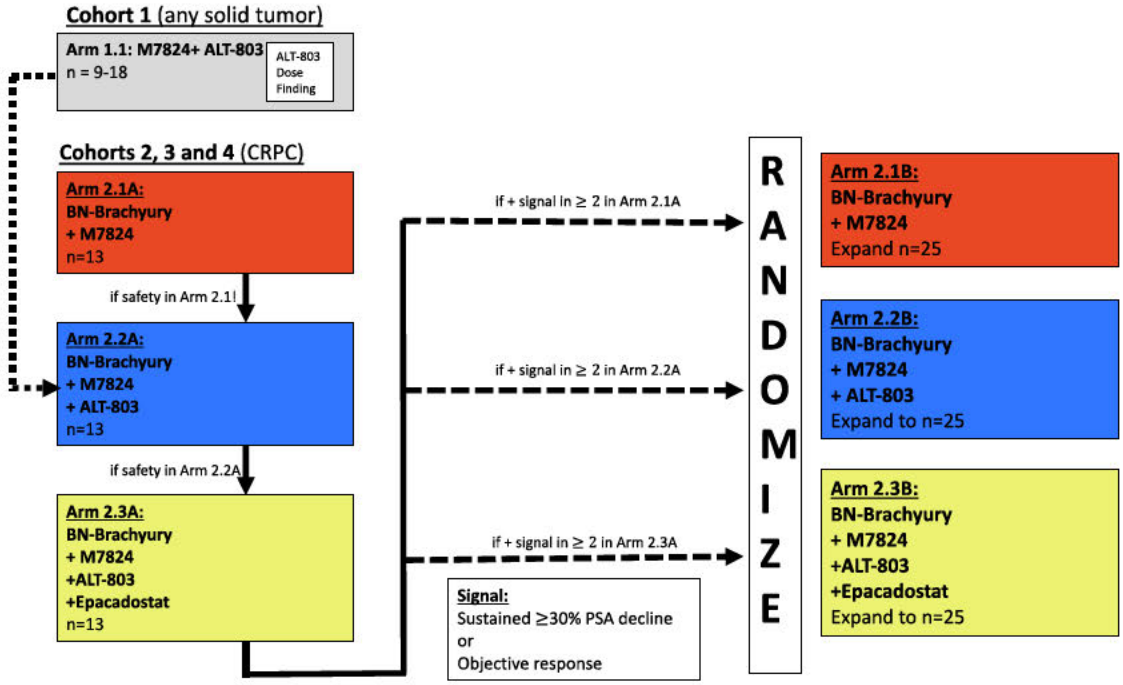
2.4 BASELINE EVALUATION

All subjects are required to complete baseline evaluations within 3 days 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
- Tc-99 whole body scintigraphy (Bone scan) if participant has prostate cancer (within 30 days of first dosing of study drug)
- CT of chest, abdomen and pelvis (within 30 days of first dosing of study drug)
- Concomitant medications and adverse events evaluation
- EKG
- Serum pregnancy test (β-HCG) for females of childbearing-potential and women < 12 months since the onset of menopause (within 3 days prior to study therapy)
- Chemistry: sodium, potassium, chloride, bicarbonate, calcium, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, and total and direct bilirubin
- Serum PSA (participants with a malignancy other than prostate cancer do not need this test)
- Testosterone level (participants with a malignancy other than prostate cancer do not need this test)
- TSH, free T4, lipase, amylase, LDH, GGT
- Hematology: CBC with differential and platelets
- Urinalysis
- HLA class I profile A,B,C and DR, DQ, Next Generation Sequencing (NGS) HLA-ABC & DRDQ, NGS HLA-DPB1 [high resolution HLA-DPB1], NGS HLA-DQA1 [high resolution HLA-DQA1](any time prior to study treatment initiation).
- Levels of Prolactin, IGF1, Androstenedione, Dihydrotestosterone (DHT), 17-OH-Progesterone, DHEA, DHEA-S, estradiol, ACTH, Cortisol (See Section **3.5** for more details)

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN



Open label Phase I/II trial with following randomization during the expansion phase IIB.

One cycle will be defined as 2 weeks (+7/-3 days).

Phase I: Cohort 1, Arm 1.1

- Up to 18 participants with any solid tumor will be enrolled in dose escalation Cohort 1 for treatment in Arm 1.1 (flat dose of M7824 + different dose levels of N-803).

Phase IIA: sequential enrollment into Cohort 2A, Arms 2.1A, 2.2A. and 2.3A

- Concurrently with the enrollment to Arm 1.1A, 13 participants with CRPC will start enrollment in Cohort 2A for treatment in Arm 2.1A (M7824 + BN-Brachyury).
- When safe dosing of N-803 is identified during Phase I, 13 participants have been enrolled in arm 2.1A and the first 6 participants, treated in Arm 2.1A, have met safety requirements, 13 participants with CRPC will start enrollment in Cohort 2A for treatment in Arm 2.2A (M7824 + BN-Brachyury + N-803).
- When 13 participants have been enrolled in Arm 2.2A and the first 6 participants, treated in Arm 2.2A, have met safety requirements, 13 participants with CRPC will start enrollment in Cohort 2A for treatment in Arm 2.3A (M7824 + BN-Brachyury + N-803 + Epacadostat).

Phase IIB: expansion with randomized enrollment into Cohorts 2D and 2R, Arms 2.1B, 2.2B and 2.3B.

- Each Arm in Cohort 2: 2.1B, 2.2B and 2.3B will be open for additional enrollment (25 evaluable participants total) when the initial 13 participants have accrued, safety requirements have been met and a positive signal (defined as Objective Response by RECIST 1.1 or sustained PSA decrease ≥ 30% sustained for > 21 days) in ≥ 2 participants has been observed.
- If only one arm is open for additional enrollment, participants will be directly assigned to this arm. If 2 arms are open for additional enrollment, participants will be randomized between these 2 open arms. If 3 arms are open for additional enrollment, participants will be randomized between these 3 open arms.

The first subject of each arm (1.1, 2.1A, 2.2A and 2.3A) will be observed for at least 13 days before the second subject can be treated. If no DLT is observed within that period, the second participant can enroll. An interval of 2 days without a DLT must pass before treatment of the next participant until after participant 7 begins treatment i.e. before treating participants 3, 4, 5 and 6, 2 days must pass without any observed DLT.

Treatment will continue until disease progression or unacceptable toxicity.

Safety Design Summary:

The phase I (i.e. safety evaluation) portion of this study refers to the first 6 participants treated on arm 1.1 (at the given dose level for arm 1.1), arm 2.1A, arm 2.2A, and arm 2.3A. These participants are evaluated for DLT. If there are <2 DLTs in the first 6 participants of each arm, the respective combination is considered to be safe. The phase II portion of the study applies to the potential expansion of arms 2.1, 2.2 and/or 2.3. This will also include all participants treated during Part A (arm 2.1A, 2.2A, and 2.3A), and Part B (on an arm that expanded based on prespecified efficacy endpoints). Changing the suffix to 'B' from 'A' indicates that a participant was enrolled during part B, the period of time when it has been determined which arms have expanded. During Part B, safety will have already been determined.

3.1.1 Dose Limiting Toxicity

Dose-limiting toxicity (DLT) will be defined as any one of the following adverse events, possibly attributable to study drugs, that occur within 21 days of the start of therapy. For arm 1.1, this applies to all participants treated on a given dose level. For arms 2.1A, 2.2A and 2.2B, this applies to the first 6 participants on a given arm:

- Any grade ≥ 4 hematologic toxicity or grade 3 thrombocytopenia (platelets 25-50,000) with associated bleeding, except CD4 lymphocyte count or other T lymphocyte subset count.
- Any grade ≥ 3 non-hematologic toxicity, **except for any of the following**:
  - transient (≤ 48 hour) grade 3 fatigue, local reactions, flu like symptoms, fever, headache, or nausea, emesis, and diarrhea not controlled with adequate medical management, or
  - Any CTCAE Grade 3 skin toxicity lasting less than five days.
  - Electrolyte abnormalities that can be easily managed with replacement therapy.
  - Asymptomatic Grade 3 lipase or amylase elevation.

- Any grade 3 or higher adverse event that is included in the known safety profile of the investigational agents, as judged by the investigator. Since the goal of the safety evaluation for the combination is to determine if there are any increased or unexpected toxicities due to the combination of therapies that would not be expected with either agent alone, observation of a grade 3 or higher toxicity known to be associated with either of the four investigational agents would not be considered a DLT. See Section **14** for expected toxicities.

Criteria are based on the NCI Common Terminology Criteria for Adverse Events, Version 5.

3.1.2 Phase I, Dose Escalation: Cohort 1, Arm 1.1

9 to 18 participants with any solid tumor will be enrolled in Cohort 1.

Dose escalation (**Table 1**) will proceed in dose levels of 3–6 participants. The MTD is the dose level at which no more than 1 of up to 6 participants experience DLT during 21 days after the start of therapy, and the dose below that at which at least 2 (of ≤6) participants have DLT as a result of the drug. If a participant did not experience DLT and did not finish 21 days of treatment, he or she will not be evaluable for toxicity and will be replaced in the dose level.

The first 3 participants will be treated with M7824 (1,200 mg IV every 2 weeks) plus N-803 (10 mcg/kg SC every 2 weeks), Dose Level 1 (DL1).

If no dose limiting toxicity (Section **3.1.1**) is observed at DL1:

Next 3 participants will be enrolled and receive M7824 (1,200 mg IV every 2 weeks) plus N-803 (15 mcg/kg SC every 2 weeks), Dose Level 2 (DL2).

If no DLT (Section **3.1.1**) is observed at 15 mcg/kg of N-803:

Next 3 will be enrolled in DL2. If ≤ 1 DLT in 6 participants treated at DL2, 15 mcg/kg will be the N-803 dose for Cohort 2(2A, 2D, 2R). If ≥ 2 dose limiting toxicities at 15 mcg/kg:

Next 3 will be enrolled in DL1. If ≤ 1 DLT in 6 treated participants, 10 mcg/kg will be the N-803 dose for Cohort 2 (2A, 2D, 2R). If ≥ 2 dose limiting toxicities at 10 mcg/kg:

Next 3 participants will be treated with M7824 (1,200 mg IV every 2 weeks) plus N-803 (8 mcg/kg SC every 2 weeks), Dose Level -1 (DL-1). If ≤ 1 dose limiting toxicity is observed DL-1:

Next 3 will be enrolled in DL -1. If ≤ 1 dose limiting toxicity in 6 treated participants, 10 mcg/kg will be the N-803 dose for Cohort 2 (2A, 2D, 2R). If ≥ 2 dose limiting toxicities at 10 mcg/kg, next Amendment will be submitted with another combination of drugs.

Table 1: Dose Escalation Schedule

Dose Escalation Schedule		
Dose Level	N-803	M7824
Level 1	10 mcg/kg	1,200 mg

Dose Escalation Schedule		
Dose Level	N-803	M7824
Level 2	15 mcg/kg	1,200 mg
Level -1	8 mcg/kg	1,200 mg

N-803

Intra-participant dose escalation/de-escalation is not permitted for subjects enrolled during Phase I in the Arm 1.1.

Participants will receive assigned dose and in case of DLT attributed to N-803 will be taken off N-803 treatment and continue M7824 treatment only. Subjects enrolled onto Arm 1.1 who have either had a DLT or completed the DLT evaluation period will be part of the DLT evaluation of the phase I dose level.

M7824

During phase I Dose modifications of M7824 are not allowed. If a participant experiences side effects, requiring dose modification of M7824, the participant will be considered having DLT and taken off M7824 and N-803 treatment.

3.1.3 Phase IIA: sequential enrollment into Cohort 2A, Arms 2.1A, 2.2A. and 2.3A

3.1.3.1 Arm 2.1A

13 participants with CRPC will be enrolled in Arm 2.1A. Enrollment will start simultaneously with enrollment to Arm 1.1

Participants will be treated with combination of M7824 (1,200 mg IV) and BN-Brachyury.

A treatment combination will be determined safe if < 2 of the first 6 participants enrolled in the arm experience a DLT (See Section **3.1.1**). If 2 DLT happen in first 6 participants enrolled, enrollment in that arm will be halted and an amendment will be submitted with another combination of drugs.

3.1.3.2 Sequential Arm 2.2A

13 participants with CRPC will be enrolled in Arm 2.2A. Participants will be treated with combination of M7824, BN-Brachyury and N-803.

Enrollment will start when MTD of N-803 is identified in Cohort 1, Arm 1.1, 13 participants are enrolled in arm 2.1A and the first 6 participants, treated in Arm 2.1A, have met safety requirements.

A treatment combination will be determined safe if < 2 of the first 6 participants enrolled in the arm experience a DLT (See Section **3.1.1**). If 2 DLTs happen in first 6 participants enrolled, enrollment in that arm will be halted and an amendment will be submitted with another combination of drugs

3.1.3.3 Sequential Arm 2.3A

13 participants with CRPC will be enrolled in Arm 2.3A. Participants will be treated with combination of M7824, BN-Brachyury, N-803 and Epacadostat.

Enrollment will start when 13 participants are enrolled in arm 2.2A and the first 6 participants, treated in Arm 2.1A, have met safety requirements.

A treatment combination will be determined safe if < 2 of the first 6 participants enrolled in the arm experience a DLT (See Section **3.1.1).** If 2 DLTs happen in the first 6 participants enrolled, the enrollment in that arm will be halted and an amendment will be submitted with another combination of drugs.

3.1.3.4 General rule

During Phase IB (when enrollment of first 6 participants has finished and safety requirements are met) if one drug is discontinued due to toxicity, participants can continue treatment with the other drug(s) at the discretion of the investigator. Applies for participants 7-12 in Arms 2.1A, 2.2A and 2.3A. This also applies to any participant who is being evaluated for safety and has passed the 3-week DLT period.

3.1.4 Phase IIB: expansion with randomized enrollment into Cohorts 2D and 2R, Arms 2.1B, 2.2B and 2.3B

For each Arm (Cohort 2D and 2R): 2.1B, 2.2B and 2.3B will be open for additional enrollment (25 evaluable participants total) when the initial the 13 participants have been accrued, safety requirements are met and a positive signal (defined as Objective Response by RECIST 1.1 or sustained PSA decrease ≥ 30% sustained for > 21 days) in ≥ 2 participants is observed.

If only one arm is open for additional enrollment, participants will be directly assigned to this arm. If 2 arms are open for additional enrollment, participants will be randomized between these 2 open arms. If 3 arms are open for additional enrollment, participants will be randomized between these 3 open arms. If a participant is ineligible for enrollment to Arm 2.3A or randomization and potential enrollment to arm 2.3B due to a QT interval or due to use of a concomitant medication that is not allowed due to potential drug-drug interactions with epacadostat, that participant may be directly assigned to Arm 2.3B.

During Phase IIB in each arm, for toxicity not requiring discontinuation of IND agent, these agents may be held at the discretion of the investigator and may be reinitiated after the toxicity has improved.

During Phase IIB in case when one drug is discontinued due to toxicity, participants may continue treatment with the other drug(s) at the discretion of the investigator.

3.2 STUDY STOPPING RULE

Accrual will be halted to all open study arms if there is an occurrence of a grade 5 toxicity within 30 days of receiving any study treatment that is possibly attributable to the treatment regimen. Prior to resumption of the study, an expedited safety report will be sent to and reviewed by FDA. SAE also must be evaluated by the clinical investigators.

3.3 DRUG ADMINISTRATION

3.3.1 General rule:

A window of +7/-3 days for every two weeks study drug(s) dosing is allowed in the event of scheduling issues (i.e., holiday, bad weather or other scheduling issues).

3.3.2 BN-Brachyury (MVA-BN-Brachyury and FPV-Brachyury)

BN-Brachyury collectively refers to the priming doses (MVA-BN-Brachyury) and the boost doses (FPV-Brachyury).

MVA-BN-Brachyury will be administered as 2 priming doses 2 weeks apart, on Day 1 of Cycle 1 and Day 1 of Cycle 2. Administration of each of the 4 subcutaneous injections that comprise 1 dose of MVA-BN-Brachyury is preferred to be given in different limbs, in the upper arm and/or upper outer thigh. Each 0.5mL injection of MVA-BN-Brachyury consists of a nominal virus titer of 2.0×10^8 infectious units (Inf.U.)

One dose of FPV-Brachyury = one 0.5 mL injection. One injection = nominal 1×10^9 Inf.U in 0.5 mL.

The first dose of FPV-Brachyury will be given 2 weeks after second dose of MVA-BN-Brachyury, then every 4 weeks until 6 months, then every 3 months until reaching 2 years from the first dose of MVA-BN-Brachyury. At that point, FPV-Brachyury may be continued at 6month dosing intervals.

FPV-Brachyury is to be administered via subcutaneous injection in either the upper arm or outer thigh. The same area of injection is preferred, but not required, for all FPV-Brachyury vaccines. The injection must be delivered within 4 hours of completion of preparation to ensure stability.

3.3.3 M7824

Subjects will be scheduled to receive M7824 at a flat dose of 1,200 mg IV once every 2 weeks.

Subjects will receive M7824 via IV infusion over 1 hour (-10 minutes / +20 minutes, that is, over 50 to 80 minutes) once every 2 weeks. M7824 will be administered as a "flat" dose of 1,200 mg independent of body weight. M7824 is administered as an intravenous infusion with a mandatory 0.2 micron in-line filter.

M7824 may be administered via pre-existing peripheral or central vascular access device (VAD). Prior to administration via a port, the primary material of the port must be confirmed to be titanium. If the primary material of the port is not titanium, the port must not be used for administration of M7824.

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 to a particular participant, an antihistamine and with acetaminophen (for example, 25-50 mg diphenhydramine and 500-650 mg acetaminophen within approximately 30 to 60 minutes prior to dosing of M7824 is mandatory for the first 2 infusions, after which premedication is optional and at the discretion of the Investigator. If Grade ≥ 2 infusion reactions are seen during the first two infusions, premedication should not be stopped. Steroids as premedication are not permitted.

Table 2: Treatment modifications for infusion-related reactions caused by M7824 with signs/symptoms occurring on the day of infusion (during or after) or the day after infusion irrespective of resolution.

NCI-CTCAE Grade	Treatment Modification for M7824
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Consider decreasing the M7824 infusion rate by 50% and monitoring closely for any worsening. If the M7824 infusion rate has been decreased by 50% or interrupted due to an infusion reaction, the next infusion will be given at the decreased rate. If no infusion reaction is observed at the next scheduled infusion, the infusion rate may be returned to baseline at the subsequent infusions based on investigator's medical judgment.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤ 24 hours.	Consider temporarily discontinuing M7824 infusion. Consider resuming infusion at 50% of previous rate once infusion related reaction has resolved or decreased to at least Grade 1 in severity and monitor closely for any worsening. Infuse at 50% rate for all future doses.
Grade 3 or Grade 4 – severe or life-threatening *Grade 3:* Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); hospitalization indicated for clinical sequelae. *Grade 4*: Life-threatening consequences; urgent intervention indicated.	Stop the M7824 infusion immediately and disconnect infusion tubing from the subject. For grade 3 events: Consider withdrawing immediately from M7824 treatment and not offering any further M7824 treatment based upon if the clinical condition can be safely managed. For grade 4 events: Withdraw immediately from treatment and do not offer further treatment.

If hypersensitivity reaction occurs, the subject should be treated according to the best available medical practice. Hypersensitivity reactions may require immediate intensive care. Bintrafusp alfa should be administered in a setting that allows 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. Potent steroids (e.g. dexamethasone), catecholamines (e.g. epinephrine), 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

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.

3.3.4 N-803

N-803 will be given via subcutaneous injection at a dose of 8-15 μg/kg every 2 weeks.

The dose will be determined as described in Section **3.1.2**. N-803 dosing will be calculated using a weight obtained within 5 days prior to the first dose. The dose will be re-calculated at the beginning of each subsequent cycle in the event of a 10% or greater weight change. If the weight at the beginning of each subsequent cycles is within 10%, the previous dose may be used or the dose may be re-calculated based on local site procedures.

Injection should occur in the abdomen and injection sites should be rotated per institutional guidelines and each injection site separated by at least 1 inch. Depending on the injection volume required, the dose of N-803 may be administered as a single injection or multiple injections at the discretion of the investigator.

Doses of N-803 can be administered on an outparticipant basis. If the first dose of the 1st cycle is well tolerated after 2 hours of monitoring, subsequent doses may be administered with 30 minutes of monitoring post dose. N-803 will not be self-administered.

3.3.4.1 Pre- and post-N-803 therapy intervention guidelines for fever/chills

N-803				
Condition	**Agents**	**Dose**	**Route**	**When**
Fever/chills	Antipyretic*			
	Acetaminophen	up to 650 mg; or	Orally	Prior to each dose & repeat 4 hours after dosing. Repeat every 4-6 hours if fever present.
	Ibuprofen	up to 600 mg; or	Orally	Prior to each dose & repeat 4 hours after dosing. Repeat every 4-6 hours if fever present.
	Naproxen	up to 500 mg	Orally	Prior to each dose & repeat 8 hours after dosing. Repeat every 12 hours if fever present.
*Antipyretic medication including acetaminophen, ibuprofen, or naproxen may be given per physician discretion following the recommended dosing thresholds: Acetaminophen: not to exceed 3000 mg (3 grams) in 24 hours Ibuprofen: not to exceed 3200 mg in 24 hours				

N-803				
Condition	**Agents**	**Dose**	**Route**	**When**
	Naproxen: not to exceed 1000 mg in 24 hours			
Note: The use of systemic steroid medications may result in loss of therapeutic effects of the study drug and should be avoided; however in the event of a life-threatening inflammatory reaction to N-803, the IV administration of dexamethasone or other steroid-based medication is warranted. Prednisone should be avoided.				

3.3.4.2 Skin Rash in Association with Subcutaneous Administration of N-803

Based on current experience, localized skin rashes are common with subcutaneous administration. If a rash occurs and the rash area surrounding the N-803 injection site is > 6 cm and symptomatic (painful and/or itchy), it may be treated (at the discretion of the treating physician) with topical 0.05% clobetasol propionate (i.e. 0.05% Cormax) or 0.1% triamcinolone (i.e., Kenalog) cream. Diphenhydramine may be administered pre- (25-50 mg TID orally) and post-dosing (25-50 mg TID orally x 2 days) of N-803 at the discretion of the treating physician. Diphenhydramine should be eliminated if not tolerated. Other agents may be administered at the discretion of the treating physician.

Premedication may be administered pre- (e.g. diphenhydramine 25-50mg PO or IV) and post N-803 dose (e.g. diphenhydramine 25-50 TID PO x 2 days) at the discretion of the treating physician.

Participants may complete and return N-803 INJECTION SITE REACTION DIARY (optional) after each N-803 injection (See **Appendix B**)

3.3.5 Epacadostat

Epacadostat is formulated as a 25 mg tablet, a 100 mg tablet, and a 300 mg tablet. However, only the 100 and 300 mg tablets are anticipated to be used for this trial. Epacadostat will be administered at a dose of 600 mg orally twice daily without regard to food (total daily dose = 1,200 mg). Doses should be taken at approximately the same time each day. If a dose is missed, it may be taken within 4 hours of the scheduled time. If 4 or more hours have passed, the dose will be considered missed and the next dose should be taken at the regularly scheduled time. Participants may complete and return Participant's Diary (optional) every cycle (**Appendix C**).

Epacadostat will be given first in Arm 2.3A to facilitate timing of fasting pre-dose blood sample on cycle 1 day 1 (can be sampled at any time before the first Epacadostat dose) and fasting pre-dose and 2 hour post-dose blood sampling that will occur on C2D8.

3.3.6 Sequence and Monitoring of Dose Administration

When administering concurrent investigational agents on the same day, the following sequence of administration is preferred.

Acetaminophen 650 mg and Benadryl 50 mg by mouth will be given within 30 to 60 minutes prior to M7824 infusion.

3.3.6.1 Arm 1.1

M7824 will be administered first. Participants will be monitored for symptoms of delayed infusion reaction for 60 +/- 10 minutes. N-803 administration is preferred to occur at 60 minutes following M7824 infusion completion, but may be given as long as 5 hours after the M7824 infusion finishes. If no M7824 infusion reactions have occurred, participants can receive N-803 immediately following M7824 infusion completion and forego the 60 minutes waiting period, starting at the 4th

M7824 infusion. Participants must be observed for 2 hours after the first N-803 dose. If no reactions are observed, the participants need to be monitored for only 30 +/- 10 minutes after subsequent doses.

3.3.6.2 Arms 2.1A and 2.1B

Preferably, BN-Brachyury will be injected first, followed by M7824 administration. Participants will be monitored for symptoms of delayed infusion reaction for 60 +/- 10 minutes.

3.3.6.3 Arms 2.2A and 2.2B.

Preferably, BN-Brachyury will be injected first, followed by M7824 administration. Participants will be monitored for symptoms of delayed infusion reaction for 60 minutes +/- 10 minutes. N-803 administration is preferred to occur at 60 minutes following M7824 infusion completion, but may be given as long as 5 hours after the M7824 infusion finishes. If no M7824 infusion reactions have occurred, participants can receive N-803 immediately following M7824 infusion completion and forego the 60 minutes waiting period, starting at the 4th M7824 infusion. Participants must be observed for 2 hours after the first N-803 dose. If no reactions are observed, the participants need to be monitored for only 30 minutes +/- 10 after subsequent doses.

3.3.6.4 Arms 2.3A and 2.3B.

Preferably, BN-Brachyury will be injected first, followed by M7824 administration. Participants will be monitored for symptoms of delayed infusion reaction for 60 +/- 10 minutes. N-803 administration is preferred to occur at 60 minutes following M7824 infusion completion, but may be given as long as 5 hours after the M7824 infusion finishes. If no M7824 infusion reactions have occurred, participants can receive N-803 immediately following M7824 infusion completion and forego the 60 minutes waiting period, starting at the 4th M7824 infusion. Participants must be observed for 2 hours after the first N-803 dose. If no reactions are observed, the participants need to be monitored for only 30 +/- 10 minutes after subsequent doses. Epacadostat can be given any time after the M7824 infusion is completed. If no reactions are observed, the participants need to be monitored for only 30 +/- 10 minutes after subsequent doses.

3.3.6.5 Vital Signs Monitoring

For all participants receiving N-803 and/or M7824, vital signs will be measured before, at least one time during the infusion of M7824 and after infusion. Vital signs must be measured within 30 minutes before and 30 minutes following the N-803 injection.

3.4 DOSE MODIFICATIONS

During DLT period dose modifications are not allowed.

During expansion phase:

3.4.1 BN-Brachyury vaccine:

BN-Brachyury vaccine dose will not be modified.

3.4.2 M7824

Dose reductions to 900 mg every 2 weeks for toxicities attributed to M7824 will be allowed at the discretion of the investigator.

3.4.3 N-803

Dose reductions to 8 or 10 mcg/kg for toxicities attributed to N-803 will be allowed at the discretion of the investigator.

3.4.4 Epacadostat

Dose reductions to 400 mg BID, 200 mg BID, 100 mg BID for toxicities attributed to Epacadostat will be allowed at the discretion of the investigator.

In cases of skin toxicities grade 3 or greater that are attributed to epacadostat, epacadostat should be held until resolved or improved to grade 1. In such cases, epacadostat will be restarted at the next lower dose when improved to grade 1.

3.4.4.1 Procedures for Subjects Exhibiting Serotonin Syndrome (SS)

The following procedures will be implemented if there is a clinical concern for developing SS. The signs/symptoms of SS, including tremor; hyperreflexia; spontaneous, ocular, or inducible clonus; together with agitation, fever, diaphoresis, or muscle rigidity:

- Immediately interrupt epacadostat.
- Immediately interrupt any SSRI or SNRI administration.
- Provide appropriate medical management of the participant until all signs/symptoms are resolved (eg, IV fluids and/or sympathomimetic amines for hypotension, benzodiazepines for agitation, administration of 5-hydroxytryptamine antagonists such as cyproheptadine).
- If participant chooses to remain in the study, restart treatment with epacadostat after the SSRI or SNRI has been discontinued, no sooner than 5 half-lives have elapsed for the specific SSRI or SNRI in question, and after resolution of signs/symptoms of SS. The SSRI or SNRI dosing MAY NOT be restarted while the participant is receiving epacadostat on study.
- If participant chooses to withdraw from the study, or must restart treatment with SSRI or SNRI, the participant should be scheduled for a follow-up visit. Treatment with SSRI or SNRI may be initiated 2 weeks after resolution of signs and symptoms of SS. Epacadostat will not be continued in these cases.

Table 3: Signs and Symptoms of Serotonin Syndrome

Seriousness	Autonomic signs	Neurological signs	Mental status	Other
Mild	Afebrile or low-grade fever Tachycardia Mydriasis Diaphoresis or shivering	Intermittent tremor Akathisia Myoclonus Mild hyperreflexia	Restlessness Anxiety	

Seriousness	Autonomic signs	Neurological signs	Mental status	Other
Moderate	Increased tachycardia Fever (up to 41 °C) Diarrhea with hyperactive bowel sounds Diaphoresis with normal skin color	Hyperreflexia Inducible clonus Ocular clonus (slow continuous lateral eye movements) Myoclonus	Easily startled Increased confusion Agitation and hypervigilance	Rhabdomyolysis Metabolic acidosis Renal failure Disseminated intravascular coagulopathy (secondary to hyperthermia)
Severe	Temperature often more than 41 °C (Secondary to increased tone)	Increased muscle tone (lower limb > upper) Spontaneous clonus Substantial myoclonus or hyperreflexia	Delirium Coma	As above

Please refer to the Boyer NEJM 2005 [59] for more details about SS.

A Patient card explaining the symptoms for serotonin syndrome will be provided for participants enrolling in arm 2.3 A and for participants who may be randomized to arm 2.3 B.

3.4.5 Suggested evaluation of suspected bleeding or hemorrhage events and treatment modification

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

3.4.5.2 In this protocol, anemia may be due to M7824 (documented in 29% of patients) and/or SX-682. M7824 treatment-related anemia is an AESI (see Investigators' Brochure). Notably, there are many reasons for hemorrhage and/or anemia in patients with advanced cancer, and Hb level of at least 9 g/dL is required for this study. A thorough investigation of new anemia cases of unspecified etiology is recommended:

3.4.5.3 Participants must enter the study with Hgb values at least 9 g/dL and baseline anemia evaluation is conducted per recommendations below.

3.4.6 Consider hematology consult for severe and or refractory anemias.

3.4.6.1 All relevant hematologic testing for treatment related anemias should be done prior to blood transfusion, if clinically feasible.

3.4.6.2 Transfusion should be performed at the discretion of the investigator, based on clinical assessment and considered when participant experiences significant anemia.

3.4.6.3 Guidance for evaluation of baseline anemia or suspected treatment-related anemias is provided below. Investigators may consider the following laboratory evaluations in participants with anemia.

3.4.6.4 Hb and CBC with differential (e.g. MCV, RDW, ANC, hematocrit, reticulocytes counts)

3.4.6.5 Peripheral blood smear for cell morphological assessment

3.4.6.6 Complete metabolic panel including liver panel-LFTs, bilirubin, LDH, renal function, and serum folate, B12 values and other chemistries

3.4.6.7 Coagulation factors (PT, PTT, INR)

3.4.6.8 Urinalysis including culture

3.4.6.9 Iron panel (TIBC, ferritin, Fe)

3.4.6.10 Discuss further management with Principal Investigator for clinically significant treatment related anemias.

3.4.7 Immune-Related Adverse Events

The effects of N-803 and Epacadostat, on the irAEs that may be seen with M7824 are unknown.

If, in the judgement of the investigator, an irAE observed outside of the DLT period is wholly or partially due to M7824, N-803, or Epacadostat, that agent may be held temporarily, permanently discontinued, or dose adjusted (See Section **3.4**).

There will be no dose modifications for BN-Brachyury. Therefore, in such cases, BN-Brachyury can be held or discontinued, at the discretion of the investigator.

The management of immune-related adverse events associated with immune checkpoint inhibitors (e.g. M7824) should follow published national guidelines. Investigators may alter management plans based on published guidelines and/or best professional judgement, including consultation with specialists The National Comprehensive Cancer Network (NCCN Guidelines®), may be found here:

https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf

Additional information may also be found here:

https://ascopubs.org/doi/pdf/10.1200/JCO.2017.77.6385

- In addition to the above guidelines, the following recommendations should be considered when managing irAEs:
  - • Permanent treatment discontinuation is required in case of immune-related Grade 4 rash/inflammatory dermatitis, nephritis, autoimmune hemolytic anemia, hemolytic uremic syndrome, aplastic anemia, immune thrombocytopenia, acquired thrombotic thrombocytopenic purpura inflammatory arthritis, myositis and polymyalgia-like syndrome.
  - • For Grade 4 immune-related lymphopenia, permanent treatment discontinuation will be required, if lymphopenia is considered immune-

related in nature, no clear alternative explanation exists for the event, and it does not resolve within 14 days. Permanent treatment discontinuation is not required when the AE is manifested by a single laboratory value out of normal range without any clinical correlates. In this case, treatment should be held until the etiology is determined. If the event is not considered immune-related and resolves to Grade ≤ 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

3.4.8 Discontinuation

Treatment will be discontinued in case of:

- Any Grade 4 adverse drug reactions (ADRs), as defined by CTCAE v5 and assessed as related to combined treatment 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 participant (e.g. placement of a pleurx catheter for recurrent inflammatory pleural effusions)

3.4.9 Dose hold

During the DLT periods of the Phase I and IIA dose holds will result in the participant being replaced. Outside of DLT period, dose(s) may be held at the discretion of the investigator (e.g., in cases where the participant requires an elective procedure or is recovering from a non-treatment-related illness) and continuation of study participation will be at the discretion of the investigator. In such cases, the planned visit and medical studies may be skipped.

For cases in which hold of one study agent, but not the other scheduled agent(s), is indicated on a given cycle (N), the following cycle will be (N+1). However, in cases where all agents are held, the missed cycle (N) can be delayed. When the investigator determines it appropriate to resume study agent(s), that will be named cycle N. Since arms 2.1, 2.2 and 2.3 do not include BN-brachyury dosing at every visit, a situation where *all* other agent(s) are held at cycle N, and cycle N dose not include BN-brachyury administration, the next scheduled visit will be cycle N+1, if BN-brachyury is administered.

During Phase IIB:

N-803 may be delayed if on the day of a planned dose for either of the following situations:

- the participant has a fever of > 101°F (38.3 °C)
- if in the opinion of the treating physician, holding would be of benefit to the participant

If after a 1-week rest, the participant no longer meets either of the above criteria for dose delay; the participant may resume treatment with the intent of giving all remaining doses of N-803 for the treatment cycle, but the missed dose will not be made up.

- Hypotension (systolic blood pressure < 90 mm Hg)

N-803 dosing should be held for hypotension (defined as systolic blood pressure less than 90 mm Hg) if in the presence of any clinically significant symptoms (in the opinion of the treating physician), until the systolic blood pressure reading is stable. If mild dehydration is suspected, an IV fluid bolus may be used per standard of care.

3.5 STUDY CALENDAR

Procedure(s)	Screening	Baseline[1]	Cycles 1-2 [2, 23]		Cycles 3-N [2]	28 Days Safety FU[14]	Long Term FU[15]
			D1	D8[28]	D1		
M7824[3]			X		X		
N-803[4]			X		X		
MVA-BN-Brachyury [5]			X		X		
FPV-Brachyury [6]			X		X		
Epacadostat [7]			X		X		
Physical exam, weight and ECOG	X	X	X	X	X	X	
Vital Signs	X	X	X[8]	X	X[8]	X	
CBC w/differential, Platelets	X	X	X	X	X	X	
Biochemical profile[9]	X	X	X	X	X	X	
Amylase, lipase, LDH, GGT		X	X		X	X	
Adverse event evaluation		X	X	X	X	X	X
Concomitant meds		X	X	X	X		
CK, Uric Acid, Total Protein, CRP			X		X		
Thyroid tests TSH, T3, T4		X	X		X	X	
PT and PTT	X		X		X		
Serum PSA[10]	X	X	X		X	X	
Testosterone level[10]	X	X	X		X		
TBNK phenotyping[19]			X		X		
IGF-1, Prolactin, Androstenedione, Dihydrotestosterone (DHT), 17-OH-Progesterone, DHEA, DHEA-S, estradiol, ACTH, Cortisol[26]		X					
ACTH and Cortisol[26, 27]					X		
Radiologic Evaluation[11]	X	X			X		X
Bone scan [12]		X			X		X
Histologic confirmation of dx	X						
Medical history	X						
Height	X						
EKG[25]	X	X			X	X	

Procedure(s)	Screening	Baseline[1]	Cycles 1-2 [2, 23]		Cycles 3-N [2]	28 Days Safety FU[14]	Long Term FU[15]
			D1	D8[28]	D1		
HIV, Hepatitis B and C serology and/or viral load	X						
Serum pregnancy test	X[20]	X[20]	X[20]		X[20]		
HLA A,B,C and DR, DQ, NGS HLA-ABC & DRDQ, NGS HLA-DPB1 [high resolution HLA-DPB1], NGS HLA-DQA1 [high resolution HLA-DQA1]		X[21]					
Urinalysis[22]	X	X	X		X		
Research blood for M7824 Pharmacokinetics [16]			X		X		
Research blood for ADA[17]			X		X		
Research blood for tryptophan and kynurenine [18]			X	X	X[24]	X	
Research blood for Immunologic Parameters [19]			X		X		
NIH Advance Directive Form[13]		X					
Phone call or e-mail for progression every 6 month							X

[1] Baseline evaluations do not need to be repeated if performed on screening in designated time frame.

[2] Cycle length is 2 weeks (+7/-3 days). Evaluation performed at baseline do not need to be repeated on Day 1 of Cycle 1 if performed in designated time frame.

[3] 1,200 mg of M7824 via IV infusion on Day 1 of each cycle.

[4] N-803 (8-15 mcg/kg) subcutaneous injection on Day 1 of each cycle.

[5] MVA-BN-Brachyury subcutaneous injection on Day 1 of Cycle 1 and Day 1 of Cycle 2.

[6] FPV-Brachyury subcutaneous injection on Day 1 of Cycle 3, then on Day 1 of cycles 5, 7, 9, 11 and 13, then every 3 months until reaching 2 years. After 2 years every 6 months.

[7] 600 mg of Epacadostat orally twice daily every day (1200 mg total).

[8] For vital signs on Day 1 see Section **3.3.6.5** . All protocol mandated vital sign measurements may be performed within a time frame of +/- 10 minutes of the planned time.

[9] Biochemical Profile: electrolytes, BUN, creatinine, AST, ALT, total and direct bilirubin, calcium, phosphorus, albumin, magnesium.

[10] For participants with prostate cancer only. To be performed every 4 weeks.

[11] CT scan of chest, abdomen and pelvis (or MRI of abdomen if it is clinically indicated when CT is not appropriate). Every 12 (+/-1) weeks after start of study therapy. If participant taken off treatment for reason other than disease progression, he/she should be followed by this evaluation every 12 weeks. If the participant came off treatment for a reason other than disease progression and has subsequently started another line of systemic treatment, the follow up CT imaging included in this evaluation may be omitted.

[12] Every 12 (+/-1) weeks after start of study therapy for patients having Prostate Cancer. If participant taken off treatment for reason other than disease progression, he/she should be followed by this evaluation every 12 weeks. If the participant came off treatment for a reason other than disease progression and has subsequently started another line of systemic treatment, the bone scan may be omitted.

[13] As indicated in section **12.3**, all subjects will be offered the opportunity to complete an NIH Advance Directive 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.

[14] +/- 1 week. If subjects are not willing to come to NIH to FU safety visit, they will be contacted by phone call or e-mail for survival, adverse events and further tumor therapy.

[15] If participant taken off treatment for reason other than disease progression, he/she may remain on protocol to be followed every 12 weeks (to monitor for disease progression) until disease progression or the participant starts other cancer therapy. If subjects are not willing to come to NIH for these visits, they will be contacted by phone call or e-mail for disease progression and adverse events every 6 month.

[16] Prior to infusion and immediately after infusion on Day 1 of cycles 1 and 3. Prior to infusion on Day 1 of cycles 2, 6 and at the time of taking a participant off treatment (whatever comes first). Per PI discretion samples may be taken prior to infusion every 12 weeks.

[17] Prior to infusion of M7824 on Day 1 of cycles 1, 3, and 6 and at the time of taking a participant off treatment (whatever comes first). Per PI discretion, samples may be taken prior to infusion every 12 weeks.

[18] Only for participants assigned to be treated with Epacadostat. On Day 1 Cycle 1, a fasting blood sample will be drawn at any time pre-dose of Epacadostat. On Day 8 of Cycle 2, a sample will be drawn fasting (for 8 hours), within 10 minutes before the participant takes that dose of Epacadostat and 2 hours (+/- 5 minutes) post Epacadostat dose (also fasting).

[19] Prior to treatment on Day 1 of cycles 1, 2, 6 and 12. Per PI discretion additional samples might be collected every 12 weeks and at the time of taking a participant off treatment.

[20] Applies to females only.

[21] These may be performed any time prior to study treatment initiation. Participants who have had HLA typing previously performed at NIH do not require retesting.

[22] In participants who have difficulty providing a urine sample (e.g., participants with incontinence due to treatment for prostate cancer), urinalysis collection outside of the DLT period may be skipped at investigator discretion.

[23] +/-21 days is allowed for collection of research samples following C1 and C2 visits.

[24] Prior to treatment on Day 1 of cycles 4, 6, 10 and 12

[25] Every 12 weeks +/- 2 weeks for participants receiving Epacodostat

[26]Obtained between the hours of 7am-9am, after fasting for at least 8 hours.

[27] To monitor for adrenal insufficiency, every 4 weeks +/- 2 weeks, starting at cycle 4. Participants already diagnosed with adrenal insufficiency at baseline are excluded from this testing. Participants testing positive for adrenal insufficiency will receive appropriate medical management

[28] +/-2 days is allowed for Day 8 visits in C1 and C2.

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 are performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by an insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.6.2 Compensation

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

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 28-30 days following the last dose of study therapy.

3.7.1 Criteria for removal from protocol therapy:

- Participant requests to be withdrawn from active therapy.
- Unacceptable Toxicity.
- Positive pregnancy test or intent to become pregnant.
- Investigator discretion.
- Initiation of alternative anticancer therapy including another investigational agent. Exception: Palliative radiation given outside of the DLT period is allowed.
- Progressive disease evidenced by radiographic or symptomatic progression (see Section **6.3.3**).

- Intercurrent illness that prevents further administration of treatment.

3.7.2 Off-Study Criteria

- Completion of 28 day follow up assessment after removal from protocol therapy for disease progression. If participant is taken off treatment for reason other than disease progression, he/she will be taken off study when there is information available about disease progression or the participant begins an alternative anti-cancer therapy.
- Death.
- Lost to follow up.
- Participant requests to be removed from the study.
- Investigator discretion.
- PI decision to close the study.
- Screen failure.

3.7.3 Lost to Follow-up

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

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

- The site will attempt to contact the participant and reschedule the missed visit within 2 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

4.1 GENERAL GUIDANCE

Supportive care with blood components, antibiotics, analgesics, general medical therapy, etc., will be delivered as required.

Immunotherapy including interferon, immunosuppressive drugs (for example, chemotherapy or systemic steroids except for short term treatment of allergic reactions, endocrine replacement therapy or low dose prednisone [≤ 10mg daily] or equivalent, or for the treatment of irAEs or other appropriate short- term steroid use), or other experimental pharmaceutical products are prohibited. Short term administration of systemic steroid or other immunosuppressant such as infliximab or mycophenolate (that is, for allergic reactions or management of irAEs) is allowed. Steroids with no or minimal systemic effect (topical, inhalation), are allowed. Physiologic doses of steroids are

permitted, e.g. a patient recently on abiraterone (administered with 10 mg of prednisone daily) who is tapering off of prednisone is allowed to continue that taper.

Any live vaccine therapies for the prevention of infectious disease are prohibited. Administration of inactivated vaccines is allowed (for example, inactivated influenza vaccine).Locally approved COVID vaccines are permitted.

Antiemetics may be used for the treatment of nausea and vomiting but should not be used prophylactically during the first cycle. Steroid-based anti-emetics are not allowed.

4.2 N-803 (FORMERLY ALT-803)

Central nervous function may be affected with N-803. Caution should be used with psychotropic medications.

Nephrotoxic, myelotoxic, cardiotoxic, or hepatotoxic medications should be avoided if possible as they may further increase toxicities that have been associated with N-803.

Interferon-alfa is prohibited while on study.

Beta-blockers and other antihypertensives may potentiate the hypotension seen with N-803. Therefore, administration of these agents should be avoided during N-803 treatment period, unless clinically indicated. If a participant who is to receive N-803 is on a beta-blocker or other antihypertensive, that agent may be discontinued starting on the day of the first treatment with N-803, if the investigator determines that stopping the agent is safe. Anti-hypertensive management decisions will be made on a case by case basis. For example, an anti-hypertensive may be resumed or added at any point if the investigator believes it to be clinically indicated e.g. if a participant experiences uncontrolled hypertension while receiving N-803 treatment on study. For participants on antihypertensives at baseline, the agent will be resumed if clinically indicated by blood pressure readings in the days following N-803 treatment cessation.

If a localized skin rash at the injection site occurs that is >6 cm and symptomatic, it may be treated with 0.05% clobetasol propionate or 0.1% triamcinolone cream or similar product at the discretion of the treating physician.

Administration of additional glucocorticoids is discouraged during the N-803 treatment period as the use of systemic steroid medications may result in loss of therapeutic effects of the study drug. However systemic steroids may be used to treat an irAE. Sustained use of steroids or steroid use to treat immune-related toxicity may be an indication to permanently or temporarily discontinue N-803.

4.3 EPACADOSTAT

The chronic use of systemic antibiotics (> 14 days) concurrently with epacadostat doses > 300mg BID is prohibited unless medical monitor review and approval.

Two metabolites of epacadostat, M11 and M12, exhibit moderate inhibition of CYP1A2, CYP2C8 (M12 only), and CYP2C19. Metabolites of epacadostat may also inhibit CYP2B6 and CYP3A4. OATP1B1 and OATP1B3 may be inhibited by M9 and M11 (metabolites of epacadostat).

Agents listed in **Appendix E** are prohibited while on study for patients receiving epacadostat doses > 300 mg BID. All other agents that are substrates of these enzymes/transporters should be evaluated on a case-by-case basis since the potential for a drug-drug interaction exists especially for agents with a narrow therapeutic index. Warfarin is prohibited in patients taking Epacadostat.

Potential for a drug-drug interaction between combined oral contraceptives and epacadostat exists. However, as currently written, only males with CRPC will enroll onto the Arms with epacadostat and therefore any potential drug interaction with oral contraceptives in this study is not relevant.

Please refer to the Flockhart Table (https://drug-interactions.medicine.iu.edu/MainTable.aspx), the FDA-approved prescribing information, and consult with a clinical pharmacist to determine the enzyme/transporter interaction potential of medications with epacadostat.

Use of any UGT1A9 inhibitor from screening through follow-up period, including the following: diclofenac, imipramine, ketoconazole, mefenamic acid, and probenecid is prohibited in patients receiving epacadostat > 300mg BID (see **Appendix D**).

There is a rare chance that epacadostat could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome (SS), when administered in combination with other serotonergic agents. This syndrome has been most closely associated with use of MAOIs, meperidine, linezolid, or methylene blue; all of these agents are prohibited during the study . Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin/norepinephrine reuptake inhibitors (SNRIs) are permitted in the study. Serotonin syndrome usually manifests with autonomic changes, mental status changes, and neurological findings. These mild, moderate, and severe signs and symptoms of SS (summarized in **Table 3**) should be evaluated in the context of possible comorbid conditions as well.

Participants in this study will not be recommended to take antidepressants that affect serotonin levels unless determined to be clinically indicated at the discretion of the investigator.

5 CORRELATIVE STUDIES FOR RESEARCH

5.1 BIOSPECIMEN COLLECTION

Test/assay	Volume (approx.) per time point	Type of tube*	Collection point	Location of specimen analysis
M7824 Pharmacokinetics	4 mL blood	Serum Separator Tubes (SST®)	See study calendar **3.5**	EMD Serono (Processed in [redacted] Lab)
ADA by ELISA	4 mL blood	Serum Separator Tubes (SST®)	See study calendar **3.5**	EMD Serono (Processed in [redacted] Lab)
Tryptophan and kynurenine plasma levels by liquid chromatography tandem mass spectrometry (LC-MS)	4 mL blood	Serum Separator Tubes (SST®)	See study calendar **3.5**	Incyte Corporation (Processed in [redacted] Lab)

Test/assay	Volume (approx.) per time point	Type of tube*	Collection point	Location of specimen analysis
Immunologic Parameters (including vesicles EV) by ELISA and FACS	76-96 mL blood	**For C1 D1 time point**: 2 (8 mL) SST tubes and 8 (10 mL) green top sodium heparin tubes **For all other time points:** 2 (8 mL) SST tubes and 6 (10 mL) green top sodium heparin tubes	See study calendar **3.5**	LTIB or [redacted] Lab (Processed in Frederick)
*Please note that tubes and media may be substituted based on availability with the permission of the PI or laboratory investigator.				

All samples will be originally send either to BPC (Section **5.2.2) or** Clinical Services Program – Leidos Biomedical Research, Inc. (CSP) (Section **5.2.1**) for barcoding, initial processing and storage. From this facility samples will be sent to the designated places for analysis in batch shipments or upon request.

5.1.1 M7824 Pharmacokinetics

PK measurements of M7824 will be taken to collect sparse PKs data which will provide insight into population PKs of M7824 in participants receiving these novel combinations.

The schedule is in the study calendar **3.5.** Serum M7824 PK measurements will be done at EMD Serono.

5.1.2 ADA

Anti-Drug Antibody (ADA) development is an accepted mechanism of loss of efficacy administered human monoclonal antibodies. Measuring titers will ensure that lack of efficacy of M7824 is not due to ADA development.

Schedule is in study calendar **3.5.** The investigation will be done by EMD Serono using ELISA.

Samples will be shipped to EMD Serono for analysis.

5.1.3 Tryptophan and kynurenine plasma levels

To understand Epacadostat's effects on metabolism of tryptophan and kynurenine (see section **1.2.4)** while on this combination therapy, serum or plasma levels of tryptophan and kynurenine will be measured by liquid chromatography tandem mass spectrometry (LC-MS/MS) and World Wide Clinical Trials (WWCT) for analysis.

The schedule is included in the study calendar **3.5**

This will be done by Incyte Corporation. Samples will be logged into a biospecimen inventory and stored at -80 until for analysis.

Please ship to the following address and notify personnel at the phone number below:

[redacted]

An email will be sent to [redacted] with an electronic roster and tracking information before samples ship.

5.1.4 Immunologic Parameters (per PI discretion in selected participants)

Vaccination with BN-Brachyury has been shown to induce antigen specific T cells in patients receiving the vaccine. This may be beneficial to participants, and is hypothesized to be enhanced with addition of M7824, N-803 and Epacadostat. Studying the immunologic parameters below be useful in gaining insight into circulating the immune phenotype of a participant responding to treatment. This has potential to aid in biomarker development.

Blood will be collected according to Study Calendar **3.5.**

The following immune assays may be performed at the Laboratory of Tumor Immunology and Biology at the NCI's Center for Cancer Research (CCR) in select participants where adequate samples are available:

PBMC:

1. PBMCs may be analyzed for changes in standard immune cell types (CD4 and CD8 T cells, natural killer [NK] cells, regulatory T cells [Tregs], myeloid-derived suppressor cells [MDSCs], and dendritic cells) as well as 123 immune cell subsets, as described elsewhere [60] [61].
2. PBMCs from selected subjects may be analyzed for function of specific immune cell subsets, including CD4 and CD8 T cells, NK cells, Tregs, and MDSCs.
3. PBMCs may be analyzed for tumor antigen-specific immune responses to CEA, MUC-1 and Brachyury using an intracellular cytokine staining assay. PBMCs will be stimulated in vitro with overlapping 15-mer peptide pools encoding the tumor-associated antigens listed above; control peptide pools will involve the use of human leukocyte antigen peptide as a negative control and CEFT peptide mix as a positive control. CEFT is a mixture of peptides of CMV, Epstein-Barr virus, influenza, and tetanus toxin. Post-stimulation analyses of CD4 and CD8 T cells will involve the production of IFN-γ, IL-2, TNF, and the degranulation marker CD107a. If sufficient PBMCs are available, assays may also be performed for the development of T cells to other tumor-associated antigens. A detailed description of this assay has been previously reported [8].
4. Analyses of soluble factors:

- Sera may be analyzed pre- and post-therapy for the following soluble factors: sCD27, sCD40 ligand using commercial ELISA kits.
- Sera may be analyzed for changes in cytokines (IFN-γ, IL-10, IL-12, IL-2, IL-4, etc.), chemokines, antibodies, tumor-associated antigens, and/or other markers using ELISA or multiplexed assays (e.g. Mesoscale, Luminex, cytokine bead array).

Immunologic studies will be repeated more frequently if clinically indicated, and any abnormalities potentially related to treatment will be followed until they have resolved, stabilized, or have been determined not to be treatment-related.

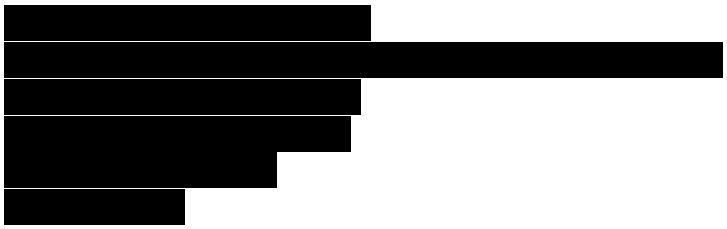
5. Prostate-specific Membrane Antigen (PSMA) positive extracellular vesicles (EV) and immune EVs.

This is an exploratory endpoint. Samples collected as described under immunologic parameters be used for EV analysis.

There is an unmet need for biomarkers predictive of clinical response pre-treatment, as well as early on in treatment of CRPC. Extracellular vesicles (EVs) are biologically active particles produced in large quantities by tumor and immune cells in response to stressors. Circulating EVs display multiple cell surface markers expressed on the cells that produce them. This biological information can potentially be exploited for development of personalized and adaptive treatments for participants. Prostate specific membrane antigen (PSMA) is over expressed on all prostate cancers and is also expressed on EVs. Recent data suggests that PSMA+ EV concentration may reflect prostate cancer disease status, making PSMA+ EV concentration a promising biomarker for response to immunotherapy.

Schedule is in study calendar **3.5**

The nanoFACS technique of high -resolution analyses and sorting of single EVs by flow cytometry was developed at the NCI. EV subset phenotypes may serve as a potential biomarker for response to treatment. Serum and/or plasma samples may be evaluated for EV subsets in collaboration with:



5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

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

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

Clinical Services Program - Leidos Biomedical Research, Inc.

Attn: [redacted]

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

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

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

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

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

It is the intent and purpose of the subcontractor to accept only 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 participant-specific information is encoded in this ID.

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

5.2.2 Samples Managed by [redacted] Blood Processing Core (BPC)

5.2.2.1 BPC contact information

Please e-mail [redacted] at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page [redacted].

For immediate help, call [redacted] (main blood processing core number) or, if no answer, [redacted] (main clinical pharmacology lab number).

For questions regarding sample processing, contact [redacted]

5.2.2.2 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 [redacted] lab personnel, who are issued individual user accounts. Installation of Labmatrix is limited to computers specified by [redacted]. 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 participants without Labmatrix access. The data recorded for each sample includes the participant ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Participant demographics associated with the clinical center participant number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

5.2.2.3 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.

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

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

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

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

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

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

Document AEs from the first study intervention, study day 1, through 30 days after the subject received the last product administration. After 30 days, only adverse events which are serious and related to the study investigational agent need to be recorded.

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

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the participant's outcome.

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**.

6.2 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)
- Identified or coded, linked 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.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

GDS policy does not apply to this protocol.

6.3 RESPONSE CRITERIA

Restaging bone scans and CT scan of chest, abdomen and pelvis will be obtained **every 12 weeks.** Participants in the M7824 plus N-803 safety cohort who do not have prostate cancer will be exempt from bone scans.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[62]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

For exploratory purpose, changes in PSA and measurable lesions will be analyzed for efficacy according to the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) recommendations. The recommended PSA progressions criteria will not be applied to the study as the criteria are arbitrarily proposed and do not necessarily reflect overall disease status. PSA values will be captured at each visit and PSA declines and progression will be followed. PSA is not sufficient in the evaluation of disease progression in this participant population. This is consistent with the recent recommendations by the PCWG2. Progression will be determined by radiographic evidence as discussed below or by clinical symptoms (symptomatic clinical progression).

6.3.1 Disease Parameters

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

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

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

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

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

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

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

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be

recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.2 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the

next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for PSA response (in recurrent prostate cancer) have been published[63-65].

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

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

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

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

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

6.3.3 Response Criteria by RECIST (version 1.1)

6.3.3.1 Evaluation of Target Lesions

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

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

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

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

6.3.3.2 Evaluation of Non-Target Lesions

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

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

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

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

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

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

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.

6.3.3.3 Evaluation of Best Overall Response

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

For Participants with Measurable Disease (i.e., Target Disease)

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

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

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

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

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

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

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

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

6.3.4 Duration of Response

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

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

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

6.3.5 Progression-Free Survival

Measured as the length of time during which the participant is free from new metastatic lesions visible on imaging or progression of metastatic lesions from baseline by RECIST 1.1.

6.4 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each participant 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. A copy of the CTCAE version 5 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc).

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: https://irbo.nih.gov/confluence/pages/viewpage.action?pageId=36241835#HRPPPolicies-800Series-ComplianceandResearchEventReportingRequirements

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING /IRB REPORTING

7.2.1 Expedited Reporting

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

800Series-ComplianceandResearchEventReportingRequirements. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

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

7.3 NCI CLINICAL DIRECTOR REPORTING

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

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

To report these deaths, please send an email describing the circumstances of the death to NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 INSTITUTIONAL BIOSAFETY COMMITTEE (IBC) REPORTING CRITERIA

7.4.1 Serious Adverse Event Reports to IBC

The Principal Investigator (or delegate) will notify IBC of any unexpected fatal or life-threatening experience associated with the use of BN-Brachyury as soon as possible but in no event later than 7 calendar days of initial receipt of the information. Serious adverse events that are unexpected and associated with the use of the BN-Brachyury, but are not fatal or life-threatening, must be reported to the NIH IBC as soon as possible, but not later than 15 calendar days after the investigator's initial receipt of the information. Adverse events may be reported by using the FDA Form 3500a.

7.4.2 Annual Reports to IBC

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

7.4.2.1 Clinical Trial Information

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

- the title and purpose of the trial
- clinical site
- the Principal Investigator
- clinical protocol identifiers;
- participant population (such as disease indication and general age group, e.g., adult or pediatric);

- the total number of participants planned for inclusion in the trial; the number entered into the trial to date whose participation in the trial was completed; and the number who dropped out of the trial with a brief description of the reasons
- the status of the trial, e.g., open to accrual of subjects, closed but data collection ongoing, or fully completed,
- if the trial has been completed, a brief description of any study results.

7.4.2.2 Progress Report and Data Analysis

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

- a narrative or tabular summary showing the most frequent and most serious adverse experiences by body system
- a summary of all serious adverse events submitted during the past year
- a summary of serious adverse events that were expected or considered to have causes not associated with the use of the gene transfer product such as disease progression or concurrent medications
- if any deaths have occurred, the number of participants who died during participation in the investigation and causes of death
- a brief description of any information obtained that is pertinent to an understanding of the gene transfer product's actions, including, for example, information about dose-response, information from controlled trials, and information about bioavailability.

7.5 NIH Required Data and Safety Monitoring Plan

7.5.1 Principal Investigator/Research Team

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

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator.

Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

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

7.5.2 Data Safety Monitoring Board (DSMB)

The DSMB is an independent group of at least 3 experts that monitors participant safety and advises The Sponsor. DSMB members will be separate and independent of study staff participating in this trial and should not have scientific, financial, or other conflicts of interest related to this

trial. The DSMB will consist of members with appropriate expertise to contribute to the interpretation of data from this trial. A quorum will consist of a simple majority.

The DSMB will review cumulative safety data from this trial at least annually.

The DSMB will meet when trial halting criteria (see Section **3.2)** are met, or as requested by the sponsor or PI.

The DSMB will have a final review meeting at the end of the study.

Procedures for DSMB reviews/meetings will be defined in the DSMB charter. The DSMB will review applicable data, including, but not limited to, enrollment, demographics, dosing data, clinical laboratory data, and safety data, at scheduled timepoints during this trial as defined in the DSMB charter. The DSMB will review blinded aggregate data in the open session of the DSMB meetings.

Additional data may be requested by the DSMB, and interim statistical reports may be generated as deemed necessary and appropriate by the Sponsor. As an outcome of each review/meeting, the DSMB will make a recommendation as to the advisability of proceeding with study product administration, and to continue, modify, or terminate this trial.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

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

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for 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.

8.1.3 Life-threatening

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

8.1.4 Severity

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

8.1.5 Relationship to Study Product

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

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product(s) and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs assessed as severe allows ongoing surveillance of these events to characterize and understand them in association with the use of these investigational products.

Only AESIs that match the definition of SAE will be reported as other SAEs within 7 days from the knowledge of event. Other non-SAE AESIs should do not need to be reported to OSRO but only collected in the clinical database.

The adverse events related to mucosal bleeding, regardless of site, will be collected as an AESI to enable evaluation of potential risk factors, such as site/past radiation/associated infection at site/recent instrumentation and other variables such as time to onset, exposure history, grade of bleeding, anatomical sites, etc. can be collected.

8.2 ASSESSMENT OF SAFETY EVENTS

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

SAEs will be:

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

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

8.3 REPORTING OF SERIOUS ADVERSE EVENTS

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

8.5 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

8.5.1 EMD Serono

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.

- 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 and M9241

- 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 and M9241 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 and M9241.

Contact information for submission of reportable events to EMD Serono:

Fax: +[redacted]

OR

E-mail: [redacted] specifying

- PROTOCOL Number and/or Title
- EMD Serono assigned Study Number
- SUBJECT Number
- SITE Number/PI Name
- SAE/ONSET DATE

8.5.2 Immunity Bio

To be sent by Office of Sponsor and Regulatory Oversight, CCR, NCI/NIH:

- Serious AEs (SAEs), whether related or not related to study drug, and pregnancies must be reported to NantBio (ImmunityBio drug safety affiliate) Drug Safety (Nant) within 2 business days with regards to Nant drug use.

- In 2 business days, Nant will be receiving notification for not related SAEs and preliminary SUSARs not the full assessment of the event (i.e., narrative which would come latter) SAEs must be recorded on an OSRO SAE report form or MedWatch form.
- OSRO will be responsible for reporting of pregnancies unless it became SAE because of adverse fetal outcomes.
- The Sponsor will be responsible for submitting all safety correspondence to the FDA. Nant will be provided with a simultaneous copy of all Serious adverse event submissions filed with the FDA. Sponsor will provide NantBio (ImmunityBio's affiliate for drug safety) a copy of the Annual Report concurrently with the submission of the Annual Report to the FDA.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE notification should be sent within 2 business days to Nant using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

To be sent by study team:

- The Investigator will ensure that all SAEs in the clinical database are reported to Nant and any applicable health authority during the conduct of the study. This reconciliation will occur at least quarterly and be initiated by the investigator.
- Pregnancies on a Pregnancy Surveillance Form (Nant can provide) will be reported by study team when it became SAE because of adverse fetal outcomes.
- Investigator will request a reconciliation report from: [redacted] During reconciliation, any events found to not be reported previously to Nant must be sent to: [redacted]

Contact information for submission of all SAEs to NantCell:

All SAEs and any reports submitted to the FDA should simultaneously be faxed or e-mailed to NANT at:

Fax Number: [redacted]

Email: [redacted]

8.5.3 Bavarian Nordic, Inc.

To be sent by OSRO:

- All SAEs and all pregnancy reports must be reported to Bavarian Nordic Pharmacovigilance by within 2 business days or 3 calendar days (whichever comes first) of the investigator's knowledge of the event by facsimile, email, or other appropriate method using the Medwatch form (or a specific pregnancy report form if applicable). This instruction pertains to initial reports as well as any follow-up reports.
- The company will be included in the original report send to OSROsafety@mail.nih.gov.

- At the request of Bavarian Nordic, the investigator may send an email to the address below, providing a preliminary notification of an SAE within 24 hours of the investigator's first knowing of the event.

Contact for SAE reports to BN:

[redacted]

[redacted]

[redacted] #, PI name/site#, SAE/onset dates

8.5.4 Incyte

To be sent by OSRO:

All suspected unexpected serious adverse events that are considered related to Epacadostat treatment and will be reported to the FDA will be reported to Incyte within 2 business days or 3 calendar days (whichever comes first) of the investigator's knowledge recorded on the MedWatch Form or an OSRO SAE report form and sent to: [redacted]

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 participant becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy 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 should be followed up and documented for reporting requirements.

8.6.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 4 months after the last dose of study therapy.

Pregnancy of the participant's partner is not considered to be an AE. The outcome of all pregnancies occurring from the date of the first dose until 4 months after the last dose should, if possible, be followed up and documented for reporting requirements. Pregnant partners may be offered the opportunity to participate in an institutional pregnancy registry protocol (e.g., the NIH IRP pregnancy registry study) to provide data about the outcome of the pregnancy for safety reporting purposes.

8.7 Regulatory Reporting for Studies Conducted Under CCR-Sponsored IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and

the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

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

8.8 SPONSOR PROTOCOL DEVIATION REPORTING

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

It is the responsibility of the study Staff to document any protocol deviation identified by the Staff or the site Monitor in the CCR Protocol Deviation Tracking System (PDTS) online application. The entries into the PDTS online application should be timely, complete, and maintained per CCR PDTS user requirements. In addition, any deviation to the protocol should be documented in the participant's source records and reported to the reviewing IRB per their guidelines. OSRO required protocol deviation reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure:

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

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

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

OSRO SROS Monitoring visits and related activities will be conducted throughout the life cycle of each protocol. The first activity is before the study starts to conduct a Site Assessment Visit

(SAV) (as warranted), followed by a Site Initiation Visit (SIV), Interim Monitoring Visit(s) (IMVs), and a study Close-Out Visit (COV).

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

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

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

The primary objective of this trial is to determine if there is clinical benefit to any of a set of 3 possible treatments for participants with CRPC:

- BN Brachyury + M7824
- BN-Brachyury + M7824 + N-803
- BN-Brachyury + M7824 + N-803 + Epacadostat

The secondary objectives of this trial are to evaluate and compare the immune response with clinical outcomes in participants treated with any of the set of 3 possible treatments with CRPC and to characterize the safety profile of the above combinations and M7824 + N-803. Progression free survival (PFS) will also be estimated in each arm as a secondary objective.

10.2 SAMPLE SIZE DETERMINATION

- A set of 3 possible treatments will be explored in order to determine if there is any substantial benefit to participants using any of these treatments. For each of the 3 arms, the trial will aim to determine if there is either an objective clinical response or PSA decline of >=30% sustained for a minimum of 21 days. Experiencing any of these would be considered a positive outcome ('efficacy').
- A separate cohort (Cohort 1.1) will enroll up to 18 participants, and function to determine safe dosing in N-803 in combination with M7824. See Section **3.1.2** for details.
- Phase II data from a trial of PSA-TRICOM vs. placebo in CRPC demonstrated an ORR of 0% in measurable disease (in placebo and controls) and a PSA decline >=30% in 0% of participants receiving placebo[19]. This historic information is the basis for the statistical plan below.
- In order to establish at least potential utility from each of the regimens, the primary objective would be to determine if using the proposed agents would rule out a 10% efficacy rate and result in an efficacy rate consistent with 35%. As such, each arm 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 or PSA

decline of >30% ('efficacy') rate of 10% (p0=0.10) in favor of an improved efficacy rate of 35% (p1=0.35). There is no multiplicity adjustment for the 3 Simon 2-stage designs. With alpha=0.05 (probability of accepting a poor treatment=0.05) and beta = 0.10 (probability of rejecting a good treatment=0.10), the first stage for each arm will enroll 13 evaluable participants, and if 0 to 1 of the 13 demonstrate efficacy, then no further participants will be accrued in that arm. If 2 or more of the first 13 participants demonstrate efficacy, then that arm will continue to accrue participants until a total of 25 evaluable participants have been enrolled.

- Following this expansion to 25 participants, if there are 2 to 5 participants with efficacy out of 25 participants, this would be an uninterestingly low efficacy rate. If there were 6 or more of 25 (24.0%) who experienced any efficacy, this would be sufficiently interesting to warrant further study in later trials. Under the null hypothesis (10% efficacy rate), the probability of early termination is 62.1%.
- With 3 arms, the trial will aim to keep enrolling participants by using the following algorithm: at first, participants will enroll on arm 2.1 for the initial 13 participants in the arm. Then, after these 13 evaluable participants have enrolled, if adequate safety is demonstrated in the safety arm 1.1 and in arm 2.1 (<2 of the first 6 participants in the first stage of arm 2.1 have a DLT), arm 2.2 will open and enroll participants onto the first stage. Then, after the 1st stage of arm 2.2 has completed enrollment of 13 evaluable participants, if arm 2.2 is adequately safe (<2 of the first 6 participants in the first stage of arm 2 have a DLT), the first stage of arm 2.3 will open and accrue 13 evaluable participants.
- After accruing all 39 evaluable participants to the first stages of the three arms, if both arms 2.1 and 2.2 demonstrate adequate first-stage efficacy, then participants will be randomized between the second stages of both arms 2.1 and 2.2. Otherwise, if there is only adequate efficacy on one of the first two arms, then participants will begin to enroll directly onto the second stage of the arm with adequate efficacy.
- Finally, if arm 2.3 also demonstrates adequate efficacy in the first stage, this arm will begin to have its second stage participants randomized against participants from one or two other arms if there is adequate efficacy from the first stage of at least one of these two arms; otherwise it will accrue participants to the second stage without randomization. The randomization would continue for all included arms until enrollment of 25 evaluable participants in each arm. This may result in some participants never being randomized, but rather accrued to the single open available arm if only one arm is available to accrue participants. Thus, randomization will take place for the second stage participants during the time in which 2 or more arms are available to be randomized, and otherwise accrual will take place without randomization to the one open arm. As a result, randomization will take place when practical to do so, but not all 2nd stage participants may be randomized. By this algorithm, there is no bias in assignment to treatment, and the aim is to randomize as many participants as practical while any others are enrolled directly into the only available arm.
- At the end of the trial, the arms will be evaluated with respect to safety and clinical benefit/efficacy. In the absence of appreciably worse toxicity, the arm with the greatest fraction and number of participants experiencing efficacy will be considered for evaluation in future studies.

- It is expected that approximately 1 to 2 participants per month may enroll onto this trial. With 3 arms of up to 25 evaluable participants apiece, up to 75 evaluable participants may be required. In order to allow for up to 20 inevaluable participants and screen failures, plus 18 for the safety cohort 1, the accrual ceiling for this trial will be set at 113 participants.

10.3 POPULATIONS FOR ANALYSIS

In the M7824 + N-803 safety cohort, all participants who receive at least one dose of both agents will be evaluable for safety and toxicity evaluations. All participants will be evaluable for toxicity from the time of their first treatment with either agent.

In each of the phase II arms in the phase II cohort (sequential cohorts) a modified intention to treat population will be used. Only those participants who have measurable disease present at baseline including a PSA determination, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

10.4 STATISTICAL ANALYSIS

10.4.1 General approach

Participants in the M7824 + N-803 safety arm 1.1 will be evaluated with respect to the grades and types of toxicities obtained. The results will be presented descriptively, and tabled if appropriate. Participants included in the phase II cohort will have their efficacy evaluated as being consistent with clinical benefit or not (PR+CR or PSA decline of >30% for 21 days), and appropriate confidence intervals will be formed.

10.4.2 Analysis of the primary endpoints

Safety will be evaluated in the initial 18 participant safety arm 1.1 by determining the grades and types of toxicity experienced by each participant and reporting these findings. Since the objective will be to determine the safe combination of agents to use in the phase II cohort, the focus will be on reporting the number of DLTs encountered by the participants at the dose levels evaluated and how that relates to the use of the agents in phase II.

In the phase II cohort (sequential cohort), the participants will be scored according to the degree of clinical response obtained (CR, PR, SD, PD) as well as whether the participant is able to sustain a PSA decline of 30% or more for >21 days (attaining a CR or PR, and/or PSA decline of 30% or more for >21 days). The participants who attain these outcomes will be considered to have demonstrated efficacy of the agents. The fraction of participants who experience treatment efficacy will be reported along with two-sided 80% and 95% confidence intervals.

10.4.3 Analysis of the secondary endpoints:

Progression free survival will be estimated in each cohort, from the on study date until progression or death without progression. The 6 month PFS probability will be estimated and reported with a 95% confidence interval.

Correlation of immunologic outcomes with clinical data and outcomes will be performed by testing the association between the immune outcomes and clinical outcomes, using appropriate non-parametric techniques, such as comparing those with and without efficacy (clinical benefit) with a Wilcoxon rank sum test, separately within each arm.

The participants who are enrolled in the phase II arm (s) will have their grades and types of toxicities noted and tabled as appropriate, as a secondary analysis.

10.4.4 Safety analysis

In addition to monitoring safety in the initial safety arm 1.1, the participants who are enrolled in the phase II arm(s) will have their grades and types of toxicities noted and tabled as appropriate.

10.4.5 Baseline descriptive statistics

Baseline demographic data on all participants in the phase II cohort will be reported separately by arm.

10.4.6 Planned interim analysis

Each of the 3 planned phase II arms will be evaluated for efficacy after the initial stage of the two stage Simon optimal designs.

10.4.7 Exploratory analyses

Specific analyses may include but are not limited to descriptive evaluation of pre- and post-treatment samples as well samples taken on treatment for the following:

- Brachyury-specific T-cell response utilizing intracellular cytokine staining after stimulation with 15-mer peptide pools encoding brachyury
- Immunoscore by analysis of 123 lymphocyte subsets
- Serum prognostic markers sCD27 and sCD40L
- TCR clonality
- PSMA+ and immune cell extracellular vesicles (EVs)

Each of these measures is a quantitative parameter, and the results will be presented using descriptive statistics.

Additional assays may be performed on an exploratory basis as described in Section **5**. Any data resulting from these assays will be evaluated using descriptive techniques only.

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

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

A CRADA (02561) is in place with Bavarian Nordic, Inc for the supply of BN-Brachyury.

A CRADA (03058) is in place with Altor Bioscience for the supply of ALT-803 (Note: No updated CRADA applicable due to acquisition by Immunity Bio at this time).

A CRADA (03142) is in place with Incyte for the supply of Epacadostat.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

Subjects from all racial/ethnic groups and both genders are eligible for this study if they meet the eligibility criteria. While prostate cancer is the main malignancy being studied and only occurs in males, females will be eligible for enrollment in the M7824 + N-803 safety cohort 1. To date, no information suggests that differences in drug metabolism, immune response, or disease response would be expected in one group compared with another. Efforts will be made to extend accrual to a representative population, but in this preliminary study, a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially toxic and/or ineffective treatments on one hand and the need to explore gender and ethnic aspects of clinical research on the other hand. If differences in outcome that correlate with ethnic identity are noted, accrual may be expanded or a follow-up study may be written to investigate those differences more fully.

12.2 PARTICIPATION OF CHILDREN

Because no dosing or adverse event data are currently available on the use of each individual agent in participants <18 years of age, children are excluded from this study.

12.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, it is possible that subjects enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of this study. In the event this occurs, because there is a prospect of direct benefit from research participation (section **12.5**), the subjects will remain in the study. In addition, one of the study objectives is progression free survival; taking participants off study would cause loss of valuable data. 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 LAR, as needed. Please see Section **12.6** for consent procedure.

12.4 PARTICIPATION OF SUBJECTS WHO REFUSE BLOOD TRANSFUSIONS

Adults who will refuse transfusions are excluded from the protocol. Blood transfusions may be necessary to treat known potential risks of bintrafusp alfa and participants who will decline are at increased risk.

12.5 RISKS/BENEFITS ANALYSIS

12.5.1 Risks

12.5.1.1 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.

12.5.1.2 Risks due to Radiation

The study will involve radiation from the following sources:

- Up to 5 CT scans (C/A/P) per year for disease assessment
- Up to 5 bone scans (for Prostate Cancer Participants) per year for disease assessment

Subjects in this study may be exposed up to 7.45 rem maximum annually depending upon how much they weigh.

12.5.1.3 Risks due to contrast dye used in CT scans

If contrast dye is used, there is a risk for allergic reaction to the dye. Participants who are allergic to or sensitive to medications, contrast dye, iodine, or shellfish should notify their physician. Participants with kidney failure or other kidney problems should notify their physician.

12.5.1.4 Risks due to bone scan

The bone scan carries no greater risk than conventional X-rays. The tracers in the radioactive substance used in a bone scan produces very little radiation exposure. The risk of having an allergic reaction to the tracers is low.

12.5.1.5 Risks due to MRI

People are at risk for injury from the MRI magnet if they have some kinds of metal in their body. It may be unsafe to have an MRI scan in participants with pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metal prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, tattoos, an implanted delivery pump, or shrapnel fragments. Welders and metal workers may have small metal fragments in the eye. Participants will be screened for those conditions before having any MRI scan.

In addition, all magnetic objects (like watches, coins, jewelry, and credit cards) must be removed before entering the MRI scan room.

Participants 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. Everyone having a research MRI scan will be fitted with hearing protection.

There are no known long-term risks of MRI scans.

12.5.1.6 Risks due to gadolinium enhanced MRI

The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling.

Mild symptoms from gadolinium infusion occur in fewer than 1% of those who receive it and usually go away quickly. Mild symptoms may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number, fewer than one in 300,000 people, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. Participants should not receive gadolinium if they have previously had an allergic reaction to it.

Participants with kidney disease are at risk for a serious reaction to gadolinium contrast called “nephrogenic systemic fibrosis (NSF)”. This condition always involves the skin and can also

involve the muscles, joints and internal organs. NSF has resulted in a very small number of deaths. Participants will not receive gadolinium for a research MRI scan if your kidney function is below the safe level.

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

12.5.1.7 Risks due to biopsy

There are potential risks associated with this procedure including pain or bleeding caused by the anesthesia needle as well as the biopsy procedure itself. An allergic reaction to the local anesthetic may occur. There may be bruising at the site of biopsy. Continuous bleeding and infection are rare and very often is easily controlled.

12.5.1.8 Risks due to Electrocardiogram (ECG)

Other than possibly experiencing some minor skin irritation from the electrodes, there are no anticipated risks related to complete the electrocardiogram and/or the echocardiogram

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 participant 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 (see section **12.3**) 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 in a private area 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: https://ccrod.cancer.gov/confluence/pages/viewpage.action?pageId=73203825.

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

For participants addressed in section **12.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.6**.

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, 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(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference for 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 (NCI) has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict

confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

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

The study participant's contact information will be securely stored at 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 Center for Cancer Research (CCR). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at CCR.

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 MVA-BN-BRACHYURY (BB-IND 17851)

14.1.1 Source

MVA-BN-Brachyury is an active cancer immunotherapy. This phase I study is being conducted under an IND held by the Center for Cancer Research (CCR), National Cancer Institute (NCI). Bavarian Nordic, Inc. is the manufacturer of MVA-BN-Brachyury-TRICOM and is a CRADA partner.

14.1.2 Toxicity

MVA-BN-derived vectors that encode heterologous (non-vaccinia virus) antigens are being developed for the treatment of cancer. In GLP studies, MVA-BN and MVA-BN-derived vectors have been administered to 5 different animal species, including primates. In addition, MVA-BN and MVA-BN-derived vectors have been administered in clinical trials to over 10,500 human subjects, including immunodeficient individuals. No marked toxicity and no drug-related serious AEs have occurred in any of these studies. The most common side effects associated with MVA-

BN and other MVA-BN-derived vaccines include mild to moderate flu-like symptoms such as: fever, chills, muscle or joint ache, and tiredness (fatigue). In addition, some localized reactions at the site where the vaccine is injected under skin (subcutaneously). These injection site reactions may include any or all of the following: swelling, localized pain, hardness of a small area of skin around the injection site induration), and redness. The most common side effects from the use of fowlpox vaccines are mild and may include the following: fever, tiredness (fatigue), low red blood cell count (anemia), low white blood cell count (leucopenia). In addition, some localized reactions at the site where the vaccine is injected under skin (subcutaneously). These injection site reactions may include any or all of the following: swelling, localized pain, hardness of a small area of skin around the injection site induration), and redness.

A prior study of MVA-BN-Brachyury performed at the NCI demonstrated minimal toxicity related to vaccine. The most common adverse events were injection site reaction and transient flu-like symptoms.

Suspected ADR Reported by >1% of Subjects in the Completed MVA-BN Clinical Trials[a] (N=8992[b])

Preferred Term (PT)	No. of reports by subjects	Frequency %
Injection site pain	7370	82.0%
Injection site erythema	5875	65.3%
Injection site swelling	4488	49.9%
Injection site induration	3988	44.4%
Injection site pruritus	3573	39.7%
Myalgia	3017	33.6%
Fatigue	2886	32.1%
Headache	2704	30.1%
Nausea	1316	14.6%
Rigors/chills	842	9.4%
Body temperature increased	269	3.0%
Pyrexia	259	2.9%
Injection site nodule	228	2.5%
Appetite disorder	218	2.4%
Arthralgia	209	2.3%
Injection site discolouration	207	2.3%
Pain in extremity	148	1.7%
Injection site haematoma	107	1.2%
Axillary pain	93	1.0%
Injection site warmth	90	1.0%

a POX-MVA-001, -002, -004, -005, -006, -007, -008, -009, -010, -011, -013, -023, -024, -027, -028, -029, -030, -031, -036, -037, -03X, HIV-NEF-004 and HIV-POL-002.
b Eight subjects exposed but not included in analysis. Seven subjects in POX-MVA-009 received Dryvax either on the same day or within 7 days after MVA-BN administration and were therefore not included to avoid a potential bias in the AE reporting. One subject in POX-MVA-029 was not vaccinated according to the randomization, therefore removed from analysis set.

Source: MVA-BN IB Edition 25 Table 10

14.1.3 Formulation and preparation

MVA-BN-Brachyury is supplied as a frozen aqueous suspension in 2 mL clear borosilicate glass vials. The closure is a sterile bromobutyl rubber stopper, crimped with an aluminum cap and covered with a polypropylene closure. Each 0.5mL injection will contain a nominal virus titer of 2.0×10^8 Inf.U.

MVA-BN-Brachyury is supplied frozen in single-use vials. Each vial must be thawed at room temperature for approximately 5 minutes prior to preparation and should not be re-frozen after thawing. The thawed suspension will appear milky and may contain clumps or aggregates. To ensure homogeneity, the vial should be swirled gently, but not shaken, for approximately 30 seconds immediately (within 3 minutes) prior to use. The thawed drug product is to be drawn into a syringe with an appropriately sized safety-shielded needle suited to patient comfort (e.g., 22- to 28-gauge).

14.1.4 Stability and Storage

MVA-BN-Brachyury should be stored frozen at -80°C +/- 10°C and remain frozen until use. Vials should not be refrozen once thawed.

Once drawn into a syringe, the dose should be stored at 2-8°C or ambient room temperature until administration. Vaccine should be administered within 4 hours of completion of dose preparation and should be brought to room temperature prior to administration.

14.1.5 Administration procedures of MVA-BN-Brachyury

See Section **3.3.1**.

14.2 FPV-BRACHYURY (BB-IND 17851)

14.2.1 Source

FPV-Brachyury is an active cancer immunotherapy. This phase I study is being conducted under an IND held by the Center for Cancer Research (CCR), National Cancer Institute (NCI). Bavarian Nordic, Inc. is the manufacturer of FPV-Brachyury and is a CRADA partner.

14.2.2 Toxicity

Fowlpox-derived vectors that encode heterologous (non-vaccinia virus) antigens are being developed for the treatment of cancer. In GLP studies, Fowlpox- -derived vectors have been administered to 5 different animal species, including primates. In addition, Fowlpox-derived vectors have been administered in clinical trials to over 1000 human subjects. No marked toxicity and no drug-related serious AEs have occurred in any of these studies.

14.2.3 Formulation and Preparation

One vaccine dose has a nominal virus titer of 1×10^9 Inf.U FPV-Brachyury vaccine in 0.5 mL of the drug product. This dose will be used for the boost vaccination of subjects receiving FPV-Brachyury.

14.2.4 Stability and Storage

FPV-Brachyury should be stored frozen at -80°C +/− 10°C and remain frozen until use. Vials should not be refrozen once thawed.

Once drawn into a syringe, the dose should be stored at 2 - 8°C or ambient room temperature until administration. Vaccine should be administered within 4 hours of completion of dose preparation and should be brought to room temperature prior to administration.

14.2.5 Administration Procedures

See Section **3.3.1**.

14.2.6 Incompatibilities

There are no known drug interactions associated with the use of Fowlpox-derived vectors. No marked toxicities or serious AEs have been noted in clinical trials conducted with Fowlpox-derived vectors

14.3 M7824 (MSB0011359C, BINTRAFUSP ALFA) (BB-IND 17851)

14.3.1 Source

M7824 is manufactured and supplied for the trial by EMD Serono Research and Development Institute

14.3.2 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). Patients will be pre-medicated to prophylax against infusion reactions. The following additionally significant immune-mediated adverse reactions have occurred in less than 1% of 1738 patients 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 patients, 3 patients 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 TEAE Leading to Permanent Treatment Discontinuation by System Organ Class and Preferred Term in ≥ 2 participants in the Pooled Analysis of Dose Expansion Cohorts (Source: Investigator Brochure v6)

Primary System Organ Class Dictionary-Derived Term	EMR200647-001 (N = 539) N (%)	MS200647-0008 (N = 91) N (%)	Total (N = 630) N (%)
Participants with any SAE	321 (59.6)	50 (54.9)	371 (58.9)
Blood and lymphatic system disorders	27 (5.0)	0	27 (4.3)
Anaemia	19 (3.5)	0	19 (3.0)
Endocrine disorders	11 (2.0)	2 (2.2)	13 (2.1)
Adrenal insufficiency	5 (0.9)	2 (2.2)	7 (1.1)
Gastrointestinal disorders	64 (11.9)	13 (14.3)	77 (12.2)
Abdominal pain	5 (0.9)	1 (1.1)	6 (1.0)
Gastrointestinal haemorrhage	7 (1.3)	1 (1.1)	8 (1.3)
Upper gastrointestinal haemorrhage	2 (0.4)	4 (4.4)	6 (1.0)
Vomiting	6 (1.1)	0	6 (1.0)
General disorders and administration site conditions	70 (13.0)	10 (11.0)	80 (12.7)
Disease progression	43 (8.0)	6 (6.6)	49 (7.8)
General physical health deterioration	6 (1.1)	0	6 (1.0)
Pyrexia	8 (1.5)	1 (1.1)	9 (1.4)
Hepatobiliary disorders	10 (1.9)	8 (8.8)	18 (2.9)
Cholangitis	2 (0.4)	5 (5.5)	7 (1.1)
Infections and infestations	54 (10.0)	9 (9.9)	63 (10.0)
Pneumonia	14 (2.6)	3 (3.3)	17 (2.7)
Sepsis	8 (1.5)	0	8 (1.3)
Metabolism and nutrition disorders	25 (4.6)	3 (3.3)	28 (4.4)
Decreased appetite	5 (0.9)	3 (3.3)	8 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	61 (11.3)	8 (8.8)	69 (11.0)
Keratoacanthoma	9 (1.7)	0	9 (1.4)
Squamous cell carcinoma of skin	22 (4.1)	1 (1.1)	23 (3.7)
Tumour haemorrhage	8 (1.5)	2 (2.2)	10 (1.6)
Renal and urinary disorders	14 (2.6)	0	14 (2.2)
Acute kidney injury	10 (1.9)	0	10 (1.6)
Respiratory, thoracic and mediastinal disorders	68 (12.6)	6 (6.6)	74 (11.7)
Dyspnoea	26 (4.8)	0	26 (4.1)
Pneumothorax	6 (1.1)	1 (1.1)	7 (1.1)
Pulmonary embolism	9 (1.7)	0	9 (1.4)

As of the data cutoff of 24 August 2018, 7 deaths (1.1%) were reported as due to treatment-related TEAE, however an additional death (primary cause of intra-abdominal hemorrhage, assessed as treatment-related) started more than 30 days after the end of treatment and is therefore is not included in above count of treatment-related death. In Study EMR200647-001, 3 participants had a treatment-related death: 1 participant had dyspnea, hemolysis and thrombocytopenia, 1 participant had an intracranial tumor hemorrhage and 1 participant had pneumonia. In Study MS200647-0008, 4 participants had a treatment-related death: 2 participants died due to ILD, 1 participant due to sudden death and 1 participant due to septic shock. Please refer to IB v 6.0

Section 5.2.2.9 for a summary of the SAEs from the Sponsor's Global Drug Safety database from 25 August 2018 to 31 December 2019 for ongoing studies.

Important identified risks have been identified as IRRs including hypersensitivity, irAEs including immune related pneumonitis, hepatitis, colitis, nephritis and renal dysfunction, endocrinopathies, rash, myositis, myocarditis, and encephalitis, and skin lesions with hyperkeratosis, keratoacanthoma, cutaneous squamous cell carcinoma possibly due to TGFβ inhibition. The important identified risks with bintrafusp alfa observed to date were overall manageable. Anemia, alterations in wound healing or repair of tissue damage, and embryofetal toxicity remain as important potential risks. Mucosal bleeding events of mild to moderate severity were observed in participants treated with bintrafusp alfa in ongoing studies and are a potential risk for bintrafusp alfa. Events may include epistaxis, hemoptysis, gingival bleeding or hematuria amongst others. In general, these reactions resolve without discontinuation of treatment. The iRAEs Guillain-Barré Syndrome, uveitis, pancreatitis and myasthenia gravis/myasthenic syndrome are also important potential risks.

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 patients 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, patients will be notified of the same possible risk in the informed consent document for this study.

Risk of Rapid Progression:

The experimental drug 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.

14.3.2.1 Risk for cutaneous keratocanthoma/squamous cell carcinoma with administration of M7824

All cases of skin lesions suspicious for the above will be referred to Dermatology at the NIH. Patients wills then undergo routine follow-up skin exams and treatment as deemed appropriate by the Dermatologist.

14.3.3 Formulation and Preparation

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

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

14.3.4 Stability and storage

M7824 must be stored at 2℃ to 8℃ until use. Product stored at room temperature for extended periods of time might be subject to degradation. M7824 must not be frozen. Rough shaking of the reconstituted solution must be avoided.

The chemical and physical in-use stability for the infusion solution of M7824 in 0.9% sodium chloride for injection has been demonstrated for a total of 72 hours at room temperature; however, from a microbiological point of view, the diluted solution should be used immediately and is not intended to be stored unless dilution has taken place in controlled and validated aseptic conditions. No other drugs should be added to the infusion containers containing M7824. See Manual of Preparation of approved ancillary supplies.

14.3.5 Administration procedures

See section **3.3.3**.

14.4 N-803, FORMERLY ALT-803 (BB-IND 17851)

14.4.1 Source

N 803 is manufactured and supplied by Immunity Bio.

14.4.2 Toxicity

The most common toxicities (≥20%) of N-803 include, but may not be limited to, fatigue, fever, rigors, headache, hyper- and hypotension, injection-site reactions, laboratory abnormalities – such as hypoalbunemia and associated symptoms, and pain (e.g., back pain). Less common toxicities that may be serious include neutropenia and cardiac toxicities (e.g., atrial fibrillation).

14.4.3 Formulation and preparation

N-803 is a soluble complex consisting of two protein subunits of a human IL-15 variant associated with high affinity to a dimeric human IL-15 receptor α (IL-15Rα) sushi domain/human IgG1 Fc fusion protein. The IL-15 variant is a 114 aa polypeptide comprising the mature human IL-15 cytokine sequence with an Asn to Asp substitution at position 72 of helix C (N72D). The human IL-15Rα sushi domain/human IgG1 Fc fusion protein comprises the sushi domain of the human IL-15 receptor α subunit (IL-15Rα) (aa 1-65 of the mature human IL-15Rα protein) linked with the human IgG1 CH2-CH3 region containing the Fc domain (232 amino acids). Aside from the N72D substitution, all of the protein sequences are human. Based on the amino acid sequence of the subunits, calculated molecular weight of complex comprising two IL-15N72D polypeptides and a disulfide linked homodimeric IL-15RαSu/IgG1 Fc protein is 92.4 kilodaltons (kDa). Each IL-15N72D polypeptide has a calculated molecular weight of approximately 12.8 kDa and the IL-15RαSu/IgG1 Fc fusion protein has a calculated molecular weight of approximately 33.4 kDa. Both the IL-15N72D and IL-15RαSu/IgG1 Fc proteins are glycosylated resulting in an apparent molecular weight of N-803 as approximately 113 kDa by size exclusion chromatography. The isoelectric point (pI) determined for N-803 ranges from approximately 5.5 to 6.5. Thus, the fusion protein is negatively charged at pH 7. The calculated molar extinction coefficient at A280 for N-

803 is 116,540 M-1, or 1.26 OD280 for a 1 mg/mL solution of N-803, or one OD280 is equivalent to 0.79 mg/mL solution of N-803.

The biological drug product, N-803, is formulated in a phosphate buffered saline solution. The drug substance is produced by a recombinant mammalian cell line and is manufactured using protein-free media.

14.4.4 N-803 is supplied at a concentration of 2 mg/mL and is administered undiluted subcutaneously. Stability and storage

Study medication is provided in a 2mL vial containing 0.6 mL of ALT 803 at a concentration of 2 mg/mL. Intact vials are stored at a temperature between 2℃ and 8℃. The duration of time during which the product remains stable at room temperature will be obtained from Immunity Bio.

14.4.5 Administration procedures

N-803 is administered subcutaneously. See section **3.3.4**

14.5 EPACADOSTAT

14.5.1 Source

Epacadostat is manufactured and supplied by Incyte

14.5.2 Toxicity

As monotherapy, epacadostat was generally well tolerated in subjects with refractory solid tumors at doses of up to 700 mg BID, and there appeared to be no correlation of dose with toxicity. Of the 52 subjects who were administered epacadostat, the median duration of treatment was 51.5 days. Eight subjects (15.4%) had an AE leading to death; of these 8 subjects, the cause of death was disease progression for 7 subjects and hypoxia for the remaining subject. Twenty-five subjects (48.1%) had an SAE during the study. Serious adverse events were observed in all 8 treatment groups. The most frequently reported SAE was disease progression (4 subjects, 7.7%), followed by abdominal pain, nausea, and hypoxia (3 subjects each, 5.8%). Treatment-emergent AEs were reported in all subjects. Fatigue was the most frequently reported treatment-emergent AE (36 subjects, 69.2%). In INCB 24360-101, a phase I study of epacadostat, the majority of subjects (90.4%) had treatment-related AEs. Fatigue and nausea were the most frequently reported treatment-emergent AEs (25 subjects each, 48.1%). The incidence and severity of fatigue were not dose related. Thirty subjects (57.7%) had treatment-emergent AEs ≥ Grade 3 in severity and 7 subjects (13.5%) had a treatment-emergent AE leading to discontinuation of study drug and withdrawal from the study. Two DLTs occurred; 1 DLT of radiation pneumonitis at the300 mg BID dose level and 1 DLT of fatigue at the 400 mg BID dose level. An MTD was not determined. There were no clinically meaningful changes or trends noted in clinical hematology, chemistry, or urinalysis results or for vital signs, ECGs, or physical examinations.

14.5.2.1 Adverse Drug Reactions from Epacadostat IB v 13

The following represents Adverse Drug Reactions (ADRs) observed in clinical studies of epacadostat as of 29 OCT 2020. There were no suspected SARs that occurred only once or fatal/life-threatening. SARs that are considered unexpected and not included in the RSI. Please refer to Section 7.5.1 of IB v 13.0 for additional information.

Adverse drug reactions in participants treated with epacadostat monotherapy (N = 216)

- Very common: nausea and vomiting
- Common: rash maculo-papular

Adverse drug reactions that are new or occurred at a greater frequency or severity than was seen in each monotherapy drug in participants treated with epacadostat + pembrolizumab, epacadostat + nivolumab, epacadostat + durvalumab, epacadostat + atezolizumab (combinations with anti-PD-1/L1 monoclonal antibodies) (N = 1607)

- Very common: fatigue, nausea, diarrhea, rash, vomiting, pyrexia, abdominal pain, aspartate aminotransferase increased, alanine aminotransferase increased, and asthenia
- Common: rash maculo-papular, myalgia, pneumonia, pneumonitis, colitis, and adrenal insufficiency
- Uncommon: autoimmune hepatitis, drug sensitivity, meningitis aseptic, drug reaction with eosinophilia and systemic symptoms, and immune-mediated hepatitis

Adverse drug reactions that are new or occurred at a greater frequency or severity than was seen in each monotherapy drug in participants treated with epacadostat + pembrolizumab + chemotherapy, epacadostat + nivolumab + chemotherapy (combinations with anti-PD-1 monoclonal antibodies and chemotherapy) (N = 241)

- Very common: nausea, vomiting, and rash

A portion of the M7824 construct is an anti-PD-L1 monoclonal antibody. The table below contains a list of AEs considered suspected to be adverse drug reactions observed in patients receiving epacadostat in combination with anti−PD-L1 targeted therapy (atezolizumab or durvalumab).

Expected Treatment-Emergent Adverse Events for Epacadostat and Anti–PD-L1 Combination Therapy (N = 124)

System Organ Class MedDRA Preferred Term	Overall Frequency All Grades N (%)	Grade 3 or Grade 4 N (%)	Frequency of Serious Events N (%)
Endocrine disorders			
Hypothyroidism	Common – 2 (1.6)	–	–
Gastrointestinal disorders			
Diarrhea	Very common – 16 (12.9)	–	–
Nausea	Very common – 37 (29.8)	Common – 2 (1.6)	Common – 3 (2.4)
Vomiting	Very common – 19 (15.3%)	Common – 3 (2.4)	Common – 5 (4.0)
General disorders and administration site conditions			
Asthenia	Common – 2 (1.6)	Common – 1 (0.8)	–
Fatigue	Very common – 52 (41.9)	Common – 5 (4.0)	–
Investigations			
Alanine aminotransferase increased	Common – 7 (5.6)	Common – 2 (1.6)	–
Aspartate aminotransferase increased	Common – 9 (7.3)	Common – 3 (2.4)	–
Musculoskeletal and connective tissue disorders			
Arthralgia	Common – 11 (8.9)	Uncommon – 1 (0.8)	–
Respiratory, thoracic, and mediastinal disorders			
Pneumonitis	Common – 2 (1.6)	Uncommon – 1 (0.8)	–
Skin and subcutaneous tissue disorders			
Pruritus	Common – 11 (8.9)	–	–
Rash	Common – 4 (3.2)	–	–
Rash maculo-papular	Common – 12 (9.7)	Common – 4 (3.2)	–

Serotonin Syndrome

There is a potential concern that epacadostat could cause an increase in serotonin levels in the brain that might trigger serotonin syndrome, when administered alone or in combination with other serotonergic agents. This rare syndrome has been associated with some MAOIs and combinations of serotonergic drugs[59]. The clinical manifestations of serotonin syndrome range from barely perceptible to lethal. Nonclinical data suggest that serotonin syndrome is unlikely following treatment with either epacadostat alone or in combination with MAOIs such as linezolid [66].

As of 29 OCT 2019, 5 participants treated across the epacadostat program have had events reported as serotonin syndrome or symptoms of serotonin syndrome; episodes were confounded, mild or moderate in severity, and resolved (3 of 5 resolved without further incidents after dose interruption while the other 2 resolved following study treatment discontinuation). Two of the 5 participants had an event of serotonin syndrome that was reported as a serious event by the investigator. These AEs were not clinically substantiated by the sponsor to represent true events of serotonin syndrome.

The incidence of serotonin syndrome or symptoms of serotonin syndrome is rare. Participants may be provided with an informative simplified card describing the potential signs and potential symptoms of serotonin syndrome, along with instructions to seek immediate medical care if any of these signs or symptoms are observed. A neurology consult is recommended to diagnose or confirm serotonin syndrome or to rule out other etiologies.

The clinical manifestations of SS range from barely perceptible to lethal. Symptom onset is usually rapid (within 12 hours of administration) and encompasses a wide range of clinical findings.

- Mild symptoms may only consist of increased heart rate, shivering, sweating, dilated pupils, myoclonus, as well as over-responsive reflexes.
- Moderate symptoms include additional abnormalities such as hyperactive bowel sounds, high blood pressure, and hyperthermia; a temperature as high as 40°C (104°F) is common in moderate intoxication. Mental status changes include hypervigilance and agitation.
- Severe symptoms include severe increases in heart rate and blood pressure that may lead to shock. Temperature may rise to above 41.1°C (106.0°F) in life-threatening cases.

Other abnormalities include metabolic acidosis, rhabdomyolysis, seizures, renal failure, and disseminated intravascular coagulation; these effects usually arise as a consequence of hyperthermia.

There is no laboratory test for SS; therefore, diagnosis is by symptom observation. Management is based primarily on stopping the usage of the precipitating drugs, the administration of serotonin antagonists such as cyproheptadine, and supportive care including the control of agitation, the control of autonomic instability, and the control of hyperthermia. Additionally, those who ingest large doses of serotonergic agents may benefit from gastrointestinal decontamination with activated charcoal if it can be administered within an hour of overdose. The intensity of therapy depends on the severity of symptoms. If the symptoms are mild, treatment may only consist of discontinuation of the offending medication or medications, offering supportive measures, giving benzodiazepines for myoclonus, and waiting for the symptoms to resolve. Moderate cases should have all thermal and cardiorespiratory abnormalities corrected and can benefit from serotonin antagonists. The serotonin antagonist cyproheptadine is the recommended initial therapy. Additional pharmacological treatment for severe cases includes administering atypical antipsychotic drugs with serotonin antagonist activity such as olanzapine. Critically ill patients should receive the above therapies as well as sedation or neuromuscular paralysis. Patients who have autonomic instability such as low blood pressure require treatment with direct-acting sympathomimetics such as epinephrine, norepinephrine, or phenylephrine. Conversely, hypertension or tachycardia can be treated with short-acting antihypertensive drugs such as nitroprusside or esmolol; longer acting drugs such as propranolol should be avoided as they may lead to hypotension and shock. Based on preliminary studies in the rat, concentrations of epacadostat in the cerebrospinal fluid were below the quantifiable limit of detection (2 nM) after IV administration, and total brain homogenate concentrations were approximately 15% of corresponding plasma concentrations. Therefore, epacadostat exhibits apparent limited penetration across the blood brain barrier and is likely not associated with significant effects on Trp metabolism in the brain that might impact brain serotonin levels. Although this represents a theoretical risk only, use of MAO inhibitors will be prohibited in patients receiving epacadostat.

14.5.3 Formulation and preparation

The chemical name of epacadostat is (*Z*)-*N*-(3-bromo-4-fluorophenyl)-*N′*-hydroxy-4-(2-(sulfamoylamino)ethylamino)-1,2,5-oxadiazole-3-carboximidamide. Epacadostat has a molecular formula of C11H13BrFN7O4S and a molecular weight of 438.23

Epacadostat is formulated as an immediate release tablet in 25mg, 100mg and 300mg. However, only the 100mg and 300mg tablets are anticipated to be used in this trial. The tablets contain the active drug (epacadostat) along with commonly used compendial excipients (lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate).

14.5.4 Storage

Epacadostat drug product should be stored at ambient conditions (15°C- 30°C).

14.5.5 Administration procedures

Epacadostat is to be administered by mouth. See section **3.3.5**.

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APPENDICES

15.1 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.

15.2 APPENDIX B: N-803 INJECTION SITE REACTION DIARY

STUDY NUMBER: _____

Patient Number*		**Date of Study Drug Injection***	____/____/____	*To be completed by the site.

Please answer all questions below daily for 7 days, beginning with day of treatment. Be sure to bring back this completed diary to your next clinic visit.

	Instructions	**Day of Study Drug Injection** ___/___/___	**Day 1 Post Injection** ___/___/___	**Day 2 Post Injection** ___/___/___	**Day 3 Post Injection** ___/___/___	**Day 4 Post Injection** ___/___/___	**Day 5 Post Injection** ___/___/___	**Day 6 Post Injection** ___/___/___
1. Is there redness at the injection site?	Check: ☐Yes or ☐No If yes, measure longest diameter in cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm	☐Yes ☐No _____cm
2. Is there firmness or swelling at the injection site?	Check: ☐Yes or ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No	☐Yes ☐No
3. Have you experienced any pain or itching at the injection site?	Check: ☐Yes or ☐No If yes, tell us if the pain and/or itching is mild, moderate or severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe	☐ Pain ☐ Itch Mild Mild Mod Mod Severe Severe
4. Have you taken or applied any medication for injection site pain or itching?	Check: ☐Yes or ☐No Provide name of medication(s)	☐Yes ☐No Name(s):	☐Yes ☐No Name(s):	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:	☐Yes ☐No Name:
5. Have you experienced any chills?	Check: ☐Yes or ☐No If yes, tell us if the chills are mild, moderate or severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe	☐Yes ☐No Mild Moderate Severe
6. Record your daily temperature upon waking (do not drink anything 5 minutes before taking your temperature)	Check: ☐Yes or ☐No If your temperature is 101°F for more than 24 hours, call your doctor.	☐Yes ☐No _____°F Time: ___:___ AM / PM	☐Yes ☐No _____°F Time: ___:___ AM / PM	☐Yes ☐No _____°F Time: ___:___ AM / PM	☐Yes ☐No _____°F Time: ___:___ AM / PM	☐Yes ☐No _____°F Time: ___:___ AM / PM	☐Yes ☐No _____°F Time: ___:___ AM / PM	☐Yes ☐No _____°F Time: ___:___ AM / PM

Grading Injection Site Pain or Itching
Mild – Noticeable, does not interfere with activity
Moderate – Interferes with activity, limiting activities of daily living
Severe – Severely limiting self-care activities of daily living, incapacitating

Grading Chills
Mild – Mild sensitive of cold, shivering, chattering of teeth
Moderate – Moderate tremor of entire body, medication taken
Severe – Prolonged or severe, does not respond to medication

15.3 APPENDIX C PATIENT'S MEDICATION DIARY _____

Cycle_____

Participant's ID _____

INSTRUCTIONS TO THE PARTICIPANT:

- Complete one form for each cycle of treatment
- You will take Epacadostat _____mg twice a day. You should take the tablets with food at approximately the same time each day.
- Dose: _____
- Record the date, the number of tablets that you took, and when you took them.
- If you have any comments or notice any side effects, please record them in the comments column.
- Please bring this form and your bottles of Epacadostat when you come for your clinic visits.

Day	**Date**	**Time of AM Dose**	**# of Tablets Taken**		**Time of PM Dose**	**# of Tablets Taken**		**Comments**
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								

Participant's signature: _____

15.4 APPENDIX D: UDP GLUCURONOSYLTRANSFERASE (UGT1A9) INHIBITORS

Below is a list of known UDP-glucuronosyltransferase UGT1A9 inhibitors that are prohibited during the concurrent use of epacadostat at doses > 300mg BID. UGT1A9 inhibitors not on the list below should be discussed with the medical monitor before use.

acitretin, amitriptyline, androsterone, cyclosporine, dasatinib, diclofenac, diflunisal, efavirenz, erlotinib, flutamide, gefitinib, gemfibrozil, glycyrrhetinic acid glycyrrhizin, imatinib, imipramine, ketoconazole (systemic), mycophenolic acid, niflumic acid, nilotinib, phenobarbital, phenylbutazone, phenytoin, probenecid, quinidine, ritonavir, sorafenib, sulfinpyrazone, valproic acid, and verapamil.

15.5 APPENDIX E: OATP1BI & 1B3 TRANSPORTERS AND CYP1A2, CYP2C8 AND CYP2C19 SUBSTRATES

Due to the potential concern for epacadostat metabolite inhibition of CYP1A2, CYP2C8 and CYP2C19, OATP1B1 and OATP1B3 transporters with doses of epacadostat greater than 300 mg BID (eg 400 mg BID or 600 mg BID), the below medications will be prohibited immediately for concomitant use.

Participants should seek alternatives that are not in the class. If alternatives cannot be found you may contact the medical monitor to discuss if enrollment is appropriate.

OATP1B1 & 1B3 Transporters	**CYP1A2 Substrates**	**CYP2C8 Substrates**	**CYP2C19 Substrates**
• atorvastatin • bosentan • cerivastatin • danoprevir • docetaxel[b] • fexofenadine • glyburide • nateglinide • paclitaxel[b] • repaglinide • pitavastatin • pravastatin • rosuvastatin • simvastatin acid • fimasartan • glecaprevir • maraviroc • tacrolimus • voxilaprevir	**Sensitive:** • alosetron • caffeine[a] • duloxetine • melatonin • pirfenidone • ramelteon • selegiline • tacrine • tasimelteon • theophylline • tizanidine	**Sensitive:** • repaglinide • daprodustat • dasabuvir • montelukast • pioglitazone • rosiglitazone	**Sensitive:** • s-mephenytoin • lansoprazole • omeprazole • tilidine • pantoprazole • hexobarbital • diazepam • gliclazide • rabeprazole • voriconazole • proguanil

[a] An epacadostat metabolite is a moderate in vitro inhibitor of CYP1A2, thus it is recommended to avoid or limit caffeine consumption (e.g., no more than 1 cup of coffee or 2-3 soft drinks per day)

[b] Docetaxel and paclitaxel as part of combination therapy with epacadostat at doses < 600 mg BID are permitted.