PROTOCOL TITLE: Multiple-Arm Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of XmAb20717 in Combination with Standard of Care Treatment in Patients with Metastatic Castration Sensitive Prostate Cancer

WINSHIP PROTOCOL #: WINSHIP5741-22

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INVESTIGATIONAL PRODUCT (IP): XmAb20717
OTHER AGENT(S): abiraterone, enzalutamide, docetaxel, Androgen Deprivation Therapy (ADT)

SPONSOR -INVESTIGATOR (IND HOLDER): Bassel Nazha, MD
IND #: 164246

REVISION HISTORY

Revision #	Version Date	Summary of Changes
4	8/1/24	Xmab20717 dose was changed to 750mg IV every 3 weeks. Enrollment sequence was clarified to start and complete Cohort B first. Safety stopping rule was updated to include Grade 3 or Grade 4 toxicities.

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1. Study Summary

1.1 Synopsis

Title:	Multiple-Arm Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of XmAb20717 in Combination with Standard of Care Treatment in Patients with Metastatic Castration Sensitive Prostate Cancer
Study Description:	This research study is an open label, multiple-arm, Phase I-Ib study, designed to evaluate the safety, tolerability, and preliminary efficacy of XmAb20717 in combination with standard of care treatment in patients with metastatic castration-sensitive prostate cancer.
Objectives:	**Primary Objective:** To determine the safety and tolerability of XmAb20717 in combination with standard of care treatment in subjects with metastatic castration-sensitive prostate cancer (mCSPC) as assessed by frequency and intensity of adverse events. **Secondary Objectives:** i) To assess preliminary antitumor activity of XmAb20717 with standard of care treatment by: • Radiographic progression-free survival (rPFS) per PCWG-modified RECIST 1.1 as outlined in PCWG31 (soft tissue to be assessed by RECIST 1.1, and bone disease to be assessed by PCWG3) • Time to: initiation of the first subsequent therapy or death, PSA progression, radiographic soft tissue progression, bone progression, first symptomatic skeletal-related event • PSA response rate (PSA decline ≥50% from baseline up to 24 weeks from treatment initiation) and PSA undetectable rate (PSA < 0.2 ng/mL up to 24 weeks from treatment initiation) • Overall response rate (ORR) and duration of response (DOR) per PCWG-modified RECIST 1.1 (ii) Exploratory: To identify factors that may be indicative of response to XmAb20717 in combination with standard of care treatments. • Baseline tumor tissue: molecular signatures, immune and tumor cell expression of immune checkpoint markers such as PD-L1, and immune cell density. • Peripheral blood: correlative changes in peripheral T-cell subsets, T-cell activation and exhaustion, and myeloid derived suppressor cells (MDSC). • Baseline PSMA PET and FDG-PET role in mCSPC

Endpoints:	**Primary Endpoints:** Safety and tolerability: • Frequency and intensity of adverse events • Vital signs measurement • Physical examination • Clinical laboratory tests **Secondary Endpoints:** i) To assess the preliminary antitumor activity of XmAb20717 with standard of care treatment by: • Radiographic progression-free survival (rPFS) per PCWG-modified RECIST 1.1 as outlined in PCWG31 (soft tissue to be assessed by RECIST 1.1, and bone disease to be assessed by PCWG3) • Time to: initiation of the first subsequent therapy or death, PSA progression, radiographic soft tissue progression, bone progression, first symptomatic skeletal-related event • PSA response rate: PSA decline ≥50% from baseline up to 24 weeks from treatment initiation • PSA undetectable rate: PSA < 0.2 ng/mL up to 24 weeks from treatment initiation) • Overall response rate (ORR) and duration of response (DOR) per PCWG-modified RECIST 1.1 ii) Exploratory: To identify factors that may be indicative of response to XmAb20717 in combination with standard of care treatments. • Correlate baseline tumor tissue characteristics with response: – Expression profile of tumor cells and surrounding immune cells by immunohistochemistry and immunofluorescence – Genomic molecular signatures • Assessment of peripheral blood by flow cytometry for expression of T-cell subsets, T-cell activation and exhaustion, and myeloid derived suppressor cells (MDSC). • Assess the role of PSMA PET and FDG-PET in mCSPC by categorization according to PSMA-dominant, FDG-dominant, similar FDG and PSMA total activity, or negative PSMA and FDG statuses.
Study Population:	The patient population consists of subjects ≥18 years of age with advanced or metastatic hormone-sensitive prostate adenocarcinoma
Phase:	Phase I-Ib

Description of Sites/Facilities Enrolling Participants:	Winship Cancer Institute of Emory University (Atlanta, GA).
Description of Study Intervention:	Subjects meeting inclusion criteria will be enrolled into one of the three cohorts, starting with Cohort B first. After Cohort B has completed enrollment with no safety concerns leading to pausing the trial as defined by the safety stopping rule, the principal investigator and Xencor will both review the safety data from Cohort B. Once approved by the principal investigator and Xencor, enrollment in Cohort A and C can start. a. Cohort A: XmAb2071 (750mg IV every 3 weeks, up to 1 year) plus Abiraterone (1000 mg PO daily) with prednisone 5mg PO daily plus ADT b. Cohort B: XmAb20717 (750mg IV every 3 weeks, up to 1 year) plus Enzalutamide (160 mg PO daily) plus ADT c. Cohort C: XmAb20717 (750mg IV every 3 weeks, up to 1 year) plus Docetaxel (75 mg/m2 for 6 doses only every 3 weeks) plus Abiraterone (1000 mg PO daily) with prednisone 5mg PO daily plus ADT ADT may include LHRH agonist or antagonist. Subjects can enroll to this trial within 3 months of start of ADT. Participant must maintain continuous ADT during study treatment or have a history of bilateral orchiectomy.
Study Duration:	Patients will be treated until unacceptable toxicity, death, or disease progression per Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1).

1.2 Schedule of Assessments

Table 1A: Cohort A Schedule of Assessments (XmAb20717 plus abiraterone plus ADT) † ‡ (Cycle=21 days)

	Pre-treatment	Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6 +					
Day	**Screen (Days -28 to -1)**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**	EOT	14 d post-EOT (± 2 days)	28 d post-EOT (± 2 days)	Safety Follow-up 70 d post-EOT (+ 5 days)	F/U (6 and 12 mo after ETO)
Informed consent	X														
Review of inclusion /exclusion criteria	X														
Medical history	X														
Physical examination	X	X		X		X		X	X	X	X	X	X	X	
CBC/CMP PSA/ Testosterone/ TSH	X	X		X		X		X	X	X	X	X	X	X	
PT/PTTΔ	X	X		X		X		X	X	X	X	X	X		
XmAb20717		X		X		X		X	X	X					
Abiraterone + prednisone		X													
CT or MRI chest/ abdomen/ pelvis* (every 12 weeks)	X								X		X				
Nuclear medicine bone scan* (every 12 weeks)	X								X		X				

PSMA PET §	X														
FDG PET §	X														
Stool sample ¶	X								X		X				
Archival tissue collection	X														
Research blood^	X		X		X		X				X				
Monitor /record adverse events	X	X										X			
Record of medications	X	X		X		X		X	X	X	X	X	X	X	
Phone/email/ mail contact for progression /survival															X

EOT = end of treatment, PT=prothrombin time, PTT= partial thromboplastin time.
# Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.
*A MRI can be pursued when a CT scan is contraindicated. Either a CT chest/abdomen/pelvis or MRI chest/abdomen/pelvis are needed. **Staging scans are every 12 weeks** (+/- 7 days)**.**
^ Research blood: peripheral blood collection. To be collected only if the subject received the experimental drug (Xmab20717) on day 1 of the corresponding cycle and as indicated by the schedule of events.
† All days indicated in the table are +/- 2 days, except imaging (+/- 7 days)
‡ ADT may include LHRH agonist or antagonist. Subjects can enroll to this trial within 3 months of start of ADT. Participant must maintain continuous ADT during study treatment or have a history of bilateral orchiectomy.
§ PSMA PET and FDG PET should be separated by > 24 hours (typically at least the second day after one or the other PET/CT).
¶ Future stool samples are not needed if a baseline stool sample is not collected.
Δ Collect if the subject is receiving Xmab20717 on Day 1 of the corresponding cycle

Table 2B: Cohort B Schedule of Assessments (XmAb20717 plus enzalutamide plus ADT) † ‡

(Cycle=21 days)

	Pre-treatment	Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6 +					
Day	**Screen (Days -28 to -1)**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**	EOT	14 d post-EOT (± 2 days)	28 d post-EOT (± 2 days)	Safety Follow-up 70 d post-EOT (+ 5 days)	F/U (6 and 12 mo after ETO)
Informed consent	X														
Review of inclusion /exclusion criteria	X														
Medical history	X														
Physical examination	X	X		X		X		X	X	X	X	X	X	X	
CBC/CMP/PSA/ Testosterone/ TSH	X	X		X		X		X	X	X	X	X	X	X	
PT/PTT Δ	X	X		X		X		X	X	X	X	X	X		
XmAb20717		X		X		X		X	X	X					
Enzalutamide		X													
CT or MRI chest/ abdomen/ pelvis* (every 12 weeks)	X								X		X				
Nuclear medicine bone scan* (every 12 weeks)	X								X		X				

PSMA PET §	X														
FDG PET §	X														
Stool sample ¶	X								X		X				
Archival tissue collection	X														
Research blood^	X		X		X		X				X				
Monitor /record adverse events	X	X										X			
Record of medications	X	X		X		X		X	X	X	X	X	X	X	
Phone/email/ mail contact for progression /survival															X

EOT = end of treatment, PT=prothrombin time, PTT= partial thromboplastin time.
# Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.
*A MRI can be pursued when a CT scan is contraindicated. Either a CT chest/abdomen/pelvis or MRI chest/abdomen/pelvis are needed. **Staging scans are every 12 weeks.**
^ Research blood: peripheral blood collection. To be collected only if the subject received the experimental drug (Xmab20717) on day 1 of the corresponding cycle and as indicated by the schedule of events.
† All days indicated in the table are +/- 2 days
‡ ADT may include LHRH agonist or antagonist. Subjects can enroll to this trial within 3 months of start of ADT. Participant must maintain continuous ADT during study treatment or have a history of bilateral orchiectomy.
§ PSMA PET and FDG PET should be separated by > 24 hours (typically at least the second day after one or the other PET/CT).
¶ Future stool samples are not needed if a baseline stool sample is not collected.
Δ Collect if the subject is receiving Xmab20717 on Day 1 of the corresponding cycle

Table 1C: Cohort C Schedule of Assessments (XmAb20717 plus docetaxel plus abiraterone) † ‡ (Cycle = 21 days)

	Pre-treatment	Cycle 1		**Cycle 2**		**Cycle 3**		**Cycle 4**	**Cycle 5**	**Cycle 6 +**					
Day	**Screen (Days -28 to -1)**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**	**Day 1**	EOT	14 d post-EOT (± 2 days)	28 d post-EOT (± 2 days)	Safety Follow-up 70 d post-EOT (+ 5 days)	F/U (6 and 12 mo after ETO)
Informed consent	X														
Review of inclusion /exclusion criteria	X														
Medical history	X														
Physical examination	X	X		X		X		X	X	X	X	X	X	X	
CBC/CMP PSA/ Testosterone/ TSH	X	X		X		X		X	X	X	X	X	X	X	
PT/PTT Δ	X	X		X		X		X	X	X	X	X	X		
XmAb20717		X		X		X		X	X	X					
Docetaxel		X		X		X		X	X	X					
Abiraterone + prednisone		X													
CT or MRI chest/ abdomen/ pelvis* (every 12 weeks)	X								X		X				

Nuclear medicine bone scan* (every 12 weeks)	X							X		X				
PSMA PET §	X													
FDG PET §	X													
Stool sample ¶	X							X		X				
Archival tissue collection	X													
Research blood^	X		X		X		X			X				
Monitor /record adverse events	X	X									X			
Record of medications	X	X		X		X		X	X	X	X	X	X	X	
Phone/email/ mail contact for progression /survival														X

EOT = end of treatment, PT=prothrombin time, PTT= partial thromboplastin time.
# Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.
*A MRI can be pursued when a CT scan is contraindicated. Either a CT chest/abdomen/pelvis or MRI chest/abdomen/pelvis are needed. **Staging scans are every 12 weeks.**
^ Research blood: peripheral blood collection. To be collected only if the subject received the experimental drug (Xmab20717) on day 1 of the corresponding cycle and as indicated by the schedule of events.
† All days indicated in the table are +/- 2 days
‡ ADT may include LHRH agonist or antagonist. Subjects can enroll to this trial within 3 months of start of ADT. Participant must maintain continuous ADT during study treatment or have a history of bilateral orchiectomy.
§ PSMA PET and FDG PET should be separated by > 24 hours (typically at least the second day after one or the other PET/CT).
¶ Future stool samples are not needed if a baseline stool sample is not collected.
Δ Collect if the subject is receiving Xmab20717 on Day 1 of the corresponding cycle

2. Objectives (and Endpoints)

OBJECTIVES	ENDPOINTS
Primary	
To determine the safety and tolerability of XmAb20717 in combination with standard of care treatment in subjects with metastatic castration sensitive prostate cancer (mCSPC) as assessed by frequency and intensity of adverse events.	• Safety: frequency and intensity of adverse events, vital signs, physical examinations, clinical laboratory test.
Secondary	
To assess the preliminary antitumor activity of XmAb20717 with standard of care treatment	• rPFS per PCWG-modified RECIST 1.1 as outlined in PCWG31 (soft tissue to be assessed by RECIST 1.1, and bone disease to be assessed by PCWG3) • Time to: initiation of the first subsequent therapy or death, PSA progression, radiographic soft tissue progression, bone progression, first symptomatic skeletal-related event • PSA response rate: PSA decline ≥50% from baseline up to 24 weeks from treatment initiation • PSA undetectable rate: PSA < 0.2 ng/mL up to 24 weeks from treatment initiation • Overall response rate (ORR) and duration of response (DOR) per PCWG-modified RECIST 1.1
Tertiary/Exploratory	
To identify factors that may be indicative of response to XmAb20717 in combination with standard of care treatments.	• Correlate baseline tumor tissue characteristics with response: – Expression profile of tumor cells and surrounding immune

OBJECTIVES	ENDPOINTS
	cells by immunohistochemistry and immunofluorescence – Genomic molecular signatures • Assessment of peripheral blood by flow cytometry for expression of T-cell subsets, T-cell activation and exhaustion, and myeloid derived suppressor cells (MDSC) • Role of baseline PET PSMA and FDG PET in mCSPC

3. Background

In 2020, it is estimated that 191,000 men in the United States were diagnosed with prostate cancer, of which around 20% had metastatic disease. Prostate cancer continues to be the second most common cause of cancer-related death in men[1]. The treatment landscape of advanced prostate cancer is now characterized by a variety of systemic therapy options for both metastatic castration sensitive prostate cancer (mCSPC) and castration resistant prostate cancer (mCRPC). Most prostate cancer deaths occur in the mCRPC stage [2], and preventing or delaying progression from mCSPC to mCRPC remains a major treatment goal.

The backbone of mCSPC treatment is androgen deprivation therapy (ADT) as the androgen signaling pathway is critical for cancer cell growth in this disease. Several large phase III trials have demonstrated that the intensification of upfront therapy with either docetaxel chemotherapy or oral androgen signaling pathway inhibitors (abiraterone, enzalutamide, or apalutamide) results in significant improvement in overall survival compared to ADT alone [3-7]. Those agents in addition to ADT are now standard of care in mCSPC. More recently, the PEACE-1 trial showed that further treatment intensification with triplet therapy of docetaxel plus abiraterone plus ADT results in improved overall survival, setting the stage for a new standard of care option in mCSPC, one that is expected to be increasingly used in the frontline setting of mCSPC.[8]

The choice of upfront therapy in addition to ADT is guided by the volume of metastatic disease (high vs. low), performance status, the desired treatment duration, cost, the patient's comorbid conditions, among other factors [9]. Docetaxel treatment every three weeks for 6 cycles is a standard of care and preferred option for patients with high-volume and/or rapidly progressive mCSPC. Oral androgen signaling inhibitors are approved in all patients with mCSPC and are taken continuously until disease progression or unacceptable toxicity. In the absence of direct comparator trials of those three agents and no validated biomarker, the choice of the oral agent also depends on patient comorbid conditions, their preferences, concomitant medications, and treatment cost [10]. For instance, abiraterone is given with low-dose prednisone, making it a less desirable option in patients where there is a need to avoid mineralocorticoid excess[6]. Both enzalutamide and apalutamide carry an increased risk of falls and fractures compared to ADT alone. Further, there is risk of seizures with enzalutamide (0.5%)[5] and rash with apalutamide (27%)[4].

Immune-checkpoint blockade with PD-1/PD-L1 inhibitors +/- CTLA-4 inhibitors is now a bedrock of anti-cancer therapy across multiple tumor types. This group of therapies offers the potential for durable response in a significant subset of patients. Nonetheless, the benefit remains small in prostate cancer with regulatory approval only in mCRPC patients with microsatellite instability (<3% incidence). This has been attributed to an immunosuppressive tumor microenvironment with few tumor-infiltrating T cells [11]. So far, ipilimumab (anti-CTLA-4) or anti-PD-1/PD-L1 monotherapy failed to show significant benefit in unselected mCRPC patients, with overall response rates (ORR) ranging from 0 to 5%[12, 13]. Novel ways to target immune checkpoint pathways are critically needed, especially in prostate cancer, where the tumor microenvironment needs to be converted from “cold” to “hot”. Such conversion is possible with anti-CTLA-4 blockade but insufficient alone to generate antitumor response [14].

3.1 Study Rationale

Based on recent data, there is a now resurgence of interest in immune-checkpoint inhibition in prostate cancer. The preliminary analysis of the CheckMate 650 Trial combining anti-CLTA-4 plus anti-PD-1 (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg) in mCRPC showed encouraging ORR of 25% in pre-chemotherapy patients and 10% in post-chemotherapy patients, a favorable outcome compared with historical data for immune-checkpoint inhibition monotherapies (ORR, 0-5%)[15]. The results are proof-of-concept that immune-driven antitumor effect can indeed be achieved in prostate cancer when both PD-1/PD-L1 and CTLA-4 axes are targeted. However, the combination resulted in significant toxicities, with Grade 3-4 treatment-related adverse events in 42%-53% of patients. Overcoming such high level of toxicity along with identifying predictive biomarkers will be needed. Although most PD-1/PD-L1 +/- Anti-CTLA-4 studies were in mCRPC patients, investigations are now also focusing on the mCSPC to prevent or delay the invariable progression to mCRPC. For instance, Arm 3 of the ongoing Phase II/III PROSTRATEGY trial (NCT03879122) is investigating the combination of ADT plus ipilimumab alternating with docetaxel and nivolumab in patients with Mcspc

XmAb20717 is a bispecific antibody with simultaneous inhibitory effect on PD-1 and CTLA-4. This antibody has the potential of both targeting double-checkpoint positive cells in the tumor microenvironment along with alleviating the high rate of toxicities associated with combination PD-1/PD-L1 and CTLA-4 blockade, as seen in the CheckMate 650 trial. The combined PD-1/CTLA-4 blockade could allow converting the immune-microenvironment in prostate cancer from “cold” to “hot” and achieve antitumor activity. As such, we propose a Phase I-Ib trial of XmAb20717 plus standard treatments in patients with advanced or metastatic castration sensitive prostate cancer.

3.2 Clinical Experience

Data from the DUET 2 Phase 1 study of XmAb20717 in advanced solid tumors were promising, with responses observed only at the 10 mg/kg dose level[15]. The ongoing XmAb20717-04 trial sponsored by Xencor is investigating XmAb20717 alone or in combination with chemotherapy or targeted therapies in mCRPC.

In the Xencor Inc. XmAb20717-01 study, the safety profile of XmAb20717 at a dose of 10 mg/kg Q2W was considered tolerable and consistent with other anti-PD-1 and anti-CTLA-4 antibodies as single agents or in combination. Exposure-safety analysis of data from Study XmAb20717-01 indicated that Ctrough after first dose is the best predictor of Grade 3+ irAEs. A range of doses from 500 mg to 1100 mg were modeled for both safety and efficacy. Based on this modeling, a dose of 750 mg Q3W is equivalent to 10 mg/kg Q2W for a typical

75 kg patient, and the extended interval between doses would lead to lower Ctrough values that may improve safety outcomes. Additionally, exposure-efficacy analyses demonstrate that 750 mg Q3W is expected to overlap with 10 mg/kg Q2W in terms of clinical activity (Xencor XmAb20717-01 Exposure Response Analysis Report-ClinPharm-0001). Thus, a dose of 750 mg Q3W is anticipated to provide improved tolerability and similar clinical activity.

4. Study Intervention/Investigational Agent

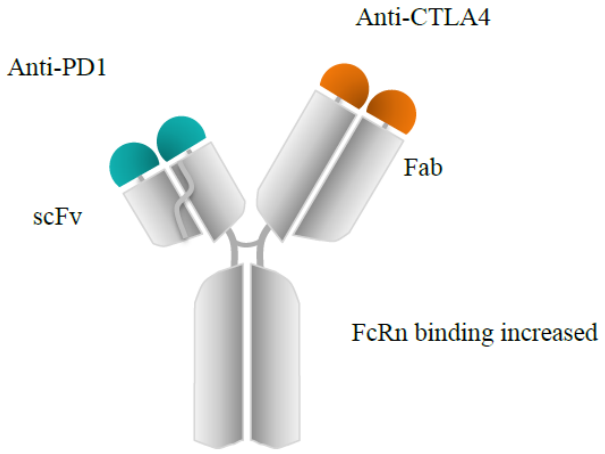
4.1 Description

XmAb20717

XmAb20717 is a humanized bsAb that binds the immune checkpoint molecules PD1 and CTLA4 in order to block signaling that prevents activated T cells from attacking and clearing tumor cells from the body.

XmAb20717 has been designed to maintain full-length humanized monospecific antibody properties in a bsAb, enabling the design of stable molecules with favorable in vivo half-life and allowing for the use of standard antibody production methods. To generate XmAb20717, Xencor humanized and affinity optimized anti-PD1 and anti-CTLA4 antibodies and combined them in a single bispecific molecule. XmAb20717 is produced as a 3-chain scFv-Fab-Fc antibody (**Figure 1**), in which the single chain variable fragment (scFv) domain targets PD1 and the fragment, antigen-binding (Fab) domain targets CTLA4. The neonatal Fc receptor (FcRn) affinity has been increased via amino acid engineering to improve serum half-life relative to antibodies containing native immunoglobulin G (IgG) Fc domains.

Figure 1: Schematic of XmAb20717 PD1 × CTLA4 Bispecific Monoclonal Antibody



CTLA4 = cytotoxic T-lymphocyte-associated protein; Fab = fragment, antigen binding; Fc = fragment, crystallizable; FcRn = neonatal Fc receptor; PD1 = programmed cell death protein 1; scFv = single-chain variable fragment (immunoglobulin fusion protein).

Abiraterone

Abiraterone acetate, the active ingredient of ZYTIGA is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). Each ZYTIGA tablet contains 250 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)- 17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate.

Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is C26H33NO2 and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

Inactive ingredients in the tablets are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, and colloidal silicon dioxide.

For full information, see FDA label for ZYTIGA (Abiraterone):
https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202379lbl.pdf

Enzalutamide
Enzalutamide is an androgen receptor inhibitor. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5- dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-N-methylbenzamide.

The molecular weight is 464.44 and molecular formula is C21H16F4N4O2S.

Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

XTANDI is provided as liquid-filled soft gelatin capsules for oral administration. Each capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl polyoxylglycerides. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

For full information, see FDA label for Xtandi (Enzalutamide)
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203415s014lbl.pdf

Docetaxel
Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.

Docetaxel is a white to almost-white powder with an empirical formula of C43H53NO14•3H2O, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

TAXOTERE (docetaxel) Injection is a sterile, non-pyrogenic, pale-yellow to brownish-yellow solution at 20 mg/mL concentration.

Each mL contains 20 mg docetaxel (anhydrous) in 0.54 grams polysorbate 80 and 0.395 grams dehydrated alcohol (50% v/v) solution, with citric acid for pH adjustment.

TAXOTERE is available in single-dose vials containing 20 mg (1 mL) or 80 mg (4 mL) docetaxel (anhydrous).

TAXOTERE Injection requires NO prior dilution with a diluent and is ready to add to the infusion solution.

For full information, see FDA label for Taxotere (Docetaxel)
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020449s084lbl.pdf

4.2 Drug Accountability

The study drugs provided for this study will be used only as directed in the study protocol. The Winship IDS (Investigational Drug Service) personnel will account for all study drugs. Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site. Study drug supplies will be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug/s in a Drug Accountability Log.
The Drug Accountability Log will record specifics to study drug dispensation such as:
• Records of product delivery, inventory, temperature monitoring, destruction, and return.
• Dosages prepared, time prepared, doses dispensed.
• Doses and/or vials destroyed.

Drug accountability may be noted by the internal monitor during site visits and at the completion of the study. The study drug supply will be disposed of per Winship's Investigational Drug Service (IDS) SOP.
Compliance will be assessed by the investigator and/or study personnel at each patient visit. This information must be captured in the source document at each patient visit.
Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

The designated site personnel will be responsible for maintaining accurate records of the quantity and dates of all study drug supplies received, dispensed, and returned, in accordance with applicable regulations and the site's SOPs. The quantity of study drug lost, destroyed, or otherwise unaccounted for must also be accounted for and documented.

5. Procedures Involved

5.1 Study Design

This is a multi-arm Phase 1-1b study of XmAb20717 in combination with standard of care treatment in patients with metastatic castration sensitive prostate cancer.

Subjects meeting inclusion criteria will be enrolled into one of the three cohorts, starting with Cohort B (enzalutamide) first. After Cohort B has completed enrollment with no safety concerns leading to pausing the trial as defined by the safety stopping rule, the principal investigator and Xencor will both review the safety

data from Cohort B. Once approved by the principal investigator and Xencor, the enrollment in Cohort A (abiraterone) and C (abiraterone plus docetaxel) can start.

The study is divided into a Screening period, Treatment period, End of Treatment (EOT) period, and Follow-up period.

During Screening period patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (e.g., full physical exam) as long as the procedures were completed within the **28-day screening period**. After signing the ICF, patients will be evaluated for entry criteria during the screening period within 28 days before administration of study drug(s).

Treatment will continue until unacceptable toxicity, death, or disease progression per RECIST 1.1, Investigator's decision to discontinue treatment, the patient withdraws consent, is lost to follow-up, or Institution decides to terminate the trial.

Patients with PD per RECIST 1.1 but with otherwise stable or improved performance and clinical status may continue to be treated in the event of a perceived benefit per Investigator and if all of following criteria are met:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG or Karnofsky performance status
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., symptomatic pleural effusion, spinal cord compression)
- Re-consent of patients using an informed consent document that details all FDA-approved therapies for their condition and the clinical benefits of those therapies that the patient would be foregoing to continue on study

Patients with a PR or SD will continue to receive treatment until achievement of a confirmed complete response (CR), disease progression, or intolerability to therapy. It is at the discretion of the Investigator to continue treating patients with a confirmed CR.

5.2 Dosing and Administration

Cohort A: XmAb20717 plus abiraterone

Regimen Description				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
XmAb20717	750mg	IV	Every 3 weeks	*3 weeks*
Abiraterone	1000mg	PO	Daily	

Cohort B: XmAb20717 plus enzalutamide

Regimen Description				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
XmAb20717	750mg	IV	Every 3 weeks	*3 weeks*
Enzalutamide	160mg	PO	Daily	

Cohort C: XmAb20717 plus docetaxel plus abiraterone

Regimen Description				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
XmAb20717	750mg	IV	Every 3 weeks	*3 weeks*
Docetaxel	75mg/m2	IV	Every 3 weeks	
Abiraterone	1000mg	PO	Daily	

Participant must maintain continuous ADT during study treatment or have a history of bilateral orchiectomy. ADT may include LHRH agonist or antagonist. Subjects can enroll to this trial within 3 months of start of ADT.

XmAb20717 administration

XmAb20717 administration should begin as soon as possible after the dosing solution is made. If there is a delay in administration, the dosing solution may be stored at 2 °C to 8 °C for no more than 24 hours or at room temperature for no more than 4 hours prior to infusion. The full calculated dose will be administered based on the subject's actual baseline weight measurement in kilograms. Following the first dose, subsequent doses will be modified only if the subject's weight changes by more than 10% from the baseline (Day -1 or Day 1, assessment closest to the first dose) weight, at which point it will be recalculated using the current weight.

XmAb20717 SHOULD NOT BE ADMINISTERED AS AN IV PUSH OR BOLUS.

XmAb20717 will be administered as an open-label solution at a constant rate over a 1-hour period. Precautions for infusion reactions/anaphylaxis should be observed during XmAb20717 administration. Due to the possibility that allergic/infusion reactions may occur, emergency resuscitation equipment (a "crash cart") should be present in the immediate area where subjects are receiving their infusions. Additional supportive measures should be available and may include, but are not limited to, acetaminophen, antihistamines, corticosteroids, IV fluids, bronchodilators, epinephrine, vasopressors, diphenhydramine, and oxygen.

All supportive measures consistent with optimal subject care will be provided throughout the study according to institution standards.

Abiraterone

Abiraterone is 1,000 mg (four 250 mg capsules) will be administered orally once daily in combination with prednisone 5 mg administered orally daily. Abiraterone must be taken on an empty stomach. No food should be

consumed for at least two hours before the dose of abiraterone is taken and for at least one hour after the dose of abiraterone is taken. Abiraterone will be prescribed by the treating physician and dispensed by Winship IDS. Abiraterone will be supplied and packaged commercially. Store as directed on the package insert.

Enzalutamide
Enzalutamide 160 mg (four 40 mg capsules) will be administered orally once daily. Swallow capsules whole. Enzalutamide can be taken with or without food. Enzalutamide will be prescribed by the treating physician and dispensed by Winship IDS. Enzalutamide will be supplied and packaged commercially. Store as directed on the package insert.

Docetaxel
Docetaxel will be administered 75 mg/m2 IV every 3 weeks. Docetaxel will be prescribed by the treating physician and dispensed by Winship IDS. Docetaxel will be supplied and packaged commercially. Store as directed on the package insert.

5.3 Dose Modification

The investigator will decide whether any AE that occurs is related to either of both drug categories (experimental and standard of care) and determine whether dose modification or discontinuation of one or all drugs is required per the guidance below.

General Safety Considerations

The following should be taken into consideration in decisions regarding management of treatment-related AEs.

- The study drug (XmAb20717) and standard of care drugs administered on the study have class-specific safety profiles based on the mechanism of action but may also cause AEs that overlap.
- As a general approach, all AEs should be managed with supportive care at the earliest signs of toxicity, including both pharmacological and nonpharmacological treatments, according to consensus management guidelines.
- Grade 2 and 3 AEs usually require dose modifications including dose reductions and interruptions. Dose interruptions of any study drug for adverse events may occur at any time and independently at the discretion of the investigator.
- Dose modifications as specified in the United States Package Insert (USPI) should be followed for each commercial drug administered.
- If XmAb20717 is interrupted for more than 12 weeks, treatment should be discontinued unless continuation is approved by the Principal Investigator.
- If XmAb20717 is permanently discontinued due to toxicity, the subject can remain on the study while receiving the standard of care drugs administered on the study (see Schedule of Events: the subject

would not need the research peripheral blood, PT/PTT collections for trial purposes on cycles where they are not receiving XmAb20717)

XmAb20717

IrAEs can happen with XmAb20717 and may involve every organ or tissue. Most irAEs occur within the first 12 weeks of exposure to an immune-checkpoint inhibitor, but some of them may appear with a delayed onset. Diagnosis of irAEs should be based on exposure to XmAb20717 and a reasonable immune-based mechanism of the observed AE. Whenever possible, histologic examination or other immune-based diagnostic evaluations should be used to support the diagnosis. Other etiologic causes, including AEs due to tumor progression, should be ruled out.

The spectrum of irAEs is wide and can be general or organ specific. Examples of general irAEs in subjects treated with immune-checkpoint inhibitors are fatigue, fever, and chills. Organ-specific irAEs consist of pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, skin adverse reactions, encephalitis, myocarditis, and endocrinopathies.

Early recognition and management of irAEs associated with immune-oncology agents may mitigate severe toxicity. Medical management of irAEs should focus on suppressing the immune response with nonsteroidal and steroidal anti-inflammatory medication. Management algorithms have been developed by the National Comprehensive Cancer Network (NCCN) and should be followed for subjects with suspected irAEs.

Dose Modification for Adverse Events Associated XmAb20717

The management principles of XmAb20717 follow the NCCN guidelines for Management of Immunotherapy-Related Toxicities. Please refer to those guidelines for any additional immune-related adverse events or for additional details as needed.

XmAb20717 should be permanently discontinued for any patient who experiences any Grade 4 toxicity that is at least possibly treatment-related.

Dermatological Adverse Event Management Algorithm

Adverse Event	Grade	Management
Maculopapular Rash	1	Continue immunotherapy Topical emollient Oral antihistamine for pruritus Treatment with moderate potency topical steroids to affected areas
	2	Continue immunotherapy Topical emollient Oral antihistamine for pruritus Treatment with moderate potency topical steroids to affected areas If unresponsive to topical within 1 week, consider prednisone 0.5mg/kg/day
	3 or 4	G3: withhold immunotherapy G4: permanently discontinue immunotherapy

		Topical emollient Oral antihistamine for pruritus Treatment with moderate potency topical steroids to affected areas
Pruritus	1	Continue immunotherapy Oral antihistamines Treatment with moderate potency topical steroids to affected areas or lidocaine patches for localized pruritus
	2	Continue immunotherapy with intensified antipruritic therapy Oral antihistamines Consider GABA agonists (gabapentin, pregabalin) Treatment with high potency topical steroids to affected areas Dermatology consultation
	3 or 4	G3: withhold immunotherapy G4: permanently discontinue immunotherapy Oral antihistamines Prednisone/methylprednisolone 0.5 – 1 mg/kg/day Consider GABA agonists (gabapentin, pregabalin) Consider aprepitant or omalizumab for refractory cases Urgent dermatology consultation
Bullous dermatitis	1	Hold immunotherapy High potency topical steroids to affected areas
	2	Hold immunotherapy until < G1 Prednisone/methylprednisolone 0.5 – 1 mg/kg/day If no improvement after 3 days, consider adding rituximab
	3 or 4	G3 and G4: Permanently discontinue immunotherapy Prednisone/methylprednisolone 1 – 2 mg/kg/day If no improvement after 3 days, consider adding rituximab or IVIG (1 g/kg/day in divided doses per package insert for 3 – 4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation
SJS or TEN	N/A	Permanently discontinue immunotherapy Prednisone/methylprednisolone 1 – 2 mg/kg/day Consider IVIG (1 g/kg/day in divided doses per package insert for 3 – 4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation

Gastrointestinal Adverse Event Management Algorithm

Adverse Event	**Grade**	**Management**
Diarrhea or colitis	1	Consider holding immunotherapy Loperamide or diphenoxylate/atropine for 2 – 3 days • If no improvement and not already done, obtain labs for infectious workup

		Hydration Close monitoring ○ If persistent or progressive symptoms, check lactoferrin o If positive, treat as G2 (below) o If negative and no infection, continue G1 management and add mesalamine, cholestyramine
	2	Hold immunotherapy Prednisone/methylprednisolone (1 – 2 mg/kg/day) No response in 2 – 3 days, continue steroids, consider adding infliximab or vedolizumab within 2 weeks
	3 or 4	G3: discontinue immunotherapy, consider resuming after resolution of toxicity G4: Permanently discontinue immunotherapy. Consider inpatient care for provision of supportive care IV methylprednisolone (1 – 2 mg/kg/day) • No response in 2 days, continue steroids, strongly consider adding infliximab or vedolizumab within 2 weeks

Hepatic Adverse Event Management Algorithm

Adverse Event	Grade	Management
Transaminitis without elevated bilirubin	1 < 3 × ULN	Continue immunotherapy, consider holding immunotherapy for concerning lab value trend Assess transaminases and bilirubin with increased frequency
	2 3 – 5 × ULN	Hold immunotherapy Monitor LFTs every 3 – 5 days Consider prednisone 0.5 – 1 mg/kg/day
	3 5 – 20 × ULN	Permanently discontinue immunotherapy Initiate prednisone 1 – 2 mg/kg/day Consider inpatient care Monitor liver enzymes every 1 – 2 days Hepatology consultation If steroid refractory or no improvement after 3 days, consider adding mycophenolate Infliximab should not be used for hepatitis
	4 > 20 × ULN	Permanently discontinue immunotherapy Initiate prednisone/methylprednisolone 2 mg/kg/day Inpatient care Monitor liver enzymes daily Hepatology consultation Liver biopsy if no contraindications If steroid refractory or no improvement after 3 days, consider adding mycophenolate Infliximab should not be used for hepatitis
Grade > 1 transaminitis with bilirubin > 1.5 × ULN (unless Gilbert's syndrome)	N/A	Permanently discontinue immunotherapy Initiate prednisone/methylprednisolone 2 mg/kg/day Inpatient care Monitor liver enzymes daily Hepatology consultation If steroid refractory or no improvement after 3 days, consider adding mycophenolate Infliximab should not be used for hepatitis

Pancreatic Adverse Event Management Algorithm

Adverse Event	Grade	Management
Elevation in amylase/lipase (asymptomatic)	Mild ≤ 3 × ULN amylase and/or ≤ 3 × ULN lipase	If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy Evaluate for pancreatitis • • Clinical assessment • • Consider abdominal CT with contrast • • Consider MRCP If evidence of pancreatitis, manage according to pancreatitis algorithm (below) Consider other causes for elevated amylase/lipase
	Moderate > 3 – 5 × ULN amylase and/or > 3 – 5 × ULN lipase	If isolated elevation of enzymes without evidence of pancreatitis, consider continuing immunotherapy Evaluate for pancreatitis • • Clinical assessment • • If persistent moderate to severe amylase and/or lipase elevation, abdominal CT with contrast or MRCP Consider other causes for elevated amylase/lipase If evidence of pancreatitis, manage according to pancreatitis algorithm (below)
	Severe > 5 × ULN amylase and/or > 5 × ULN lipase	If isolated elevation of enzymes without evidence of pancreatitis, consider continuing immunotherapy Evaluate for pancreatitis • • Clinical assessment • • If persistent moderate to severe amylase and/or lipase elevation, abdominal CT with contrast or MRCP Consider other causes for elevated amylase/lipase If evidence of pancreatitis, manage according to pancreatitis algorithm (below)
Acute pancreatitis	**1**	Consider gastroenterology referral IV hydration Manage as per elevation in amylase/lipase (asymptomatic; above)
	2	Hold immunotherapy Prednisone/methylprednisolone 0.5 – 1 mg/kg/day IV hydration

	3 or 4	G3 and G4: Permanently discontinue immunotherapy Prednisone/methylprednisolone 1 – 2 mg/kg/day IV hydration

CT =computed tomography; IV = intravenous; MRCP =magnetic resonance cholangiopancreatography; N/A = not applicable; ULN = upper limit of normal.

Pulmonary Adverse Event Management Algorithm

Adverse Event	Grade	Management
Pneumonitis	**1**	Consider holding immunotherapy Reassess in 1 – 2 weeks • • H&P • • Pulse oximetry (resting and with ambulation) Consider chest CT with contrast • • Consider repeat chest CT in 4 weeks or as clinically indicated for worsening symptoms
	2	Hold immunotherapy Consider pulmonary consultation Consider infectious workup: • • Nasal swab for potential viral pathogens • • Sputum culture, blood culture, and urine antigen test (pneumococcus, legionella) Consider bronchoscopy with BAL to rule out infection (if feasible, perform bronchoscopy with BAL prior to initiation of treatment to rule out infection) Consider chest CT with contrast • • Repeat chest CT in 3 – 4 weeks Recommend infectious evaluation with institutional immunocompromised panel Consider empiric antibiotics if infection has not yet been fully excluded Prednisone/methylprednisolone 1 – 2 mg/kg/day Monitor every 3 – 7 days with: • • H&P • • Pulse oximetry (resting and with ambulation) If no improvement after 48 – 72 hours of corticosteroids, treat as Grade 3
	3 or 4	G3 and G4: Permanently discontinue immunotherapy Inpatient care Infectious workup: • • Consider that patient may be immunocompromised • • Nasal swab for potential viral pathogens • • Sputum culture, blood culture, and urine culture Pulmonary and infectious disease consultation Bronchoscopy with BAL to rule out infection and malignant lung infiltration

		Consider empiric antibiotics if infection has not yet been fully excluded Methylprednisolone 1 – 2 mg/kg/day. Assess response within 48 hours and plan taper over ≥ 6 weeks Consider adding any of the following if no improvement after 48 hours: • Infliximab 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider • IVIG • Mycophenolate mofetil 1 – 1.5 g BID then taper in consultation with pulmonary service

BAL = bronchoalveolar lavage; BID = twice a day; CT =computed tomography; H&P = history and physical; IV = intravenous; IVIG = intravenous immunoglobulin

Endocrine Adverse Events Management Algorithm

Event	Management
Asymptomatic hypothyroidism	• Continue immunotherapy. • Monitor TSH and T4 closely, every 4-6 weeks • Consider treatment with levothyroxine if TSH >10
Symptomatic hypothyroidism	• Continue immunotherapy • Initiate treatment with levothyroxine • Monitor TSH and T4 closely, every 4-6 weeks • Consider patient referral to endocrinologist. • Exclude concomitant adrenal insufficiency (morning cortisol level)
Thyrotoxicosis	• Suspected with low or suppressed TSH with high free T4/total T3 • Consider endocrine consultation • Can continue immunotherapy if asymptomatic • Consider propranolol or atenolol or metoprolol PRN for symptoms until thyrotoxicosis resolves. • Repeat TSH/free T4/total T3 in 4-6 weeks
Hypophysitis	• Check cortisol, ACTH, TSH, free T4, LH, FSH, testosterone • Obtain Brain MRI with and without contrast with pituitary/sellar cuts if symptomatic • Endocrine consultation • Hold immunotherapy until acute symptoms resolve and hormone replacement is initiated • If acute severe symptoms with concern for mass effect, may carefully consider high-dose steroids
Hyperglycemia	• Consider new-onset immunotherapy-related Type I Diabetes Mellitus (DM)

	• Investigate for diabetic ketoacidosis if needed and per institutional guidelines. • If C-peptide is low (consistent with Type I DM), obtain endocrine consult, initiate insulin, and management any present DKA per institutional guidelines • If C-peptide is appropriate for serum glucose, continue serum glucose monitoring, continue immunotherapy, and consider alternative causes of hyperglycemia.

Renal Adverse Event Management Algorithm

Adverse Event	Grade	Management
Elevated serum creatinine/acute renal failure	1	Consider holding immunotherapy Follow creatinine and urine protein every 3 – 7 days
	2	Hold immunotherapy Follow creatinine and urine protein every 3 – 7 days Nephrology consultation, consider renal biopsy Start prednisone 0.5 – 1 mg/kg/day if other causes are ruled out For persistent G2 beyond 1 week, prednisone/methylprednisolone 1 – 2 mg/kg/day
	3 or 4	Permanently discontinue immunotherapy Consider inpatient care Prednisone/methylprednisolone 1 – 2 mg/kg/day Nephrology consultation Consider renal biopsy Consider adding one of the following if > G2 after 1 week of steroids: • Azathioprine • Cyclophosphamide (monthly) • Cyclosporine • Infliximab • Mycophenolate

Additional Immune-related adverse events management algorithm (cardiac/vascular, nervous system, musculoskeletal and connective tissue, and hematologic/immune)

Management will follow the NCCN Guidelines on Management of Immunotherapy-Related Toxicities (Version 01.2022)[16].

Docetaxel

Dose modifications is required for febrile neutropenia, ANC <500/mm^3 for >1 week, severe/cumulative cutaneous reactions, or moderate neurosensory symptoms (e.g., paresthesia, dysesthesia, pain):

- Reduce dose to 60 mg/m2; discontinue therapy if toxicities persist at lower dose.

Abiraterone

Hepatotoxicity

For patients who develop hepatotoxicity during treatment with abiraterone (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with abiraterone. Treatment may be restarted at a reduced dose of 750 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with ZYTIGA. The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

Enzalutamide

If a patient experiences a ≥ Grade 3 toxicity or an intolerable side effect, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg), if warranted. See package insert for full information

5.4 Concomitant medication

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required

- Concurrent anti-cancer therapy with agents other than the Primary Study combination drug therapy is not allowed at any time during the study.
- Participant must maintain continuous ADT during study treatment or have a history of bilateral orchiectomy. ADT may include LHRH agonist or antagonist with or without concurrent first-generation antiandrogens. Subjects can enroll to this trial within 3 months of start of ADT.
- Systemic pharmacologic doses of corticosteroids ≥ 10 mg/day prednisone are generally not permitted at the time of study enrollment. However, higher doses of corticosteroids may be allowed for subjects with a diagnosis of adrenal insufficiency. IND Sponsor consultation is required prior to enrollment of subjects with adrenal insufficiency. Subjects who require corticosteroid therapy in such doses for the management of autoimmune toxicities or palliation for pain, brain metastases, or

other disorders may remain on study if in the Investigator's judgment this is in the best interest of the subject.

5.5 Study Procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate **safety and tolerability assessments**. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

Screening Phase

Screening procedures will be performed up to **28 days** prior to enrollment unless otherwise specified. All subjects must first read, understand, and sign the IRB-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window.

The following procedures will be performed during the **Screening Visit**:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- Review of prior/concomitant medications
- Imaging by CT or MRI (chest, abdomen, pelvis)
- PSMA PET
- FDG PET
- Stool sample collection
- Clinical laboratory tests for:
    - Hematology
    - Clinical chemistry
    - TSH
    - Coagulation (PT, PTT)
    - PSA
    - Testosterone

Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments (Section 1.3). Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

- Symptom-directed physical exam

- ECOG Performance Status
- Vitals signs, weight
- Imaging by CT/MRI
- Review of prior/concomitant medications
- Review of Adverse events
- Administration study drugs
- Stool sample collection
- Clinical laboratory tests for:
  - Hematology
  - Clinical chemistry
  - TSH
  - Coagulation (PT, PTT) (only if the subject is receiving Xmab20717 during the corresponding cycle)
  - PSA
  - Testosterone

End of Treatment

- End of treatment is defined as the last planned dosing visit within the dosing period. For subjects who discontinue drug treatment, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.
- Assessments for subjects who have completed treatment and achieved disease control or have discontinued treatment due to toxicity in the absence of confirmed progressive disease are provided in the Schedule of Event.
- All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

5.6 Description of Study Procedures

Informed consent

Subjects must sign a written informed consent form(s) (ICF) prior to the initiation of any study procedures and thereafter if there are any ICF changes. Subjects will be given a signed copy of the ICF to take home. Subjects unable to provide written informed consent on their own behalf will not be eligible for the study.

Eligibility criteria

Subjects must meet all inclusion and exclusion criteria to be eligible for the study.

Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.
Details regarding all prior cancer treatments will be documented, including drug generic name, dose (if available), route of administration, start date, end date, best response, and last response to prior therapy on a separate

page in the EDC. Combination treatments should be considered as a single regimen and recorded as such in the EDC.
At Screening, a detailed prostate cancer history will be obtained, including date of initial diagnosis and cancer staging.
All medications administered to the subject from 30 days prior to first dose of XmAb20717 until 30 days after discontinuation of both XmAb20717mand the corresponding standard of care drug.

Physical examination

Physical examinations will be conducted according to the Schedule of Events. Full physical examinations will be conducted at screening/baseline, and EOT (evaluate all major organ systems, including the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, neurologic, and psychiatric).

If the Screening full physical exam is performed > 72 hours prior to the C1D1 visit, then a brief (symptom directed) physical exam must be performed within 72 hours prior to the first injection of XmAb20717.
Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight is to be recorded at each visit, height at screening/baseline visit only.

Vital signs

Vital signs (measurement of blood pressure (systolic and diastolic blood pressure), respiratory rate, heart rate, body temperature) will be evaluated according to the assessment schedules. Body weight and height is also recorded along with vital signs.
Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Clinical laboratory tests

The following clinical laboratory tests will be performed (see Schedule of Assessments 1.3)
Additional tests may be performed as clinically indicated.

Clinical laboratory parameters to be obtained include:

- Hematology and Clinical Chemistry
- Coagulation parameters: (Partial thromboplastin time, Prothrombin time, and International normalized ratio) assessments at baseline and as clinically indicated
- Thyroid function tests
    - TSH (Free T3 and Free T4 only if TSH is abnormal)
- PSA and total serum testosterone level.

The Investigator is responsible for reviewing local and central laboratory results and assessing all out-of-range findings as either clinically significant or non-clinically significant. Clinically significant laboratory results should be recorded as medical history if prior to XmAb20717 dosing at C1D1, or AEs following XmAb20717 at C1D1 in the eCRF. Clinically significant lab results based on local and central lab reports should also be reported in the EDC.

Imaging

Standard radiological assessments should take place per the study calendar with the institution standard protocol. In addition, at baseline as an exploratory imaging biomarker, ^{18}F-PSMA (PYLARIFY) PET/CT and ^{18}F-FDG PET/CT will be performed in the screening period and separated by > 24 hours (typically at least the second day after one or the other PET/CT). Both studies will take place on either the PET/CT at the Center for Systems Imaging or in case of unavailability, on any available PET/CT in the Emory Healthcare system deemed appropriate by the investigators. Typical institutional protocol will be carried out specific to that scanner from skull to thigh. This includes at least 4-6 hour NPO for FDG PET and standard point of care check for plasma glucose; if glucose over 200 mg/dL, there will be consultation with the PI as to potential rescheduling. PSMA PET does not require fasting or plasma glucose check.

Images will undergo post-hoc analysis for total tumor burden utilizing standard imaging biomarkers such as SUVmax, SUVmean, SUVpeak, and total lesion activity on absolute basis and as compared to normal liver and blood pool as measured at the aortic arch. Analysis will take place on an advanced workstation with manual and/or semi-automated tools and will be correlated to outcome at end of study. A visual analysis will also take place in which each patient will be rated as: PSMA-dominant, FDG-dominant, similar FDG and PSMA total activity, or negative PSMA and FDG.

6. Data and Specimen Banking

Blood and tumor samples will be obtained and used for medical research by the investigators of this study. *Data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, Investigators may provide de-identified data and/or specimens to other researchers. Any information that could identify participants will not be included. If data or specimens are labeled with study ID, we will not allow other investigators to link that ID to identifiable information.*

Samples and data collected under this protocol may be used to study **Prostate Cancer**. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

The results of some study tests and procedures will be used only for research purposes and will not be placed in subject's medical record. For this study, those items include: research blood collection.

Peripheral blood samples

Approximately 30 mL of peripheral blood will be collected during screening, on treatment on C1D8, C2D8, C3D8 (to be collected only if the subject received Xmab20717 on day 1 of the corresponding cycle) and at the time of end of treatment visit.

The peripheral blood mononuclear cells will be isolated from these samples and stored in -80°C freezers until analysis. Plasma will be stored in 80°C freezers until analysis.

Samples will be evaluated including but not limited to:

i. Determine whether there are phenotypic changes in of T-cell or myeloid cell surface markers (including co-stimulatory/immune checkpoint molecules) in PBMCs after treatment.
ii. Determine whether functional changes are evident in PBMCs in response to treatment and whether these data correlate with clinical outcome measures. Pending quantity of cells a variety of assays may be performed
iii. Plasma sample will be stored for future ctDNA and cytokine analysis.

Stool Samples
Stool sample for microbiome analysis will be collected at baseline, prior to C4D1 for cohort A and B, and C3D1 for cohort C, and post-treatment phase within the 14 days after the last dose of study drug.

- Stool sample for microbiome analysis

After appropriate processing, the blood samples, tissue blocks, slides or frozen tissue samples will be sent to:
Kissick Laboratory
1462 Clifton Rd, Room 420
Atlanta, Georgia, 30322
ph: 617 259 8364
email: haydn.kissick@emory.edu

7. Statistical Analysis Plan

Statistical consideration section:

Study Design and Sample Size:
This will be a multi-arm study aimed at enrolling 10 patients per cohort. The study aims to determine the safety and tolerability of XmAb20717 in combination with standard of care treatment in subjects with metastatic castration sensitive prostate cancer (mCSPC) as assessed by frequency and intensity of adverse events. Subjects meeting inclusion criteria will be enrolled into one of the three cohorts, starting with Cohort B (enzalutamide) first. After Cohort B has completed enrollment with no safety concerns leading to pausing the trial as defined by the safety stopping rule, the principal investigator and Xencor will both review the safety data from Cohort B. Once approved by the principal investigator and Xencor, the enrollment in Cohort A (abiraterone) and C (abiraterone plus docetaxel) can start.

The sample size is not hypothesis driven. In the primary analyses, descriptive statistics will be used to summarize the toxicity profile of the intervention. Toxicities will be tabulated by grade, association, and cycle number.

In the secondary analyses, the Objective response rate (ORR) or PSA response rate will be summarized with the 2-sided 95% CI using the Clopper-Pearson method. Kaplan-Meier methods will be used to estimate median survival time or time-specific survival rate with a 95% confidence interval for rPFS or a time-to-event outcome. For exploratory correlative analysis, logistic regression or Cox proportional hazard model would be applied to assess the association with baseline biomarkers measured by tissue or blood samples, e.g., peripheral T-cell profile. For the measurement repeatedly over time, a time-varying covariate analysis strategy will be

considered, such as the extended Cox model. However, due to the small sample size, the analyses will mainly be exploratory.

Stopping Rule: The safety stopping boundary is calculated based on the Bayesian Toxicity Monitoring (BTM) application (https://www.trialdesign.org) to control for the probability of excessive toxicity being less than 70%, and the target rate of grade 3 or 4 toxicity is ≤40%.

Toxicity assessment will occur after first 5 patients are enrolled in each cohort (starting with Cohort B first), and if there are ≥2 out of 5 patients who experienced grade 3 or 4 toxicity during the first cycle, the trial will be paused for further evaluation about whether to proceed. Otherwise, we will proceed until 10 patients are enrolled in cohort B, and if 5 and more patients out of 10 in cohort B have grade 3 or 4 toxicity during the first cycle, we will claim the safety concern for the proposed treatment. Once approved by the principal investigator and Xencor (as described in the above Study Design and Sample Size section), Cohort A and C can begin enrollment.

We justify the Grade 4 toxicity target rate of ≤40% based on the relatively high incidence of adverse events with anti-PD-1/CTLA-4 combined therapy. In the CheckMate 067 trial of nivolumab plus ipilimumab treatment for advanced melanoma, 59% of patients had Grade 3 or 4 treatment-related adverse events[17]. When the same combination was used for advanced renal cell carcinoma in the Checkmate 214 trial, 46% of patients had grade 3 or 4 adverse events[18]. In Checkmate 650 trial, this incidence was 42% in pre-chemotherapy cohort and 53% in post-chemotherapy cohort of men with mCRPC treated with nivolumab plus ipilimumab[19].

Safety Analysis: All patients who receive at least one dose of Xmab20717 will be evaluable for toxicity. The list of adverse events will be summarized descriptively using frequencies and percentages of all captured toxicities by severity and relevance.

Analysis of Secondary Endpoints: PSA response rate, PSA undetectable rate, ORR by immune-related RECIST (irRECIST), and ORR based on RECIST version 1.1 will be calculated along with 95% exact confidence intervals. The fold change of the numbers of CD8 T-cells or other tumor-specific T-cells before and after treatment will be described by summary statistics (mean, median, Q1, Q3, standard deviation).

Time-to-event endpoint (e.g. Time to PSA progression, rPFS, OS) will be estimated with the Kaplan-Meier method with time-specific rate estimated with 95%CI.

Analysis of Exploratory Endpoints: The change in immune system biomarkers before and after treatment will be compared using paired test, such as Wilcoxon signed-rank test.

8. Sharing of Results with Participants

In general, study staff will not provide any individual results to subjects (ex. outcome trial results or results from subject's samples studies). If something of urgent medical importance to the participating subjects will be found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence. Samples and data will only be used for research.

9. Study Timelines

Duration of therapy

XmAb20717 will be administered Q3weeks until the subject meets a condition for discontinuation of study treatment or up to 1 year in the absence of disease progression or unacceptable toxicity.

In the absence of treatment delays due to adverse event(s), patients will be treated until any one of the following:

- Tumor progression per PCWG-modified RECIST 1.1 as outlined in PCWG31
- Death
- Unacceptable toxicity
- Symptomatic deterioration
- Investigator's decision to discontinue treatment
- Patient decision to discontinue treatment
- Patient withdraws consent
- Lost to follow up

In the event of a patient's withdrawal, the Investigator will make every effort to complete the End of Treatment procedures specified in the Schedule of Events.

Duration of follow-up

Patients will be followed for approximately 28 days (Safety Follow-up) after the last dose of study drug or before initiation of new antineoplastic or investigational therapy whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Long-term follow-up should continue until the patient's withdrawal of consent or loss to follow up, death, or study termination.

Patient records may be reviewed until death to assess progression and survival. Survival information may be collected by clinic visit, email, or telephone after ending protocol treatment and until the study is terminated, the patient dies, or the patient is lost to follow-up.

A participant will be considered lost to follow-up if he fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:
The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.
- All patients will be contacted for survival every 12 weeks following the End of Treatment (EOT) visit.
- Immunogenicity samples will be taken as per schedule of events

10. Inclusion and Exclusion Criteria

Inclusion Criteria

1. Age ≥18 years.
2. Histologically confirmed adenocarcinoma of the prostate with metastatic disease
3. Castration-sensitive status: either not have been treated with ADT (hormone therapy) or not on ADT at the time of progression
    - Participants can have received up to 3 months of ADT with LHRH agonists or antagonists or orchiectomy with or without concurrent first-generation antiandrogens prior to enrolment, with no radiographic evidence of disease progression or rising PSA prior to enrollment.
4. ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).
5. Life expectancy > 12 weeks as determined by the Investigator
6. Patients must have adequate organ and marrow function, within 28 days of Cycle 1 Day 1, as defined below:

    Hematology

    Hemoglobin ≥ 9.0 g/dl (no transfusions allowed within 7 days of Cycle 1 Day 1 to meet entry criteria)

    White blood cell (WBC) ≥ 2000/µL (after at least 7 days without growth factor support or transfusion)

    Absolute neutrophil count (ANC) ≥ 1,500/mcL (after at least 7 days without growth factor support or transfusion)

    Platelets ≥ 100,000/mcL (no transfusions allowed within 7 days of Cycle 1 Day 1 to meet entry criteria)

    PT/PTT ≤ 1.5 x ULN

    Chemistry

    Total bilirubin ≤1.5 institutional upper limit of normal (ULN)

    AST/ALT ≤ 3 institutional upper limit of normal (ULN)

    Serum creatinine ≤ 2 mg/dL (or glomerular filtration rate ≥ 40 mL/min)

7. Male subjects must be surgically sterile or must agree to use adequate method of contraception from the time of consent until at least 120 days after the last dose of Xmab27017
8. Willingness and ability of the subject to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests, other study procedures, and study restrictions.
9. Completion of all previous surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy for the treatment of cancer ≥ **2** weeks before the start of study therapy. (No radiotherapy to Xmab27017 injection site within 4 weeks).
10. Evidence of a personally signed informed consent indicating that the subject is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients who have had chemotherapy or radiotherapy within 4 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier (*i.e.*, have residual toxicities > Grade 1).
2. Patients who are receiving any other investigational agents or an investigational device within 21 days before administration of first dose of study drugs
3. Prior treatment with any CTLA4, PD1, or PDL1, or directed immunotherapy
4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to [IND Agent(s)] or other agents used in study.
5. Have known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, ie, are without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), are clinically stable, and are without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
6. Active known or suspected autoimmune disease (except that subjects are permitted to enroll if they have vitiligo; type 1 diabetes mellitus or residual hypothyroidism due to an autoimmune condition that is treatable with hormone replacement therapy only; psoriasis, atopic dermatitis, or another autoimmune skin condition that is managed without systemic therapy; or arthritis that is managed without systemic therapy beyond oral acetaminophen and nonsteroidal anti-inflammatory drugs).
7. Has any condition requiring systemic treatment with corticosteroids, prednisone equivalents, or other immunosuppressive medications within 14 days prior to first dose of study drug (except that inhaled or topical corticosteroids or brief courses of corticosteroids given for prophylaxis of contrast dye allergic response are permitted.)
8. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
9. Receipt of an organ allograft
10. Known history of left ventricular ejection fraction ≤ 40%. There is no need for an echocardiogram unless clinically indicated
11. Receipt of a live-virus vaccine within 30 days prior to first dose of study drug (seasonal flu vaccines that do not contain live virus are permitted. COVID-19 vaccines are permitted).
12. Known human immunodeficiency virus (HIV) positive subject with CD4+ T-cell (CD4+) counts < 350 cells/µL, or an HIV viral load greater than 400 copies/mL, or a history of an AIDS (acquired immunodeficiency syndrome)-defining opportunistic infection within the past 12 months, or who has not been on established antiretroviral therapy (ART) for at least 4 weeks prior to initiation of study drug dosing. (Effective ART is defined as a drug, dosage, and schedule associated with reduction and control of the viral load.)
13. Known positive test for hepatitis C RNA (a subject who is hepatitis C virus [HCV] antibody positive but HCV RNA negative due to documented, curative prior antiviral treatment or natural resolution is eligible).
14. Known positive test for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb; a subject whose HBsAg is negative and HBcAb is positive may be enrolled if a hepatitis B virus [HBV] DNA test is negative, and the subject is retested for HBsAg and HBV DNA every 2 months)

11. Local Number of Participants

We will be recruiting 30 participants at Winship. Patients will be registered after signing of the informed consent document and meeting all entry requirements.

12. Recruitment Methods

Investigators, nurses (CRNs), research coordinators (CRCs) and/or data managers review lists of cancer patients who have cancer and will determine if there are patients who might be eligible for a clinical trial. The CRN/CRC/data manager reviews accessible medical records to screen further for eligibility. The CRN/CRC reviews the eligibility with the physician. Subjects will be identified by their treating physicians. Clinical care team at Winship will inform potential subjects about the known benefits and potential risks of a clinical trial as well as other available treatment options. Some of the subjects recruited for this protocol will be patients being treated at Emory and under the care of one or more of the study investigators. Some potential subjects will be identified by their treating physician and referred to Emory for possible participation in the protocol.

No incentives are provided to patients for trial participation.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.

Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

Enrolling a subject requires careful screening and determination of eligibility.

Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator.

When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, randomization and or enrollment may proceed. OnCore must be updated to reflect eligibility and on treatment status.

13. Withdrawal of Participants

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If any clinical adverse event, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of the study intervention
- If medically necessary in the opinion of the Investigator
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Subject withdraws consent for the study (note that a subject who withdraws consent for additional study treatment and procedures but not for antitumor response will continue to be followed)
- Subject is lost to follow-up
- Death

- End of Clinical Trial

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

Subjects who discontinue study treatment should undergo the EOT assessments per Section 1.3.1

14. Risks to Participants

XmAb 20717

The most common adverse reactions with XmAb20717 are skin reactions (rash and pruritus) and gastrointestinal reactions (nausea and diarrhea). The safety risks for XmAb20717 include irAEs and infusion-related reactions. An irAE of any organ can happen. In the Phase I trial of XmAb20717 in advanced solid tumors (N=145), Grade 3/4 irAE reported for ≥3 patients included rash (10.3%), aspartate aminotransferase increase (4.8%), alanine aminotransferase increase and hyperglycaemia (3.5%), lipase increase (4.2%), amylase increase and acute kidney injury (2.8%), and pneumonitis (2.1%). There were 2 Grade 5 irAEs: immune-mediated pancreatitis and myocarditis (which was heavily confounded by the subject's preexisting conditions)[15].

Abiraterone

The most common adverse reactions (≥10%) are fatigue, arthralgia, hypertension, nausea, edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory infection, cough, and headache. (6.1)
The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, and hypokalemia

Enzalutamide

The most common adverse reactions (≥ 10%) are asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo.

Docetaxel

Most common adverse are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

Other Risks

- **Blood draws** - The physical risk of drawing blood is local pain and bruising at the site of venipuncture. Qualified phlebotomists or designee will draw blood samples. Care will be taken to obtain these specimens in a safe and hygienic manner. A small number of people experience lightheadedness or fainting. There is a slight risk of infection. To minimize these risks, attempts will be made to draw study blood samples at the same time as blood draws needed for routine clinical care are obtained. Repeated blood drawing may be associated with iron deficiency anemia.
- **Data security-** Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked

room at the participating sites. Electronic files will be password protected behind an academic institutional firewall. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance and data analysis include groups such as the National Cancer Institute (NCI) and Food and Drug Administration (FDA).

- **Radiation-Related Risks:** You will be exposed to radiation from nuclear medicine and CT scans. These procedures are necessary for your medical care and will occur even if you do not participate in this study. The radiation dose estimate that you will receive is equal to or less than the radiation exposure allowed to be received by a radiation worker for 2 years. The principal risk associated with a radiation dose is the possibility of developing a radiation-induced cancer later in life. Although the risk from radiation is cumulative it is not expected to adversely affect your condition or treatment. The Emory University Radiation Safety Committee has reviewed and approved the use of radiation in this research study.

15. Potential Benefits to Participants

There is no guarantee of benefit to subjects who enroll in this protocol.

16. Data Management and Confidentiality

Data/specimens:

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. 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 Principal Investigator. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.
Data and/or data forms will be submitted in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics.

All information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored. 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 research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Samples and data collected under this protocol may be used to study prostate cancer. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

17. Provisions to Monitor the Data to Ensure the Safety of Participants

Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Classification of an Adverse Event

<u>Severity of Event</u>

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity, consistent with CTCAE version 5.0

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- **Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living.
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- **Grade 4:** Life-threatening consequences; urgent intervention indicated.
- **Grade 5:** Death related to AE.

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to each component of the investigational regimen assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product(s) must always be suspect(s). When possible, the investigator should assign attribution of each component of the investigational regimen (i.e. XmAb20717 vs. abiraterone or enzalutamide or docetaxel) when assessing an AE.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Adverse Event and Serious Adverse Event Reporting

Expectedness

Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected (based on the current version of IB's RSI). An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Adverse Event Reporting

From the time of treatment allocation through **70** days following cessation of treatment, all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.
The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.
Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.
If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment(s) (Reasonable possibility that AE is related: No, Yes) or Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 9.2 and which seriousness criteria have been met (include for NCDS trials).
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens, the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. For phase I studies any AE that constitutes a DLT should be reported like a grade 3 and 4 adverse event. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.
Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.
Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.
Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

Serious Adverse Event Reporting

For the time period beginning at treatment allocation/randomization through **70** days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be **submitted on an SAE form** and assessed by the Sponsor-Investigator in order to determine reporting criteria to regulatory authorities, IRB, DSMC, FDA and/or Xencor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible. The study IND sponsor will be responsible for notifying FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information and all other unexpected serious adverse reactions in no case later than 15 calendar days after the sponsor's initial receipt of the information.

Reporting to study supporter/IRB and or FDA.
All subjects with serious adverse events must be followed up for outcome.
Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode **within 24 hours** of the investigator receiving the follow-up information.
An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.
Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form.

Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

All SAE must be recorded on a MedWatch 3500 Form. SAE reports and any other relevant safety information are to be forwarded to the following

MedWatch 3500 Reporting Guidelines:

Note: MedWatch 3500 forms and other information related to MedWatch reporting are available at http://www.fda.gov/medwatch/index.html.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA and Xencor. Investigators will cross reference this submission according to local regulations to the Investigational Compound Number (IND, CSA, etc.) at the time of submission.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Reporting Requirements for IND holder

For Investigator-sponsored IND studies, reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR, Part 312.32. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

7 Calendar-Day Telephone or Fax Report

The Sponsor-Investigator is required to notify the FDA of a fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of *investigational agents*. An unexpected adverse event is one that is not already described in the most recent Guidance for Investigator section of the Investigator's Brochure. Such reports are to be telephoned or faxed to the FDA, within 7 calendar days of the first learning of the event.

15 Calendar-Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious unexpected adverse event that is considered reasonably or possibly related to the use of investigational agent.

Written IND Safety Reports with analysis of similar events are to be submitted to the FDA and Xencor, within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 Form but alternative formats (e.g., summary letter) are acceptable.

FDA Fax number of IND Safety Reports: 1-(800)-FDA-1078.

The IND sponsor will also make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB, which, in turn will

make a final determination. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

All Adverse Events will be reported to regulatory authorities, Xencor, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

Coordinating center reporting to the Food and Drug Administration (FDA)

The Sponsor-Investigator, as holder of the IND, will be responsible for all communication with the FDA. The Sponsor Investigator [or designee] will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.
Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but no later than 7 calendar days after initial receipt of the information.
All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information. Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800- FDA-0178) using MEDWATCH Form FDA 3500A (Mandatory Reporting Form for investigational agents). Forms are available at http://www.fda.gov/medwatch/getforms.htm.

An annual safety report containing all SAEs, expected and unexpected, will be sent to the FDA and other applicable regulatory authorities.

Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information: Protocol identifying information: protocol title and number, PI's name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. The IND sponsor will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data. The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

Monitoring Table 2

DSMP Requirement	How this Requirement is Met	Frequency	Responsible Party(ies)
Real-time review of participant data during initial data collection.	This requirement will be met per Winship's NCI approved DSMP	This will occur every time new information is obtained.	SI/study team
Site Monitoring at pre-determined intervals: The Principal Investigator has a responsibility to ensure that the study is following all aspects of the protocol.	This requirement will be met per Winship's NCI approved DSMP	biannually	DSMC
100% review of regulatory files	DSMC monitors will review the protocol, amendments, informed consent documents, IRB submissions and meet with the principal investigator for clarification of study objectives	Reviewed at first and close-out visits	DSMC
100% review of consent forms	Monthly QA check of 5-10 randomly selected consents to validate Central Subject Registration (CSR) and PRMS to conduct QA consent checks in real time as subjects are registered in OnCore vis CSR process	biannually	PRMS, QM
Review of credentials, training records, the delegation of responsibility logs (if applicable)	The Winship Associate Director for Clinical Research will establish the scope and allocate staff support to include procedures for obtaining charts, facilitating access to the electronic medical record, etc.	biannually	DSMC
Comparison of case report forms (CRF) to source documentation for accuracy and completion	The PI is responsible for ensuring that instances of egregious data insufficiencies that may impact the scientific integrity of the trial	biannually	DSMC
Review of documentation of all adverse events	During the monitoring process, the DSMB reviews trial safety data for stopping rules, deviations, study amendments, accrual rates and monitoring reports for therapeutic investigator-initiated clinical trials and any other trial as deemed necessary	biannually	DSMC
Monitoring of critical data points (eligibility, study endpoints, etc.)	The assigned monitor will randomly select subject(s) for review based on parameters in	biannually	DSMC

	Table 1 or 2 as noted above. Although the principal investigator and applicable study team members will receive notification of trial monitoring in advance, the subject selection will not be revealed in advance of the monitoring visit.		
Laboratory review of processing and storage of specimens	The assigned monitor will randomly select subject(s) for review based on parameters in Table 1 or 2 as noted above	Reviewed at first and close-out visits and at least biannually	DSMC
Assessment of laboratory specimens stored locally	If accrual at time of initial monitoring is> IO but :S 20, I 0% of subjects will be monitored at minimum. Thereafter, monitoring will not occur unless accrual reaches 30	Reviewed at first and close-out visits and at least biannually	DSMC
Test article accountability review	In addition to a comprehensive review of available toxicity data, the DSMC reviews all internal monitoring reports of trials under its purview	Reviewed at first and close-out visits and at least biannually	DSMC
Accountability logs, dispensing records, and other participant records	If accrual at time of initial monitoring is> IO but :S 20, I 0% of subjects will be monitored at minimum. Thereafter, monitoring will not occur unless accrual reaches 30.	At least biannually	DSMC
For FDA regulated studies, the following requirements apply:	monitoring activities meet the FDA's requirements as delineated in 21 CFR 50, 21 CFR 56, 21 CFR 812 for studies conducted under an IDE and 21 CFR 312 for studies conducted under an IND.	biannually	DSMC
Monitoring methods (may include centralized, on-site, and self-monitoring)	The internal monitoring team is independent from any study protocol and does not perform any trial-related specific duties in order to uphold an unbiased approach to study monitoring. Oversight of the monitoring process and identification/assignment of studies for monitoring is provided by the Manager of the Internal Monitors.	biannually	DSMC

*For international studies, you are required to engage a CRO that is working in the site country and/or to consult with Emory's legal counsel regarding compliance with the country's clinical research regulations.

18. Provisions to Protect the Privacy Interests of Participants

Participants will be assured of their voluntary participation in the study, their choice to answer or not answer any question, and the protocol for maintaining confidentiality.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. 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 IND sponsor.

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

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

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. 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 research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived

19. Economic Burden to Participants

The study supporter will pay for certain items and services the subject may receive in this study. Subjects will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for regular medical care. If subjects have insurance, Emory will submit claims to the insurance for items and services that the sponsor does not cover. Emory will send in only those claims for items and services that it reasonably believes the insurance will pay and that the sponsor has not paid. The actual amount that participants have to pay depends on whether or not they have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if in a study. If subject do not have insurance, Emory will review that particular case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if subjects have to pay any costs for taking part in the study and what those costs will be.

20. Consent Process

The initial informed consent discussion will occur in Winship Cancer Institute or the Emory Clinic.

At Winship Cancer Institute, the informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about whether to begin or continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purpose, procedures, risks and potential benefits, and their rights as a participant. The team will continue to update the patient on any new information that may affect their situation.
Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient's capacity during his/her encounters with him or her. The investigator will give the person providing consent adequate opportunity to read the consent document before it is signed and dated.
It will be explained to prospective participants that the study involves research, the purpose of the research, the expected duration of participation, as well as the approximate number of participants to be enrolled. The study procedures, and identification of research procedures v. non-research will also be thoroughly discussed. It will be explained to participants that participation is voluntary and that the subject may discontinue at any time.
Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the participant is otherwise entitled. Refusal will in no way affect the participant's future are. The participant will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation.
Any significant new findings developed during the course of the research that may affect the participant's willingness to continue to participate will be provided. Also explained will be anticipated circumstances under which the subject's participation may be terminated by the investigator without the participant's consent.
Prospective participants will be provided with a description of any reasonably foreseeable risks or discomforts as well as a description of any benefits to the participant or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed.
Prospective participants will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, sponsor, their representatives, and possibly the FDA or OHRP.
Also communicated to the participant will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., sponsor, subject, insurer). The participant is told the source of the study's funding.
All participants will be told of any additional costs that may result from participation in the research.
Consent will be done in person or remotely through secured email, phone or by electronic consenting using one of the methods that is Emory LITS approved (e.g. DocuSign) when available. We will follow Emory's guidance on use of electronic informed consent.

Non-English-Speaking Participants

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician.

A Short Form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use. Process to Document Consent in Writing: Winship SOP 2.1:"Obtaining Informed consent for Interventional clinical trial" will be followed.

Participants who are not yet adults (infants, children, teenagers): N/A

Cognitively Impaired Adults: N/A

Adults Unable to Consent: N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception): N/A

21. Setting

The research will be conducted at Emory University.

Potential participants will be identified in medical oncology clinics, multidisciplinary cancer clinic, surgical oncology clinics, and multidisciplinary tumor board at Emory University.

22. Resources Available

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation's top 25 universities for more than a decade by the U.S. News and World Report. Emory University research partners include the Georgia Institute of Technology, the University of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

Winship Cancer Institute (Winship) is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship's NCI designation was renewed in 2012 and 2016, achieving an "outstanding" rating. Winship earned the prestigious Comprehensive Cancer Center designation from the NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as 'exceptional' by the review panel.

The **Winship Clinic Building C** houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of **Emory University Hospital Tower** on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.

The **Winship Phase I Unit**, on the fourth floor of the Emory University Hospital Tower, is the largest unit in Georgia dedicated to the earliest and most critical phase of new cancer therapy evaluation. There is space for 15 private treatment bays, four clinic rooms, its own lab for doing patient blood work, a dedicated secure medication room,

computer workspace for research and other support staff, and a "fast track" bay with three chairs for rapid use in patients who, for example, might need only a research lab test done.

23. References

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined 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.

As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

APPENDIX B Drug Diary

Study ID:

[*Drug*] Pill Diary

Subject Initials:___ Subject ID: _____ Cycle: _____

Instructions:
Planned Daily Dose: **__mg**
REMINDERS:
1.
2.

Day	Date	Time	# of Tablets taken	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Record all medications taken during this cycle for example prescriptions and over the counter including vitamins.

Name of Medication	Why did you take the medication?	Date Medication Started	Date Medication Stopped

APPENDIX C Abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee

Abbreviation or special term	Explanation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors

Abbreviation or special term	Explanation
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula

Abbreviation or special term	Explanation
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCLC	Small cell lung cancer
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization