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UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
SEATTLE CHILDREN'S

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Title of Protocol:
TRAMP: Tumor Necrosis Factor- α Blockade and AR Inhibition in Men with CRPC

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IND Sponsor:
Ruben Raychaudhuri, MD

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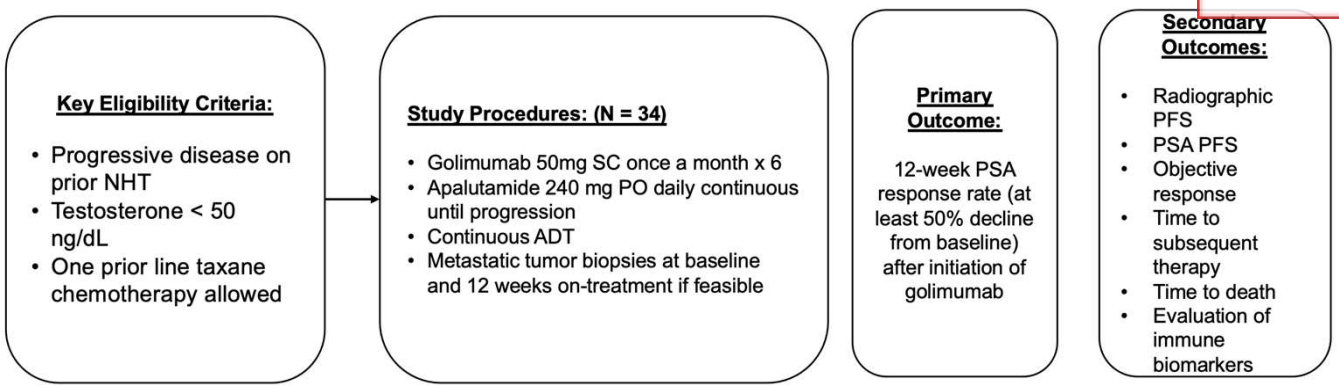
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PROTOCOL SYNOPSIS

Protocol Title	TRAMP: Tumor Necrosis Factor- α Blockade and AR Inhibition in Men with CRPC
Protocol Numbers	UW RGR number: RG1123487 (Janssen protocol number: 56021927PCR2051)
IND Sponsor (if applicable)	Dr. Ruben Raychaudhuri
Funding Sponsor (if applicable)	Janssen Scientific Affairs, LLC
Supplier of Investigational Product	Janssen Scientific Affairs, LLC
Trial Phase	Phase 2
Trial Type	Open-label, single-center
Clinical Indication	Metastatic Castration-Resistant Prostate Cancer (mCRPC)
Study Objectives	To determine the clinical activity of apalutamide in combination with golimumab in men with mCRPC who have progressed on prior Novel Hormonal Therapy (NHT) using a primary endpoint of 12-week PSA_{50} response rate.
Study Design	Phase 2 single-arm, single-center
Population	Adults with mCRPC that have progressive disease on NHT
Primary Endpoints	12-week PSA_{50} response rate
Secondary Endpoints	• Objective response rate • PSA PFS • Radiographic PFS • Time to subsequent antineoplastic therapy • Overall survival
Type of Control	Historical
Investigational Product	Apalutamide, Golimumab
Dose	Apalutamide PO 240mg daily, Golimumab SC 50mg q4weeks up to 6 doses
Route of Administration	As above
Regimen	Combination treatment: • Androgen Deprivation Therapy (ADT) with LHRH agonist/antagonist, • Apalutamide, and • Golimumab
Trial Blinding	None
Treatment Groups	NA
Treatment Schedule/Schema	See below schema.
Efficacy Assessments	Monthly
Number of Subjects	N=34 (accounting for 10% dropout)
Estimated Duration of Trial	3 years
Duration of Participation	6-month treatment period

Trial Schema:

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Phase 2 Trial Schema: TRAMP: Tumor Necrosis Factor-α Blockade and AR Inhibition in Men with CRPC. NHT, novel hormonal therapy; CSPC, castration-sensitive prostate cancer; CRPC, castration-resistant prostate cancer; PFS, progression-free survival.

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ABBREVIATIONS

ADT	Androgen deprivation therapy
ANC	Absolute neutrophil count
AR	Androgen receptor
AS	Ankylosing spondylitis
ALT	Alanine transaminase
AST	Aspartate transaminase
BCR	Biochemical recurrent
CNS	Central nervous system
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DNA	Deoxyribonucleic acid
DSP	Digital spatial profiling
ECOG	Eastern cooperative oncology group
EU	European Union
FDA	Food and Drug Administration
FHCC	Fred Hutch Cancer Center
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HGPIN	High-grade prostatic intraepithelial neoplasia
ICF	Informed consent form
IL	Interleukin
IV	Intravenous
LHRH	Luteinizing hormone releasing hormone
mAb	Monoclonal antibody
NHT	Novel hormonal therapy
nr-axSpA	Non-radiographic axial spondyloarthritis
PC	Prostate cancer
PFS	Progression free survival; pre-filled syringe
PI	Principal investigator; package insert
PIA	Proliferative inflammatory atrophy
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetics
PO	Per os (by mouth)
PSA	Prostate specific antigen
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
RNA	Ribonucleic acid
SC	Subcutaneous
TB	Tuberculosis
T1D	Type 1 diabetes
TME	Tumor microenvironment
TNF	Tumor necrosis factor
UC	Ulcerative colitis
ULN	Upper limit normal

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1.0 INTRODUCTION

1.1 Background

Prostate Cancer in the U.S.
Metastatic castration-resistant prostate cancer (mCRPC) is responsible for over 30,000 deaths per year in the United States [1]. Existing therapeutic approaches often target the androgen receptor (AR) leading to improved clinical outcomes compared to androgen deprivation therapy (ADT) alone [2–6]. However, treatment resistance and disease progression invariably occur. The continued lethality of this disease underscores the importance of testing therapeutics aimed at mechanisms of resistance.

The role of cytokines in prostate cancer.
Prostate cancers (PC) typically arise in the periphery of the prostate gland where focal areas of epithelial atrophy occur (proliferative inflammatory atrophy – PIA) [7]. These areas are often associated with acute or chronic inflammation and show morphological transitions to high-grade prostatic intraepithelial neoplasia (HGPIN) [8]. Moreover, pro-inflammatory and immunosuppressive cytokines that mediate intracellular communication and regulate downstream gene transcription have been implicated in promoting carcinogenesis in a variety of tumor types, including PC [9,10]. Similarly, there have been various clinical studies showing a correlation between inflammatory markers and: (i) clinicopathologic features; (ii) prognostic factor in the development of CRPC and metastases, and (iii) responses to treatment such as docetaxel chemotherapy [11–13]. Many of the cytokines are key in both pro- and anti-tumor responses, e.g., locally produced IL-8 may provide a mechanism for immune suppression by recruiting suppressive myeloid cells (polymorphonuclear myeloid derived suppressor cells) to the tumor microenvironment (TME) [14].

TNF-α mediates resistance to AR antagonists and may be negative predictive biomarker.
TNF-α is a pleiotropic cytokine produced by many different types of cells [15]. TNF-α is a "master regulator" of pro-inflammatory cytokine production and is a central player in inflammatory cell activation and recruitment. TNF-α sits at the forefront of a complex cytokine cascade mediated through the activation of a proinflammatory transcription factor nuclear factor kappa-B [16]. It is suggested to play a critical role in the development of many chronic inflammatory diseases [17]. It was previously thought to have anti-tumor effects, now shown to mediate pro-survival signaling of tumor cells and elicit pro-tumor immune changes in the tumor microenvironment, including in PC [18–22]. Additionally, TNF-α promotes tumor cell migration and metastases in PC models [23]. **It is unknown if TNF-α modulates AR signaling and contributes to castration resistance in men with PC.**

1.2 Preclinical Data

Recently we have started to evaluate the function of TNF-α in PC biology and have made 3 important observations that suggest that TNF-α could be a key driver of AR-targeted therapy resistance and worthy of clinical investigation:

1. **High circulating TNF-α levels associate with prostate cancer progression and may be a negative predictive biomarker to hormone therapy in PC.** We, and others, have shown that high TNF-α levels are associated with PC disease progression, failure to respond to AR antagonists, and mortality [24–27]. In a longitudinal assessment of serum cytokines in men with biochemical recurrent (BCR) PC treated with intermittent ADT, we identified TNF-α as a potential negative predictive marker to ADT treatment [24]. Patients with higher circulating TNF-α levels prior to ADT had a shorter PSA progression free survival overall despite castrate levels of testosterone (**Fig. 1).** Further, median TNF-α levels increased over a short course of ADT which is broadly consistent with the notion that innate inflammation may play a role in disease

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progression. Although hypothesis-generating, given the small sample size, we next investigated this association in two additional PC clinical datasets.

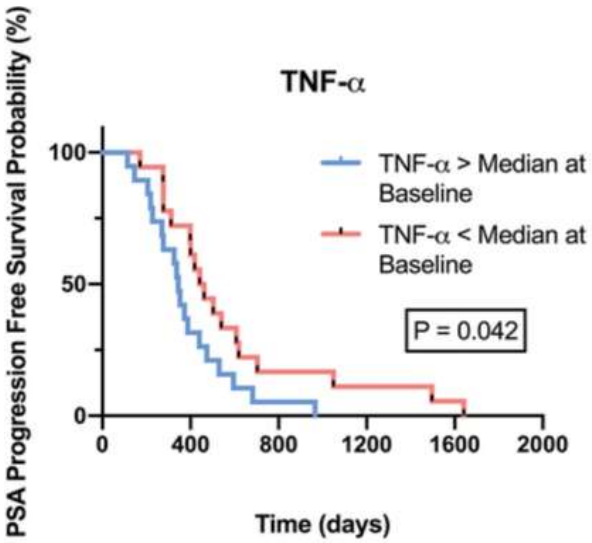


Figure 1. Elevated pre-treatment serum levels of TNF-α are associated with shorter time to PSA progression in men with BCR.

2. **<u>High protein activity of TNF-α at the transcriptomic level is associated with resistance to hormone therapy.</u>** Although the evaluation of circulating biomarkers has significant clinical utility given the ease of sample acquisition and measurement, the levels in the systemic circulation may not adequately represent protein activity in the tumor immune microenvironment. Using a public dataset of RNA sequencing from micro-dissected human PC metastases from men treated with enzalutamide (N=36) [28], we used gene expression profiles and inferred protein-based activity data using VIPER analysis to shed light on differential TNF-α activity levels between responders and non-responders, as defined as at least 50% decline in PSA (PSA50) at 12 weeks. In line with our prior findings, high TNF-α activity was associated with a failure to respond to AR antagonists (**Fig. 2**). Additionally, using single-cell RNA sequencing data, we found that the presence of CD4+ T cells in pretreatment metastases from our phase 2 study that tested ADT in combination with anti-PD-1 therapy and docetaxel in men with metastatic PC, was significantly associated with clinical non-responders (p = 0.026), defined as PSA progression by week 28 on treatment (**Fig. 3**). TNF-α was among the top three most differentially active proteins in the CD4+ T cell cluster and further supports the notion that TNF-α may be influencing resistance to hormonal therapies in the tumor microenvironment.

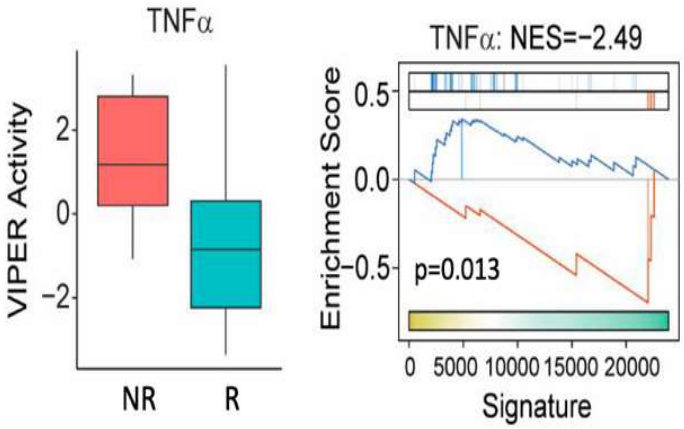


Figure 2. Boxplot indicates the TNF-α activity differences between non-responders (NR) and responders (R). Normalized Enrichment Score for the TNF-α signature in responders and non-responders to enzalutamide.

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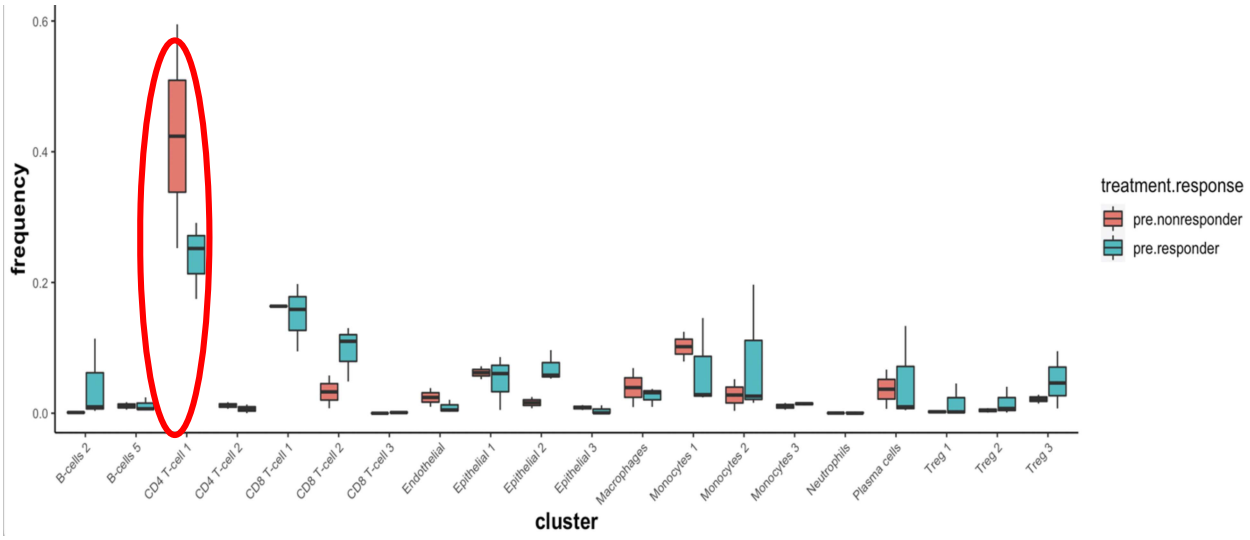


Figure 3. Boxplots compare cluster frequencies from pre-treatment metastatic prostate cancer biopsies between responders (aqua) and non-responders (red) in men treated with ADT, anti-PD-1 antibody, and docetaxel using single-cell RNA sequencing. TNF-α is one of the top three most differentially active proteins in CD4 T-cell 1 cluster (red circle).

3. TNF-α induces AR signaling and increases growth even in the presence of AR antagonists.

Our group recently showed that TNF-α induces AR signaling and increases PC cell colonies, even in the presence of AR antagonists (**Fig. 4A)**. However, inhibition of TNF-α signaling (e.g., Enbrel) subsequently rescued and even enhanced the activity of AR antagonists (**Fig. 4B)**. Finally, we demonstrated *in vivo* that genetic ablation of TNF-α signaling indeed delays tumor progression in Myc-CaP murine models (**Fig. 4C)**. Taken together, these data show that the addition of TNF-α blockade to AR antagonists is a rational approach that may increase duration of response and improve efficacy of AR antagonists.

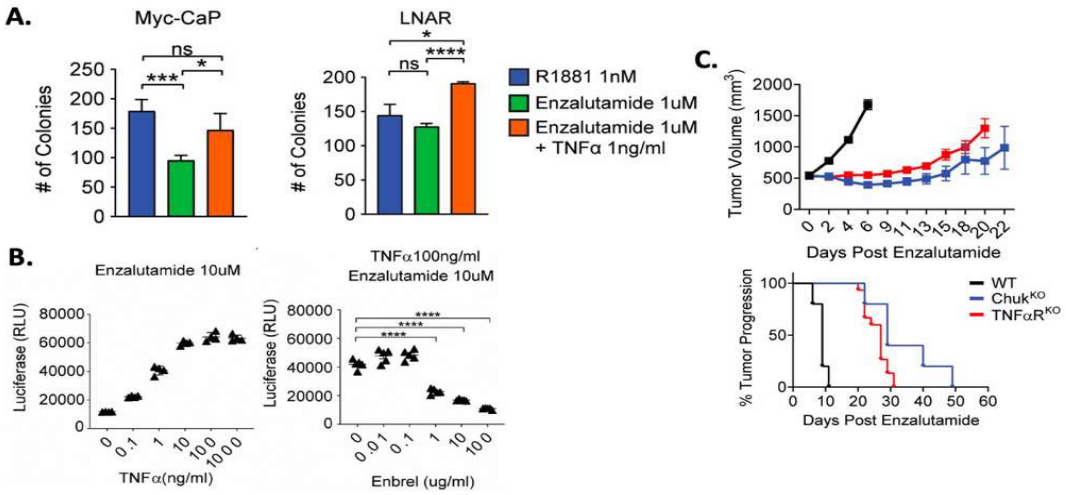


Figure 4. A) Number of colonies 16 and 21 days following in murine Myc-CaP prostate cancer cells and human LNAR prostate cancer cells. **B)** Pharmacological inhibition of TNF-α signaling (Enbrel) rescues Enzalutamide ability to inhibit androgen signaling in LNAR cells. **C)** Tumor growth and progression curve for WT, Chuk^{ko} (down regulation of NF-κB signaling) and TNF-αR^{ko} (TNFRSF1A^{ko}) in Myc-CaP tumors.

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1.3 Golimumab Clinical Data

Select information below was extracted from SIMPONI (golimumab) Investigator's Brochure – Edition 23. Please refer to it for further details.

Golimumab (CNTO 148) is a human mAb that binds to human TNFα. The drug substance is manufactured under current Good Manufacturing Practice guidelines. The Sponsor performs quality control testing for release of both the purified drug substance and the final drug product.

Based on the preclinical toxicology studies performed with golimumab, it has been considered safe to conduct clinical studies with golimumab in humans.

Golimumab is being or has been studied in the following clinical indications: RA, PsA, AS, nr-axSpA, sarcoidosis, uveitis, and asthma in adults; UC and T1D in adults and children; and pJIA in children. Development of golimumab in sarcoidosis, uveitis, and asthma in adults, and in T1D has been discontinued.

The international birth date for golimumab is 07 April 2009, based on first approval in Canada. As of 06 April 2022, golimumab is approved for SC administration in over 100 countries/territories globally, including the US, the EU, and Canada, for treatment of 1 or more of the following indications in adults: RA, PsA, AS, nr-axSpA, and UC. Golimumab for SC administration is also approved for use in children with pJIA in 74 countries/territories including the EU.

The status of the interventional studies as of 06 April 2022 are summarized below. A completed clinical study is defined as a study for which a final clinical study report (CSR) is available.

- The following clinical studies are complete:
    - 5 Phase 1 studies in adult RA participants with IV administration (C0466T01), SC administration (C0466T02, JNS012-JPN-01 and JNS012-JPN-02), and SC/IV administration (C0524T14)
    - 6 Phase 1 studies in healthy adult participants with SC or SC/IV administration (C0524T13, C0524T23, C0524T24, C0524T15, C0524T30, CNTO148NAP1001)
    - Phase 1b study in children, adolescents, and young adults with pre-symptomatic (Stage 2) T1D with SC administration (CNTO148DML1001)
    - Phase 1/2a study in adult uveitis participants with SC administration (C0524T01)
    - Phase 2 study in adult sarcoidosis participants with SC administration (1275148SCD2001)
    - Phase 2a study in adult UC participants with SC administration (CNTO148UCO2001)
    - Phase 2a study in children and young adults with new onset (Stage 3) T1D with SC administration (CNTO148DML2001)
    - Phase 2b study in adult RA participants with SC administration (C0524T02)
    - Phase 2b study in adult participants with severe, persistent asthma with SC administration (C0524T03)
    - 2 Phase 2/3 studies in adult RA participants in Japan with SC administration (JNS012-JPN-03, JNS012-JPN-04)
    - Phase 2/3 study in adult UC participants with IV administration (C0524T16)
    - Phase 2/3 study in adult UC participants with SC administration (C0524T17)
    - Phase 3 study in adult UC participants with SC administration (C0524T18)
    - Phase 3 study in adult UC participants with SC administration (CNTO148UCO3001 [Japanese UC participants])

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- 4 Phase 3 studies in adult RA participants with SC administration (C0524T05, C0524T06, C0524T11, C0524T28 [Chinese RA participants])
- 2 Phase 3 studies in adult RA participants with IV administration (C0524T12, CNTO148ART3001)
- Phase 3b study in adult RA participants with IV/SC administration (CNTO148ART3002)
- Phase 3b study in adult RA participants with IV administration (CNTO148ART3003)
- Phase 3 study in adult PsA participants with SC administration (C0524T08)
- Phase 3 study in adult PsA participants with IV administration (CNTO148PSA3001)
- 2 Phase 3 studies in adult AS participants with SC administration (C0524T09, C0524T29 [Chinese AS participants])
- Phase 3 study in adult AS participants with IV administration (CNTO148AKS3001)
- Phase 3 study in pediatric pJIA participants with SC administration (CNTO148JIA3001)
- Phase 3b study in adult RA participants with IV/SC administration (P06129)
- Phase 3b study in adult nr-axSpA participants with SC administration (P07642 [MK-8259-006])
- Phase 4 study in adult UC participants with SC administration (MK-8259-027)
- Phase 4 study in adult UC participants with SC administration (MK 8259-022)
- Phase 4 study in adult AS participants with SC administration (MK-8259-012)
- Phase 4 study in adult UC participants with SC administration (MK-8259-032)
- Phase 4 study in adult nr-axSpA participants with SC administration (MK-8259-038)

Several additional clinical studies are ongoing as per Golimumab Investigator Brochure (May 2022). An ongoing clinical study is defined as a study in which enrollment has begun, whether a hold is in place or analysis is complete, but without a final CSR available.

1.3.1. Golimumab Efficacy

The efficacy of golimumab (Simponi) has been tested across a variety of rheumatologic conditions with and without other biologic agents. Golimumab is currently FDA-approved for the treatment in combination with methotrexate in adult patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis alone or in combination with methotrexate for adult patients with active psoriatic arthritis, and in ankylosing spondylitis for adult patients.

Rheumatoid Arthritis

The efficacy and safety of golimumab were evaluated in 3 multicenter, randomized, double-blind, controlled trials (Studies RA-1, RA-2, and RA-3) in 1542 patients ≥ 18 years of age with moderately to active RA, diagnosed according to the American College of Rheumatology (ACR) criteria, for at least 3 months prior to administration of study agent. Patients were required to have at least 4 swollen and 4 tender joints. Golimumab was administered subcutaneously at doses of 50 mg or 100 mg every 4 weeks. Double-blinded controlled efficacy data were collected and analyzed through Week 24. Patients were allowed to continue stable doses of concomitant low dose corticosteroids (equivalent to ≤ 10 mg of prednisone a day) and/or NSAIDs and patients may have received oral MTX during the trials.
Study RA-1 evaluated 445 patients who were previously treated (at least 8 to 12 weeks prior to administration of study agent) with one or more doses of a biologic TNF-blocker without a serious adverse reaction. Patients may have discontinued the biologic TNF-blocker for a variety of reasons. Patients were randomized to receive placebo (n = 150), golimumab 50 mg (n = 147), or golimumab 100 mg (n = 148). Patients were allowed to continue stable doses of concomitant MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) during the trial. The use of other DMARDs including cytotoxic agents or other biologics was prohibited.

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Study RA-2 evaluated 444 patients who had active RA despite a stable dose of at least 15 mg/week of MTX and who had not been previously treated with a biologic TNF-blocker. Patients were randomized to receive background MTX (n = 133), golimumab 50mg (n = 147) + background MTX (n = 89), or golimumab 100 mg monotherapy (n = 133). The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited.

RA-3 evaluated 637 patients with active RA who were MTX-naïve and had not previously been treated with a biologic TNF-blocker. Patients were randomized to receive MTX (n = 160), SIMPONI 50 mg + MTX (n = 159), SIMP aNI 100 mg + MTX (n = 159), or SIMPONI 100 mg monotherapy (n = 159). For patients receiving MTX, MTX was administered at a dose of 10 mg/week beginning at Week 0 and increased to 20 mg/week by Week 8. The use of other DMARDs including SSZ, HCQ, cytotoxic agents, or other biologics was prohibited.

The primary endpoint in Study RA-1 and Study RA-2 was the percentage of patients achieving an ACR 20 response at Week 14 and the primary endpoint in Study RA-3 was the percentage of patients achieving an ACR 50 response at Week 24.

In Studies RA-1, RA-2, and RA-3, the median duration of RA disease was 9.4, 5.7, and 1.2 years; and 99%, 75%, and 54% of the patients used at least one DMARD in the past, respectively. Approximately 77% and 57% of patients received concomitant NSAIDs and low dose corticosteroids, respectively, in the 3 pooled RA trials.

Clinical Response

In the 3 RA trials, a greater percentage of patients treated with the combination of golimumab and MTX achieved ACR responses at Week 14 (Studies RA-1 and RA-2) and Week 24 (Studies RA-1, RA-2, and RA-3) versus patients treated with the MTX alone. There was no clear evidence of improved ACR response with the higher golimumab dose group (100 mg) compared to the lower golimumab dose group (50 mg). In Studies RA-2 and RA-3, the golimumab monotherapy groups were not statistically different from the MTX monotherapy groups in ACR responses. In the subset of patients who received golimumab in combination with MTX in Study RA-1, the proportion of patients achieving ACR 20, 50 and 70 responses at week 14 were 40%, 18%, and 12%, respectively, in the golimumab 50 mg + MTX group (N = 101) compared with 17%,6%, and 2%, respectively, in the placebo + MTX group (N = 103). ACR 20 responses were observed in 38% of patients in the golimumab 50 mg + MTX group at the first assessment (Week 4) after the initial golimumab administration.

Please refer to FDA Package Insert:
(https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125289s0064lbl.pdf) for details on clinical activity and efficacy for details in psoriatic arthritis (section 14.2) and ankylosing spondylitis (section 14.3).

1.3.2 Golimumab Safety

The frequencies of adverse drug reactions observed in Phase 2 and 3 clinical studies (C0524T02, C0524T05, C0524T06, C0524T11, C0524T28, C0524T12, CNTO148ART3001, C0524T08, CNTO148PSA3001, C0524T09, C0524T29, CNTO148AKS3001, C0524T16, C0524T17, C0524T18, C0524T03, P07642 [MK-8259-006]) from 6381 adult golimumab-treated participants are summarized below. In pooled analyses for 6381 adult subjects who received golimumab, fatal Serious Adverse Reactions occurred in < 0.1% of subjects due to septic shock (N=4).

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Table 1. Summary of Golimumab Adverse Drug Reactions in Clinical Studies and from Post-marketing Use.

Infections and infestations	
Very common:	Upper respiratory tract infection (nasopharyngitis, pharyngitis, laryngitis, and rhinitis)
Common:	Bacterial infections (such as cellulitis), lower respiratory tract infection (pneumonia), viral infections (such as influenza and herpes), bronchitis, sinusitis, superficial fungal infections, abscess
Uncommon:	Sepsis including septic shock, pyelonephritis
Rare:	Histoplasmosis, coccidioidomycosis, tuberculosis, opportunistic infections (invasive fungal infections, bacterial, atypical mycobacterial and protozoal), hepatitis B reactivation, pneumocystosis, arthritis bacterial, bursitis infective
Neoplasms benign and malignant	
Rare:	Lymphoma, leukemia, melanoma*, Merkel cell carcinoma*
Not known:	Hepatosplenic T-cell lymphoma**, pediatric malignancy
Investigations	
Common:	Alanine aminotransferase increased, aspartate aminotransferase increased
Uncommon:	Neutrophil count decreased
Blood and lymphatic system disorders	
Common:	Leukopenia (including neutropenia), anemia
Uncommon:	Thrombocytopenia, pancytopenia
Immune system disorders	
Common:	Autoantibody positive, non-serious allergic reactions
Rare:	Serious systemic hypersensitivity reactions (including anaphylactic reaction)*, sarcoidosis*
Nervous system disorders	
Common:	Dizziness, paraesthesia
Rare:	Demyelinating disorders (central and peripheral)
Cardiac disorders	
Rare:	Congestive heart failure (new onset or worsening)
Vascular disorders	
Common:	Hypertension
Rare:	Vasculitis (systemic)
Respiratory, thoracic, and mediastinal disorders	
Uncommon:	Interstitial lung disease
Gastrointestinal disorders	
Uncommon:	Constipation
Skin and subcutaneous tissue disorders	
Common:	Rash, alopecia
Uncommon:	Bullous skin reactions*, psoriasis: new onset or worsening palmar/plantar, and pustular
Rare:	Vasculitis (cutaneous), skin exfoliation*, lichenoid reactions*
Musculoskeletal and connective tissue disorders	
Rare:	Lupus-like syndrome
General disorders and administration site conditions	
Common:	Pyrexia, injection site reaction (injection site erythema, urticaria, induration, pain, bruising, pruritus, irritation, paraesthesia), infusion-related reaction*

The preferred terms presented in this table are based on the ADR terms presented in the CCDS.

* Reported from postmarketing experience with golimumab

** Observed with other TNF-blocking agents

No new ADRs were reported (1) in the interim analysis at Week 54 for study CNTO148UCO3003 (MedDRA v26.1), and (2) in the final analysis for study CNTO148JIA3003 (MedDRA v27.0).

Datasets reported from previously completed clinical studies C0524T02, C0524T05, C0524T06, C0524T11, C0524T28, C0524T12, CNTO148ART3001, C0524T08,CNTO148PSA3001,C0524T09, C0524T29, and CNTO148AKS3001, C0524T16, C0524T17, C0524T18, C0524T03, P07642 [MK-8259-006].

Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (< 1/10,000, including isolated reports), and Not Known (cannot be estimated from available data)

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1.4 Golimumab Nonclinical Data and Pharmacokinetics

1.4.1. Product Identification

Golimumab (CNTO 148) is a human mAb that binds to human TNFα. The drug substance is manufactured under current Good Manufacturing Practice guidelines. The Sponsor performs quality control testing for release of both the purified drug substance and the final drug product.

1.4.2. Physical and Chemical Characteristics

Golimumab is a mAb with a molecular weight of approximately 149,802 to 151,064 daltons. Golimumab binds TNFα with high affinity. Golimumab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα to its receptors.

1.4.3. Formulation Information

The formulation currently used in subcutaneous (SC) clinical studies is supplied as a 50 mg/0.5 mL sterile liquid in a single-use pre-filled syringe (PFS) for SC administration. Each PFS contains 50 mg (0.5 mL fill of liquid) of golimumab, in addition to histidine, sorbitol, polysorbate 80, and water-for-injection (WFI) at pH 5.5. No preservative is present.

The needle cover on the PFS contains dry natural rubber (a derivative of latex).

Detailed information on dose preparation, handling, and storage conditions will accompany the clinical drug supplies to the clinical study site. The storage conditions and expiry will be indicated on the label of the product.

1.4.4. Single dose Pharmacokinetics

The PK characteristics of golimumab are consistent with those of other IgG-based therapeutic mAbs. The following sections describe the PK of golimumab after a single dose.

- Absorption

  Following a single SC administration of golimumab to healthy participants or participants with RA, the time to reach maximum serum concentrations (tmax) ranged from 2 to 6 days. An SC injection of 50 mg golimumab to healthy participants produced a mean ± standard deviation (SD) Cmax of 3.2 ±1.4 µg/mL. Both Cmax and AUC increased proportionally with doses over the range of 50 to 400 mg following a single SC administration.

  Following a single SC injection of 100 mg in healthy participants, the absorption of golimumab was similar in the upper arm, abdomen, and thigh, with a mean absolute bioavailability of 51%. Since golimumab exhibited approximately dose-proportional PK following SC administration, the absolute bioavailability of a golimumab 50 mg or 200 mg dose is expected to be like the 100 mg dose. Golimumab exhibited similar PK profiles and variability following a single SC administration when delivered by either the needle and syringe or the autoinjector.

  This trial will utilize the 50mg single-dose prefilled syringes supplied by Janssen.

- Metabolism

  Since golimumab is an IgGk mAb, the in vitro or ex vivo experiments typically used to assess the metabolism or PK properties of small molecular weight compounds were not applicable to this molecule. Golimumab is presumably metabolized by degradation into small peptides and amino acids via catabolic pathways and eliminated in a similar manner as any other endogenous IgG.

1.4.5. Multiple Dose Pharmacokinetics

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Serum concentration-time profiles of golimumab were generally predictable after single or multiple SC administrations.

When 50 mg golimumab was administered SC to participants with RA, PsA, or AS every 4 weeks (q4w), serum concentrations reached steady state by Week 12. Trough serum golimumab concentration data through Week 256 in the 5 Phase 3 studies of RA, PsA, and AS indicated that serum golimumab concentrations were generally maintained over time and corresponded to the maintenance of clinical response in these studies.

- Use in renal/hepatic dysfunction/failure
  No PK data are available in participants with impaired renal or hepatic function. Since renal excretion and hepatic enzyme-mediated metabolism of intact golimumab are unlikely to represent major elimination pathways variations in renal and hepatic function are not expected to affect the elimination of golimumab.

1.4.6. Interactions
Specific drug interaction studies have not been conducted with golimumab.
Live vaccines and/or therapeutic infectious agents should not be given concurrently with golimumab.

1.5 Dose Rationale

Golimumab 50mg SC monthly, up to six doses, will be used in this study.

In other studies, steady state of golimumab was achieved at this same dose and route after 12 weeks of treatment. Anticipated PSA response would occur within this six-month window compared to the historical control ARN-509-001 (NCT01171898). ARN-509-001 reported on the activity of apalutamide in patients with mCRPC who had previously received ≥ 6 months of abiraterone acetate / prednisone exposure. This change in AR-directed therapy (from abiraterone acetate / prednisone to apalutamide) yielded a median time to PSA progression of 3.7 months and a 22% 12-week PSA response rate.

1.6 Apalutamide

Apalutamide (ARN-509) works through competitive AR inhibition and, unlike the older anti-androgens (e.g., bicalutamide, nilutamide), is a pure AR antagonist. It additionally can prevent AR nuclear translocation and DNA binding to nuclear response elements [29].

Based on the results from the randomized SPARTAN Study (ARN-509-003) that showed the addition of apalutamide to ongoing ADT was superior to ADT alone in delaying time to distant metastases[30,31] apalutamide was approved in 2018 in multiple countries for the treatment of men with non-metastatic castration-resistant prostate cancer (nmCRPC). Based on the results of the randomized TITAN Study (5602192PCR3002) that showed the addition of apalutamide to ongoing ADT was superior to ADT alone in improving overall survival (OS) and radiographic progression-free survival (rPFS), apalutamide was approved in multiple countries for the treatment of men with metastatic castration-sensitive prostate cancer (mCSPC; also known as metastatic hormone-sensitive prostate cancer [mHSPC]) [32]. Apalutamide is currently being developed for other indications in prostate cancer.

The therapeutic dose was selected to be 240 mg/day given orally based on an integrated approach. This dose and schedule have been tested in 5 randomized placebo-controlled Phase 3 studies (ARN-509-003, 56021927PCR3001, 56021927PCR3002, 56021927PCR3003, and 56021927PCR3011).

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The Phase 3 Study ARN-509-003 included safety data from 1,201 participants with nmCRPC who received at least 1 dose of either apalutamide or placebo (803 participants in the apalutamide arm, 398 participants in the placebo arm, and 76 participants who crossed over from placebo to apalutamide). Safety data from the crossover arm (referred to as placebo-apalutamide arm) is presented side-by-side with the apalutamide arm and placebo arm.

Table 2. Most Frequently Occurring TEAEs With Frequency of at Least 15% in any Treatment Group by Preferred Term; Safety Population (Study ARN-509-003)

	Placebo	Placebo to Apalutamide	Apalutamide
Analysis set: Safety Population	398	76	803
Subjects with 1 or more TEAEs	373 (93.7%)	68 (89.5%)	781 (97.3%)
Preferred term:			
Fatigue	85 (21.4%)	12 (15.8%)	262 (32.6%)
Hypertension	83 (20.9%)	8 (10.5%)	225 (28.0%)
Skin rash (grouped term)	25 (6.3%)	19 (25.0%)	212 (26.4%)
Diarrhea	61 (15.3%)	10 (13.2%)	187 (23.3%)
Nausea	63 (15.8%)	5 (6.6%)	157 (19.6%)
Fall (grouped term)	38 (9.5%)	8 (10.5%)	177 (22.0%)
Weight decreased	26 (6.5%)	8 (10.5%)	Weight decreased 26 (6.5%) 8 (10.5%) 157 (19.6%) 157 (19.6%)
Arthralgia	33 (8.3%)	9 (11.8%)	160 (19.9%)
Back pain	61 (15.3%)	8 (10.5%)	144 (17.9%)
Fracture (grouped term)	30 (7.5%)	7 (9.2%)	145 (18.1%)
Hot flush	34 (8.5%)	7 (9.2%)	122 (15.2%)

Note: Percent is based on the Safety population.
Note: TEAEs are those that occurred between the date of first dose of study drug and date of last dose of study drug plus 30 days. For each preferred term, participants are counted only once, even if they experienced multiple events in that preferred term.

Refer to Apalutamide's FDA label for additional pharmacology and clinical data.

1.7 Risks/Benefits

Apalutamide is a commonly used medicine in the treatment of men with advanced prostate cancer and presents no additional risk to subjects beyond the standard of care. Golimumab is considered experimental in this setting and has the potential for exposing subjects to an increased risk of infection or laboratory abnormalities such as increased aminotransferases or cytopenia (refer Table 1.3.2.). However, if disruption of TNF-α signaling with a human monoclonal antibody can sensitize PC cells to AR antagonism demonstrates efficacy, then this treatment combination may have a long-lasting biologic effect and improve patient outcomes.

2.0 OVERVIEW OF CLINICAL TRIAL

Many of the treatments for CRPC are directed at suppressing AR-signaling axis. While AR-directed therapies are initially effective, resistance inevitability occurs. Median overall survival at this advanced stage of disease varies between 1-2 years, depending on site and extent of metastatic involvement [33].

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It is well appreciated that the immune system affects cancer biology and may even play a role in mediating therapy resistance. Our preliminary studies suggest that TNF-α increases AR signaling even in the presence of AR antagonists (e.g., apalutamide), thereby driving tumor growth, progression, and treatment resistance. Disruption of TNF-α signaling with a human monoclonal antibody that inhibits biological activity of TNF-α (e.g., golimumab) may re-sensitize PC cells to AR antagonism and improve outcomes for men with CRPC.

On this basis, we are launching a single-arm phase 2 clinical trial testing the combination of apalutamide and golimumab, a TNF-α inhibitor, in men with CRPC who have progression of disease on NHT. Patients will continue with next-generation AR-directed therapy with apalutamide, to maintain suppression of AR-signaling, and golimumab will be added to their regimen. Golimumab will be dosed at the FDA-approved dose of 50mg once monthly, for up to a total of six doses. Study subjects will receive six months of golimumab and will continue apalutamide until clinical progression, radiographic progression, or intolerable toxicity. *We hypothesize that golimumab in combination with apalutamide will show clinical efficacy in men with mCRPC who have progressed on abiraterone* acetate *or enzalutamide.*

2.1 Study Objectives and Endpoints

2.1.1 Primary Objectives

Determine the clinical activity of TNF-α blockade (golimumab) and AR antagonism (apalutamide) on PSA response in subjects with CRPC after prior treatment with at least 6 months of NHT.

2.1.1.1 Primary Endpoints

- Determine the 12-week PSA50 response rate, defined by at least a 50% decline in PSA from baseline, in subjects with CRPC after combination treatment with TNF-α blockade (golimumab) and AR antagonism (apalutamide).

2.1.2 Secondary Objectives

Determine the clinical activity of TNF-α blockade (golimumab) and AR antagonism (apalutamide) on radiographic, serologic, and time-to-event parameters in subjects with CRPC after prior treatment with at least 6 months of NHT.

2.1.2.1 Secondary Endpoints

- Determine objective response rate of measurable or evaluable disease as per RECIST v1.1 criteria for soft tissue metastases
- Determine the radiographic PFS in patients using RECIST v1.1 criteria for soft tissue metastases and PCWG3 criteria for bone metastases.
- Determine PSA PFS with PSA progression defined by an increase in PSA greater than 25% and >2 ng/ml above nadir and confirmed by progression at 2 timepoints at least 3 weeks apart.
- PSA kinetics using PSA Doubling Time (PSA DT) will be determined at time of confirmatory PSA progression.
- Determine time to subsequent antineoplastic therapy.
- Assess the incidence and severity of adverse events according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2.1.3 Planned Exploratory Objectives

Correlative work will be performed to determine biomarkers predictive of response to combination therapy and deconvolute changes in the tumor microenvironment as well as AR-activity scores. Examples of correlative work may include, but will not be limited to:

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1) Identify proinflammatory cytokine signatures that are associated with response and resistance to treatment with TNF-α blockade and AR antagonists using peripheral and intra-tumoral cytokine concentrations.
2) Identify tumor AR-signatures that are associated with response and resistance to treatment with TNF-α blockade and AR antagonists using Digital Spatial Profiling from metastatic tumor biopsies.
3) Identify lymphocyte AR-signatures that are associated with response and resistance to treatment with TNF-α blockade and AR antagonists using Digital Spatial Profiling (DSP) expression measurements of AR-regulated genes from metastatic tumor biopsies.
4) Characterize the change in AR-activity scores within tumor cells and lymphocytes comparing pre-treatment DSP assessments to those determined while on-treatment.
5) Validate the above DSP data using Immunohistochemistry (IHC).
6) Next-generation sequencing of pre-treatment tumor biopsies and cell-free circulating tumor DNA (ctDNA) to identify genomic alterations correlating with response or resistance to treatment.

2.2 Study Design

This will be a single-center, single-arm phase 2 clinical trial testing the combination of apalutamide and golimumab, a TNF-α inhibitor, in men with mCRPC who have previously progressed on at least 6 months of prior NHT (abiraterone, enzalutamide, darolutamide, or apalutamide). Eligible patients must have CRPC (defined as disease progression despite a castrate serum testosterone [≤ 50/ng/dl]) and evidence of evaluable or measurable disease to enroll. Eligible patients must have documented progressive metastatic CRPC (PSA progression, soft tissue disease progression, or bone disease progression) on NHT. One prior line of taxane chemotherapy is allowed.

Eligible patients will complete trial registration and enrollment and undergo a baseline metastatic tumor biopsy when safe and feasible. Given that the patient population will be castrate-resistant, it is recommended that patients undergo a baseline metastatic biopsy prior to treatment to rule out treatment-emergent neuroendocrine / small cell variant prostate cancer. Furthermore, baseline tumor biopsies will serve as an internal control for correlative translational science and biomarker development. Subjects will then start apalutamide at the FDA approved dose (240mg PO daily), to maintain suppression of AR-signaling (see Appendix D: pill diary), and golimumab will be added to their regimen. Golimumab will be administered at 50mg subcutaneously once every four weeks for six months or until radiographic progression, intolerable toxicity whichever comes first. Study subjects will continue apalutamide until radiographic progression, intolerable toxicity, whichever comes first. If not surgically castrated, participants must be maintained on an LHRH agonist/antagonist (e.g., leuprolide, degarelix).

The primary objective will be to determine the 12-week PSA50 response rate, defined by at least a 50% decline in PSA from baseline, in subjects with CRPC after combination treatment with TNF-α blockade (golimumab) and AR antagonism (apalutamide). The 12-week PSA50 will be assessed 12 weeks after the initiation of golimumab. If a patient drops out of the study prior to 12-week PSA check, they will be considered a non-responder for the purposes of the primary analysis; however, an additional subject will be accrued to account for early dropouts. Patients with metastatic lesions visible after 12 weeks of therapy will undergo a second metastatic tumor biopsy, if feasible, for correlative science and biomarker development. Key secondary objectives will include determining objective response rate of measurable or evaluable disease as per RECIST v1.1 criteria for soft tissue metastases and Prostate Cancer Working Group 3 (PCWG3) criteria for bone metastases; radiographic

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progression free survival (PFS); PSA PFS; time to subsequent therapy; and the incidence and severity of adverse events according to National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

This study will also include several correlative studies aimed at identifying candidate biomarkers for response/resistance to TNF-α blockade. We will plan to obtain pre- and on-treatment biopsies as well as serial blood samples to develop blood-based biomarkers for response/resistance to combination therapy. Given our rapidly evolving understanding of prostate cancer biology, it is impossible to prospectively define all the relevant biomarkers for the patient population enrolled on this study. Examples of the studies to be conducted may include but will not be limited to the following. Quantification of longitudinal serum and intra-tumoral cytokine quantification to determine association with clinical outcomes and identify subset of patients that most benefit from treatment. Transcriptional profiling studies using DSP and subsequent cellular identification in both baseline and on-treatment samples to assess activation of the core AR- and TNF-α-signaling programs with treatment and to determine if TNF-α indeed modulates AR signaling in tumor cells and lymphocytes. Next-generation sequencing to assess for tumor mutational burden or homologous recombination deficiencies (HRD) that may associate with response/resistance to combination treatment. Collectively, this information will be used to develop a gene expression *response-signature*, which will be assessed in blood samples using cf-DNA.

2.3 Estimated Accrual

The phase 2 study is designed with a sample size of 31 patients. Accounting for 10% dropout, we will therefore plan to enroll 34 patients to the study (see section 15.0 'Statistical Considerations').

3.0 INCLUSION AND RECRUITMENT

3.1 Eligibility of Women and Minorities

Individuals of biologic male sex with prostates from any gender, race, or ethnicity are eligible for this study.

3.2 Recruitment of Minority Groups

The study recruitment strategy aims to achieve representation of minority groups that reflects the demographics of the affected population in the catchment area.

3.3 Inclusion Across the Lifespan

The study design and recruitment strategy aim to achieve representation of age groups that reflect the demographics of the affected population. Individuals ages 18 and over are eligible for this study.

3.4 Study Population

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: 34			
Ethnic Category	Sex		
	Females	Males	Total
Hispanic or Latino		6	6
Not Hispanic or Latino		28	28
Ethnic Category Total of All Subjects*			34

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Racial Categories			
American Indian / Alaska Native		2	2
Asian		2	2
Native Hawaiian or Other Pacific Islander		1	1
Black or African American		4	4
White		21	21
More Than One Race		4	4
Racial Categories: Total of All Subjects*			34

4.0 STUDY AGENT(S)

4.1 Golimumab

Study agent is a drug that works by targeting neutralizing the biological activity of TNF-α by binding with high affinity to the soluble and transmembrane forms of TNF-α and inhibits binding of TNFα to its receptors. It is manufactured by Janssen.

4.1.1 Golimumab will be provided by Janssen.

4.1.2 Golimumab will be stored in commercially approved single-use 0.5 mL pre-filled syringes (PFS) with histidine, sorbitol, polysorbate 80, and water-for-injection (WFI) at pH 5.5. No preservative in present. Detailed information on dose preparation, handling, and storage conditions will accompany the clinical drug supplies to the clinical study site. The storage conditions and expiry will be indicated on the label of the product.

4.2 Apalutamide

Apalutamide is an FDA-approved product that will be provided by Janssen Scientific Affairs, LLC.

4.2.1 Agent will be obtained as investigational agent handled according to the package insert.

4.3 LHRH analogues (e.g., leuprolide, Eligard, degarelix, relugolix, goserelin, etc.)

LHRH analogues are FDA-approved products that will be obtained through the commercial pharmacy and billed to subject's insurance.

4.3.1 Agent(s) will be obtained as standard of care and handled according to the package insert.

5.0 SUBJECT ELIGIBILITY

5.1 Inclusion Criteria

5.1.1 History of histologically diagnosed prostatic adenocarcinoma.

5.1.2 Participants must have progressed on no more than one novel hormonal therapy (NHT) by PSA or radiographic criteria (per PCWG3 or RECIST v1.1) and a castrate serum testosterone level (i.e., ≤50ng/dL). If progressive disease by radiographic criteria, PSA must be ≥ 2ng/ml. PSA progression will be defined as at least two successive PSA rises above the nadir, separated by ≥ 1 week, with the last determination having a value of ≥ 2 ng/mL. NHTs include but are not limited to either abiraterone, enzalutamide, darolutamide, or

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apalutamide. (Biosimilar or generic agents may be allowed at the discretion of the PI.)
Note: prior NHT exposure that did not result in disease progression will not be counted as prior line, i.e., patient's that completed prior abiraterone course in the localized setting, patients that changed NHT due to toxicity or financial toxicity.

5.1.3 Participants may have received one prior line of taxane chemotherapy in any setting

5.1.4 Participants must be ≥ 18 years of age prior to signing informed consent.

5.1.5 ECOG performance status score ≤2.

5.1.6 Clinical and laboratory values at screening.

a) Hemoglobin ≥9.0 g/dL, independent of transfusion and/or growth factors within 3 months prior to randomization

b) Platelet count ≥100,000 x 10^9/μL independent of transfusion and/or growth factors within 3 months prior to randomization

c) Absolute neutrophil count ≥1.5 x 10^3/mL

d) Serum albumin ≥3.0 g/dL

e) Serum creatinine ≤ 1.5 mg/dL.

f) Serum potassium ≥3.5 mmol/L

g) Serum total bilirubin <1.5 × ULN (Note: In subjects with Gilbert's syndrome, if total bilirubin is >1.5 × ULN, measure direct and indirect bilirubin and if direct bilirubin is ≤1.5 × ULN, subject may be eligible)

h) Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase ≤1.5 × ULN

5.1.7 Agrees to use a condom (even men with vasectomies) and another effective method of birth control if he is having sex with a woman of childbearing potential or agrees to use a condom if he is having sex with a woman who is pregnant while on study drug and for 3 months following the last dose of study drug. Must also agree not to donate sperm during the study and for 3 months after receiving the last dose of study drug.

5.1.8 Medications known to lower the seizure threshold (see list under prohibited meds) must be discontinued or substituted at least 4 weeks prior to study entry.

5.1.9 Have had no known recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation.

5.1.10 Participants must sign an informed consent form (ICF) indicating that they understand the purpose of, and procedures required for, the study and are willing to participate in the study.

5.2 Exclusion Criteria

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5.2.1 Subjects may not be receiving other investigational agents within 14 days prior to enrollment.

5.2.2 Subjects with predominant small cell or neuroendocrine variant prostate cancer on most recent standard of care biopsy.

5.2.3 Evidence of serious and/or unstable pre-existing medical, psychiatric or other condition that could interfere with patient safety.

5.2.4 Symptomatic central nervous system (CNS) metastases. Treated CNS metastases will be allowed if these are stable for at least 8 weeks prior to enrollment.

5.2.5 Uncontrolled or active infection, including:

a. Hepatitis B infection (acute or chronic) as defined according to the American Society of Clinical Oncology guidelines, or hepatitis C infection (anti-hepatitis C virus [HCV] antibody positive and HCV-RNA quantitation positive).
b. Recent serious infection (e.g., requiring IV antibiotics or hospitalization within last two months)
c. Herpes zoster infection within 2 months of screening
d. History of active granulomatous infection, including histoplasmosis, or coccidioidomycosis
e. HIV (HIV antibody positive)
f. Active or untreated latent tuberculosis
g. History of infected joint prosthesis or received antibiotics for suspected infection of a joint prosthesis in the past five years, if that prosthesis has not been removed or replaced.
h. Less serious infections (e.g., acute upper respiratory tract infection, simple urinary tract infection) need not be considered exclusionary at the discretion of the investigator.

5.2.6 Has impaired wound healing capacity defined as current skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions.

5.2.7 Major surgery within 2 weeks of the first dose, or will not have fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 2 weeks after the last dose of study drug administration (Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate.)

5.2.8 Co-administration of other TNF-α inhibitors or disease-modifying anti-rheumatic drugs (DMARDS) for the treatment of rheumatoid arthritis or other rheumatologic condition. (Note: prior exposure to TNF-α inhibitors is allowed for non-rheumatologic disease (e.g., SARS-CoV-2) if washout period > 5 half-lives prior to study enrollment.)

5.2.9 Any other issue that would impair the ability of the subject to receive or tolerate the planned treatment at the investigational site, to understand informed consent or any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g., compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

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5.2.10 Presence of significant cardiovascular disease including NYHA class II-IV heart failure, uncontrolled arrhythmia, MI or stroke within 6 months.

5.2.11 History of autoimmune disorder, including multiple sclerosis or optic neuritis, lupus or lupus-like Syndrome

5.2.12 Hypersensitivity to any biologics or known allergies or clinically significant reactions to murine, chimeric, or human proteins, mAbs, or antibody fragments.

5.2.13 Have a transplanted organ (with the exception of a corneal transplant performed > 3 months prior to first administration of study drug).

5.2.14 Currently has a malignancy or a history of malignancy within 3 years before screening (with the exception of prostate cancer, treated superficial bladder cancer, or a nonmelanoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months prior to the administration of the first study intervention

5.2.15 Immune deficiency syndrome (e.g., severe combined immunodeficiency syndrome [SCIDS], T cell deficiency syndromes, B cell deficiency syndromes, and chronic granulomatous disease)

5.2.16 Have had a Bacille Calmette-Guerin (BCG) vaccination within 12 months of screening. Patients must agree not to receive BCG vaccination during the study and within 16 weeks after the last administration of study intervention.

5.2.17 Known allergies, hypersensitivity, or intolerance to apalutamide or its excipients (refer to the Investigator's Brochure)

5.2.18 Gastrointestinal disorder affecting absorption.

5.2.19 History of seizure or any condition that in the opinion of the investigator may predispose to seizure or treatment with drugs known to lower the seizure threshold within 4 weeks prior to starting treatment with apalutamide.

6.0 SUBJECT REGISTRATION

Subjects will be registered by the Fred Hutch/UW Study Coordinator and entered in the Clinical Trial Management System (CTMS, OnCore). A complete, signed study consent and HIPAA authorization are required for registration.

Signed ICFs must remain in each subject's chart and must be available for verification by monitors or regulatory agencies at any time.

7.0 TREATMENT PLAN

7.1 Treatment Plan Overview

Phase 2 TRAMP: Tumor Necrosis Factor- α Blockade and AR Inhibition in Men with CRPC

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Patients with CRPC and disease progression after at least 6 months NHT (with or without chemotherapy) in the hormone-sensitive setting

↓

REGISTRATION

↓

Metastatic tumor biopsy (baseline)

↓

Begin treatment with apalutamide 240mg PO daily and
golimumab 50mg SC q4weeks x 6 doses with
continuous LHRH analogues

↓

Metastatic tumor biopsy 12 weeks after treatment initiation

Outline Treatment Schedule	
Day	***Treatment***
1	*Golimumab (50mg SC q4weeks)*
1 and every day thereafter until EOT	*Apalutamide (240 mg p.o. daily)*
28 (+/- 4 days) and every 28 days thereafter	*Golimumab (50mg SC q4weeks)*

7.2 Administration of Golimumab

Golimumab 50mg SC q4weeks will be administered for up to six doses.

(Note: Apalutamide 240mg PO every day will be self-administered by subjects at home. All participants will continue LHRH analogues, if not surgically castrated, according to their dosing schedule.)

7.3 Concomitant Medication and Supportive Care Guidelines

7.3.1. Golimumab

Specific drug compatibility studies have not been conducted with golimumab. However, serious infections and neutropenia were seen in clinical studies with concurrent use of anakinra, abatacept, and other biological therapeutics used to treat the same rheumatologic conditions as golimumab and is not recommended.

Participants treated with golimumab may receive concurrent vaccinations, **except for live vaccines**. Use of live vaccines could result in clinical infections, including disseminated infections. For study participants receiving a locally approved (and including emergency use-authorized) COVID-19 vaccine, to help identify acute reactions potentially related to COVID-19

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vaccines, it is recommended where possible that vaccine and study drug be administered on different days, separated by as large an interval as is practical within the protocol.

7.3.1.1. Dose Modifications

No dose modifications are advised. Decision to continue treatment if untoward side effect will be made in consultation with PI.

7.3.1.2. Allergic Reactions

Latex Sensitivity

The needle cover on the pre-filled syringe contains dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

Hypersensitivity Reactions

In post-marketing experience, serious systemic hypersensitivity reactions (including anaphylactic reaction) have been reported following golimumab administration. Some of these reactions were reported after the first administration of golimumab. If an anaphylactic or other serious allergic reaction occurs, administration of golimumab should be discontinued immediately and appropriate therapy instituted.

7.3.2. Apalutamide

Apalutamide is metabolized primarily by CYP2C8 and CYP3A4 and is excreted primarily via urine. Therefore, caution should be exercised and possibly avoided when strong CYP2C8 and CYP3A4 inhibitors are administered concomitantly (e.g., gemfibrozil, itraconazole, ketoconazole). CYP2C8/CYP3A4 inducers (rifampin) may decrease the steady state of apalutamide and decrease effectiveness, but this has not conclusively been studies in vivo.

7.3.2.1. Dose Modifications

Dose modifications are provided as guidance and should not replace the investigator's own clinical judgment.

Toxicity	Dose of apalutamide (assuming 240 mg/day dosing)
Grade 1 or 2	No change
≥Grade 3 or higher	Hold until Grade 1 or baseline, resume at full dose
First Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 180 mg (3 tablets)
Second Recurrence ≥Grade 3	Hold until Grade 1 or baseline, resume at 120 mg (2 tablets)
Third Recurrence ≥Grade 3	Discontinue
First occurrence of seizure of any grade or Grade 4 neurotoxicity	Discontinue

Rash

Dose modifications for rash are allowed only for apalutamide and are summarized in below table.
If the skin rash has any component of desquamation, mucosal involvement, or pustules, stop dosing with apalutamide, refer to dermatologist for evaluation, and a skin biopsy is recommended (in addition to the interventions listed in below Table) If the skin rash is Grade 3 or higher, asking the subject to consent to documentation by a photograph and further evaluation by a dermatologist should also be considered.

Severity	Intervention
Grade 1	• Continue apalutamide at current dose • Initiate dermatological treatment[a] ○ Topical high potency steroid lotion AND

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	○ Oral Antihistamines (e.g. hydroxyzine 10mg BID) • Monitor for change in severity[a]
Grade 2 (or symptomatic Grade 1)[b]	• Hold apalutamide for up to 28 days • Initiate dermatological treatment[a] ○ Topical high potency steroid lotion AND ○ Oral Antihistamines (e.g. hydroxyzine 25mg BID) • Monitor for change in severity[a] ○ If rash or related symptoms improve, reinitiate apalutamide when rash is Grade≤1. Consider dose reduction at a 1 dose level reduction[c].
Grade ≥3[d]	• Hold apalutamide for up to 28 days • Initiate dermatological treatment[a] ○ Topical high potency steroid lotion AND ○ Oral Antihistamines AND ○ Consider treating with prednisone 0.5-1mg/kg/day (or equivalent) for 20 days • Reassess after 2 weeks (by site staff), and if the rash is the same or has worsened, initiate oral steroids (if not already done) and refer the subject to a dermatologist ○ Reinitiate apalutamide at a 1 dose level reduction[e] when rash is Grade≤1. ○ If the dose reduction will lead to a dose less than 120mg, the study drug must be stopped (discontinued) • If after 28 days, rash has not resolved to Grade≤1, contact study PI

Note: Rash may be graded differently according to the type of rash and associated symptoms. For example, maculo-papular rash is graded by body surface area covered and not severity of the rash. Please consult NCI-CTCAE Version 4.03 for specific grading criteria for other types of rashes.

a Obtain bacterial/viral cultures if infection is suspected

b Subject presents with other rash related symptoms such as pruritus, stinging, or burning

c 1 dose level reduction = 60mg (1 apalutamide tablet)

d If there is blistering or mucosal involvement, stop apalutamide dosing immediately and contact PI

e If a subject previously started oral corticosteroids, continue for at least 1 week after resumption of reduced dose of apalutamide. If the proposed total oral steroid use will exceed 28 days, contact PI.

7.4 Duration of Therapy

Enrollment is expected to take approximately 12-18 months. Participants will receive active treatment with golimumab for up to 6 months. Apalutamide will be continued until disease progression. Subjects will be seen every 4 weeks for scheduled assessments while on active golimumab treatment. Completion of active treatment and post-treatment follow-up is expected to take 18 months. The total study duration is expected to last up to approximately 2-3 years.

7.5 Duration of Follow-Up

Subjects will be seen every 4 weeks for scheduled assessments while on active golimumab treatment. Thereafter, participants will be followed every 3 months, as standard of care for long-term survival and time-to-event updating. Laboratory evaluations will be performed monthly with golimumab treatment and radiographic (e.g., CT scan or MRI, bone scan) evaluations will be performed q12weeks. PSMA PET scans will be performed as SOC in screening and again at 12-weeks on-treatment. Participants will be requested to have baseline and 12-week on-treatment metastatic tumor biopsy, if feasible.