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Document: Clinical Protocol

Official Study Title:

A Phase 1/2a Open-label, Multicenter, Dose Escalation and Dose Expansion Study of the Safety, Tolerability, and Pharmacokinetics of HPN424 in Patients with Advanced Prostate Cancer Refractory to Androgen Therapy

Document Date: 24 September 2021

NCT03577028

CLINICAL PROTOCOL: HPN424-1001

Study Title:	A Phase 1/2a Open-label, Multicenter, Dose Escalation and Dose Expansion Study of the Safety, Tolerability, and Pharmacokinetics of HPN424 in Patients with Advanced Prostate Cancer Refractory to Androgen Therapy
Study Number:	HPN424-1001
Study Phase:	1/2a
Product Name:	HPN424
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EUDRACT Number:	2018-000135-27
ClinicalTrials.gov:	NCT03577028
Indication:	Prostate Cancer
Investigators:	Multicenter
Sponsor:	Harpoon Therapeutics, Inc. 131 Oyster Point Blvd, Suite 300 South San Francisco, CA 94080
Medical Monitor	[redacted]

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Amendment 7:	Version 8.0	24 September 2021

PROTOCOL SPONSOR APPROVAL PAGE

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Study Number:	HPN424-1001
Amendment 7:	24 September 2021

I have read and approved this protocol.

Signature: [redacted]

Name: [redacted]

Title: [redacted]

Affiliation: Harpoon Therapeutics, Inc.

INVESTIGATOR'S SIGNATURE PAGE

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I, the undersigned Principal Investigator, have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study in accordance with the protocol.

Principal Investigator
Signature:_____ Date:_____

Principal Investigator
Printed Name:_____

Title:_____

Affiliation:_____

SYNOPSIS

Sponsor: Harpoon Therapeutics, Inc.

Name of Product: HPN424

Study Title: A Phase 1/2a, Open-label, Multicenter, Dose Escalation and Dose Expansion Study of the Safety, Tolerability, and Pharmacokinetics of HPN424 in Patients with Advanced Prostate Cancer Refractory to Androgen Therapy

Study Number: HPN424-1001

Study Phase: 1/2a

Number of Sites: 15-20

Rationale: HPN424 is a tri-specific recombinant protein containing three humanized antibody-derived binding domains. The three domains of the PSMA TriTAC® molecule bind to human CD3ε, human serum albumin, and human prostate-specific membrane antigen (PSMA), respectively. PSMA is a well-validated membrane antigen specific to prostate epithelial cells which is expressed at 100-fold increased levels in human prostate relative to other normal human tissues and upregulated to an 8-12-fold increase over baseline upon malignant disease of the prostate. HPN424 is intended to redirect human T cells to kill prostate cancer cells in patients with advanced prostate cancer. The anti-CD3ε portion of the molecule provides a well-established and validated mechanism to specifically engage human effector T cells by binding to CD3ε, an invariant signaling component of the T cell receptor complex (TCR) found on T effector cells. Finally, the middle section of the TriTAC binds to human serum albumin, a mechanism known to confer prolonged residence time in blood circulation.

Therapeutic choices are limited for metastatic castrate-resistant prostate cancer (mCRPC). HPN424 is a tri-specific recombinant protein construct that offers the potential benefit of highly effective immunotherapy for mCRPC. Nonclinical data suggest that HPN424 has substantial anticancer activity in animal models and *in vitro* studies with human patient specimens. The toxicity profile seen in nonclinical studies of HPN424 is consistent with its target physiological activity, based on clinical experience with other T-cell activating agents (including the approved CD19 × CD3 BiTE, blinatumomab).

Primary Objectives:

Dose Escalation: Assess safety and tolerability at increasing dose levels of HPN424 in successive cohorts of patients with metastatic castrate resistant prostate cancer (mCRPC) to estimate the maximum tolerated dose (MTD) or maximum administered dose (MAD) and select the recommended Phase 2 dose(s) (RP2D), and dosing regimen for further investigation

Dose Expansion: Evaluate preliminary clinical efficacy at RP2D(s)

Secondary Objectives:

Dose Escalation:

- Evaluate the overall safety profile of HPN424 administered by intravenous (IV) infusion or subcutaneous (SC) injection
- Characterize single dose and multiple dose PK of HPN424
- Evaluate immunogenicity against HPN424
- Evaluate preliminary clinical anti-tumor activity
- Characterize the impact of HPN424 on activation of circulating lymphocytes and systemic soluble immune factors

Dose Expansion:

- Further characterize the safety and tolerability of HPN424 at the RP2D(s)
- Characterize single dose and multiple dose PK of HPN424 at the RP2D(s)

- Evaluate immunogenicity against HPN424
- Characterize the impact of HPN424 on activation of circulating lymphocytes and systemic soluble immune factors

Study Design:

HPN424-1001 is a Phase 1/2a, open-label, multicenter, safety and PK study of HPN424 in adults with histologically or cytologically confirmed adenocarcinoma of the prostate with progressive metastatic disease which, in the opinion of the Investigator, requires initiation of new treatment.

The study will be divided into 2 parts: Dose Escalation and Dose Expansion. As an added safety measure for this first in human (FIH) trial, single patient cohorts will initially be enrolled and treated. Dose Escalation will then proceed following a 3 + 3 design to evaluate 2 treatment arms in parallel:

- Fixed Dosing
- Step Dosing

During single patient dose escalation and in the 3 + 3 dose escalation Fixed Dosing arm, patients will receive the Target Dose (the intended dose for a particular cohort) starting on Cycle 1 Day 1 and beyond. Patients in the Step Dosing arm will initiate treatment with one (or more) Priming Dose(s) followed by the Target Dose level for the duration of treatment.

Dose escalation will continue until the MTD is declared, RP2D(s) are identified, or the Sponsor decides to stop enrollment in one or more arms. A Cohort Review Committee (CRC) comprised of selected Investigators and Sponsor representatives including the Medical Monitor will monitor safety throughout the trial. Following completion of the DLT period for all patients in a given dose cohort, the CRC will review the safety, clinical activity, and any available PK and pharmacodynamic data prior to opening the next higher dose level.

During Dose Escalation, additional patients may be enrolled and treated at dose levels previously determined to be safe by the CRC, i.e., backfilling previously cleared dose levels, after review and approval by the Sponsor. For example, these backfill cohorts may explore intermediate or lower dose levels, different priming dose levels, different schedules (e.g., split-dosing), or modified premedication use based on emergent safety and available PK data.

Patients actively receiving therapy may be considered for intra-patient dose escalation to receive a dose level no higher than the highest dose that has previously been deemed safe and tolerable (and thus below the MTD) by the CRC, following review and approval by the Medical Monitor.

During Dose Expansion, up to an additional 20 evaluable patients will receive HPN424 at the RP2D(s) established in the Dose Escalation stage of the study. While the intention is to study a single RP2D(s), additional expansion cohorts of up to 20 patients per expansion cohort may be added at the recommendation of the CRC

HPN424 will be administered by either intravenous (IV) infusion or subcutaneous (SC) injection. All patients will be administered HPN424 once weekly (QW) during 21-day cycles. Pre-infusion medications will be administered as indicated based on assigned cohort and route of administration.

Patients may continue to receive HPN424 treatment beyond disease progression provided there is clinical benefit (NLCB, per PCWG3 guidelines), as determined by the Investigator and upon consultation with the Medical Monitor. Disease assessments (PSA, bone scans and CT/MRI) should continue irrespective of whether study treatment is missed or delayed.

Dose Limiting Toxicity (DLT) Definition:

Severity of adverse events (AEs) will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. During Dose Escalation, any of the following AEs occurring within 21 days after first administration of the Target Dose which are attributable to HPN424 and unrelated to mCRPC, intercurrent illness, or concomitant medications will be classified as DLTs:

Hematological:

- Prolonged myelosuppression, defined as CTCAE Grade ≥3 hematologic parameters (absolute neutrophil count [ANC] <1000/mm^3, platelet count <50,000/mm^3, or hemoglobin [Hgb] <8 g/dL) in a bone marrow with <5% blasts and no evidence of leukemia or abnormal dysplasia, that lasts longer than 21 days from the point of detection
- Grade ≥3 neutropenia with infection
- Grade 4 neutropenia lasting >5 days
- Febrile neutropenia (defined as an ANC <1.0 x 10^9/L with a single temperature of >38.3°C or 101°F, or a sustained temperature of ≥38°C or 100.4°F for more than one hour)
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia

Non-hematological:

- Grade ≥3 non-hematological toxicities are considered DLTs, with the following *exceptions*:
    - Grade 3 nausea/vomiting/diarrhea or Grade 4 vomiting/diarrhea lasting <72 hours in the absence of maximal medical therapy are NOT considered a DLT.
    - Grade 3 fatigue lasting less than 7 days is NOT considered a DLT.
    - Non-hematologic laboratory Grade 3 AE that is asymptomatic and/or rapidly reversible (returned to baseline or to Grade ≤1 within 7 days) unless identified as clinically relevant by the Investigator is NOT considered a DLT
    - Events of increased blood pressure are not considered DLTs if associated with symptoms of cytokine release syndrome (CRS) or infusion-related reaction (IRR) and resolve in concordance with CRS symptom resolution and do not result in additional safety events
- Dose delay or dose interruption ≥3 weeks is considered a DLT.
- Hy's Law (concomitant ALT or AST elevation of >3 times the upper limit of normal [ULN] and total bilirubin elevation of >2xULN without a clear alternative etiology) is considered a DLT.
- Grade 4 IRR or CRS (per ASTCT), with or without pre-medication, is considered a DLT.
- Grade 3 IRR or CRS (per ASTCT) that occurs despite pre-medication is considered a DLT

In Dose Escalation, clinically important or persistent toxicities (e.g., toxicities responsible for significant dose delay) that are not included in the above criteria may also be considered a DLT following review by the Investigators and Harpoon. To be considered a DLT, the AE must represent a clinically significant shift from baseline and must be considered related or suspected to be related to HPN424 by the Investigator or Sponsor. Dose modification guidelines for patients who experience treatment-related AEs are specified in the protocol.

Concomitant Medication: Pre-medications will be administered as indicated based on assigned cohort. Modifications to premedication regimens are permitted if deemed necessary by CRC or following discussion between the Sponsor and Investigator, and according to institutional standards.

Number of Patients (Planned): Up to 150 patients with mCRPC may be enrolled. The Dose Escalation stage may include up to 130 patients, depending on the number of cohorts evaluated. Up to 20 evaluable patients will be enrolled in Dose Expansion. Additional expansion cohorts of up to 20 patients per expansion cohort may be added if the CRC determines more than one RP2D.

Study Population:

Inclusion Criteria:

Each patient must meet the following criteria to be enrolled in this study:

1. Male patients ≥18 years of age at the time of signing informed consent
2. Histologically or cytologically confirmed adenocarcinoma of the prostate
3. Progressive metastatic castrate-resistant prostate cancer (mCRPC):
   a. Serum testosterone levels less than 50 ng/dL (or ≤0.50 ng/mL or 1.73 nmol/L) within 28 days prior to start of study drug
   b. Radiographic evidence of metastatic disease
   c. Disease progression on the prior systemic regimen, per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria described in protocol (Appendix 6):
      i. A sequence of at least 2 rising PSA values measured at a minimum of 1 week apart with a 2 ng/mL minimum starting value, or
      ii. Appearance of two or more new lesions on bone scans, or
      iii. Progressive visceral disease, or
      iv. Progressive nodal disease; previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed.
4. Must have received at least 2 prior systemic therapies approved for mCRPC
5. Ongoing androgen depletion therapy with a gonadotropin releasing hormone analog or inhibitor, or orchiectomy (surgical or medical castration)
6. For patients previously treated with first generation anti-androgens, discontinuation must have occurred ≥4 weeks (for flutamide or nilutamide) or ≥6 weeks (for bicalutamide) prior to start of study drug, with no evidence of an anti-androgen withdrawal response (i.e., no decline in serum PSA)
7. For patients previously treated with a second-generation anti-androgen (e.g., enzalutamide or equivalent) or with abiraterone acetate, discontinuation must have occurred 2 weeks or 5 half-lives prior to start of study drug
8. For patients previously treated with systemic chemotherapy, targeted therapy, immunotherapy, or treatment with an investigational anticancer agent, discontinuation must have occurred ≥2 weeks, or at least 4 half-lives (up to 4 weeks), whichever is longer, prior to start of study drug
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
10. Adequate bone marrow function, including:
    a. Absolute neutrophil count (ANC) ≥1500/mm^3 or ≥1.5 x 10^9/L
    b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L
    c. Hemoglobin ≥9 g/dL (no transfusions allowed within 1 week prior to start of study drug)

11. Adequate renal function, including:
    a. Estimated creatinine clearance ≥50 mL/min as calculated using the method standard for the institution
12. Adequate liver function, including:
    a. Total serum bilirubin ≤1.5 x upper limit of normal (ULN) unless the patient has documented Gilbert syndrome in which case the maximum total serum bilirubin should be 5 mg/dL
    b. Aspartate and alanine transaminase (AST and ALT) ≤2.5 x ULN
13. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for adverse events (AEs) not constituting a safety risk per the Investigator
14. If of reproductive potential, willing to use 1 effective method of contraception (as defined in this protocol) during the treatment period, if partner is a female of childbearing potential
15. Willing to complete all scheduled visits and assessments at the institution administering therapy
16. Able to read, understand and provide written informed consent.

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from the study:

1. Previously treated or current brain metastases
2. Untreated spinal cord compression. Participants must be neurologically stable off steroids for at least 4 weeks prior to first dose of study drug
3. Ongoing treatment with anti-tumor necrosis factor (TNF) alpha therapies, systemic corticosteroids (prednisone dose >10 mg per day or equivalent), or other immune suppressive drugs
4. History of or known or suspected autoimmune disease (exception(s): patients with vitiligo, resolved childhood atopic dermatitis, hypothyroidism, or hyperthyroidism that is clinically euthyroid at Screening are allowed)
5. History of clinically significant cardiovascular disease such as symptomatic congestive heart failure (CHF), uncontrolled hypertension defined as sustained BP >150 mmHg systolic, or >100 mmHg diastolic despite optimal antihypertensive treatment (BP must be controlled at screening), unstable angina pectoris, clinically-significant cardiac arrhythmias, history of stroke (including TIA, or other ischemic event) within 6 months before first dose of study drug, myocardial infarction within 6 months before first dose of study drug, history of thromboembolic event within 3 months before first dose of study drug
6. Known active or chronic hepatitis B or hepatitis C as demonstrated by hepatitis B surface antigen (HBsAg) positivity and/or anti-hepatitis C virus (HCV) positivity, respectively, or known history of human immunodeficiency virus (HIV) seropositive status
7. Clinically active liver disease, including liver cirrhosis of Child-Pugh class B or C
8. Second primary malignancy that has not been in remission for greater than 3 years. Exceptions that do not require a 3-year remission: non-melanoma skin cancer, resected melanoma in situ, or non-muscle invasive urothelial carcinoma.

9. In the judgment of the Investigator, patient has a clinically significant concurrent illness or psychological, familial, sociological, geographical, or other concomitant condition that would not permit adequate follow-up and compliance with the study protocol
10. Any serious underlying medical or psychiatric condition (e.g., alcohol or drug abuse), dementia or altered mental status or any issue that would impair the ability of the patient to understand informed consent or that in the opinion of the Investigator would contraindicate the patient's participation in the study or confound the results of the study
11. Known hypersensitivity, allergies, or intolerance to immunoglobulins, or to any excipient contained in HPN424 (see Investigator's Brochure)
12. Is a participant or plans to participate in another interventional clinical study, while taking part in this protocol. Participation in an observational study is acceptable

Test Product; Dose; and Mode of Administration: HPN424 will be administered once weekly at the assigned dose level as either a one-hour IV infusion or by SC injection. Patients in Dose Expansion will receive HPN424 at the RP2D(s). Patients may continue weekly HPN424 treatment as long as they are receiving clinical benefit (as determined by the Principal Investigator and upon consultation with the Medical Monitor).

Reference Therapy; Dose; and Mode of Administration: Not applicable.

Duration of Study: Patient participation includes Screening (28 days), Treatment Period (ongoing in 21-day cycles), End of Treatment visit (within 7 days after the last dose of HPN424), and Safety Follow-up (SFU; 28 days [+7 days] after the last dose of HPN424), after which patients will enter long term follow-up (LTFU) for survival. Duration of the study depends on the dose escalation and length of treatment for each patient; the study as a whole is expected to last approximately 48 months until the last patient completes the SFU.

Safety Assessments: Safety assessments include adverse events, clinical laboratory tests, vital signs, electrocardiograms (ECGs), physical examinations, ECOG scores, and concomitant medications. Anti-drug antibodies (ADA) will be assessed.

Efficacy Assessments: Efficacy assessments include prostate-specific antigen (PSA) and radiological imaging including bone scans and CT/MRI as appropriate. Optional PSMA PET scans may be performed at selected sites. Responses will be assessed by the Investigator according to PCWG3 criteria.

Pharmacokinetics and Pharmacodynamics: Serum levels of HPN424 will be measured periodically (per the Schedule of Assessments) for all patients. Pharmacodynamics assessments include cytokines, lymphocyte immunophenotyping, and circulating tumor cells (CTCs).

Study Endpoints:

Primary Endpoints:

- Dose Escalation: Number and severity of DLTs following treatment with escalating doses of HPN424
- Dose Expansion: Overall response rate (ORR) as assessed by PCWG3 criteria for response

Secondary Endpoints:

- Adverse events (NCI CTCAE version 5.0)
- Laboratory abnormalities (NCI CTCAE version 5.0)
- Progression-free survival (PFS) using PCWG3 criteria
- Duration of response (DOR) using PCWG3 criteria
- Overall survival (OS)
- Effects on PSA
- Effects on CTCs

- Pharmacokinetic parameters of HPN424:
  - Single dose - maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the single dose concentration-time curve over dosing interval τ ($AUC_{sd, \tau}$), area under the concentration-time curve extrapolated to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), and clearance (CL) as data permit
  - Multiple dose (assuming steady state is achieved) - maximum concentration ($C_{ss, max}$), time to maximum concentration ($T_{ss, max}$), area under the steady state concentration-time curve over dosing interval τ ($AUC_{ss, \tau}$), $t_{1/2}$, minimum concentration ($C_{ss, min}$), CL, volume of distribution (V_{ss}), and accumulation ratio ($AUC_{ss, \tau}/AUC_{sd, \tau}$) as data permit
- Incidence and titers of anti-drug antibodies against HPN424
- Pre- and post-dose quantification of soluble cytokines in serum
- Exploratory assessment of biomarkers and characterization of immune cell infiltration and activation in the tumor microenvironment

Statistical Methods: Descriptive statistics will be used to summarize baseline characteristics, HPN424 treatment, safety variables and preliminary efficacy. Categorical or nominal variables will be summarized by frequency and percentage. Continuous variables will be summarized using standard summary statistics (N, mean, standard deviation, median, minimum, and maximum). Where appropriate, 95% confidence intervals around point estimates will be presented.

Sample Size Determination: Up to 150 patients with mCRPC may be enrolled. Dose Escalation may include up to 130 patients, depending on the dose at which the MTD and RP2D(s) are determined. The sample size and design of Dose Escalation are consistent with those in other oncology studies used to determine MTD. The traditional 3 + 3 dose escalation scheme employs the standard National Cancer Institute definition of MTD (dose associated with DLT in <33.3% of patients).

Dose Expansion will include up to 20 evaluable patients using a Simon 2-stage design to assess the preliminary clinical efficacy of HPN424 at the RP2D(s). Power calculations based on a Simon 2-stage minimax design test the null hypothesis that ORR $\leq$0.01 versus the alternative hypothesis that ORR $\geq$0.15, with a Type 1 error rate of 0.05 and power of 80%. A sample size of 14 evaluable patients will be enrolled in the first stage. If the total number responding is $\geq$1, an additional 6 evaluable patients will be enrolled in the second stage. If Dose Escalation goes on to the second stage, a total of 20 patients will be evaluated. If the total number responding is $\leq$1, the effectiveness of the drug based on the ORR endpoint will be rejected.

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ADA	anti-drug antibody
ADT	androgen deprivation therapy
AE	adverse event
ALB	Albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APC	androgen presenting cell
AST	aspartate aminotransferase (SGOT)
ASTCT	American Society for Transplant and Cellular Therapy
AUC_{inf}	area under the concentration-time curve extrapolated to infinity
$AUC_{sd, \tau}$	area under the concentration-time curve over dosing interval τ after a single dose
$AUC_{ss, \tau}$	area under the concentration-time curve over dosing interval τ at steady state
AUC_{τ}	area under the concentration-time curve over dosing interval τ
BAP	bone-specific alkaline phosphatase
BiTE	bi-specific T cell engager
BUN	blood urea nitrogen
C(x)D(y)	Cycle(x) Day(y)
Ca	Calcium
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
Cl	Chloride
CL	Clearance
C_{max}	maximum concentration after single dose
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CRC	Cohort Review Committee
CRF	case report form
CRP	C-reactive protein
CRPC	castrate-resistant prostate cancer
CRS	cytokine release syndrome
$C_{ss, max}$	maximum concentration at steady state
$C_{ss, min}$	minimum concentration
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
DIC	disseminated intravascular coagulation
DLT	dose-limiting toxicity
DOR	duration of response
EC_x	concentration that produces x% of maximal effect
ECG	Electrocardiogram

ECOG	Eastern Cooperative Oncology Group
EOI	end of infusion
EPCAM	epithelial cell adhesion molecule
FDA	United States Food and Drug Administration
FIH	first in human
FOLH1	folate hydrolase 1
GCP	Good Clinical Practices guidelines
HBsAg	hepatitis B surface antigen
Hct	Hematocrit
HCV	hepatitis C virus
Hgb	Hemoglobin
HIPAA	Health Information Portability and Accountability Act
HSA	human serum albumin
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IRRs	infusion-related reactions
IV	Intravenous
K	Potassium
K_D	dissociation constant
kDa	Kilodalton
LDH	lactic dehydrogenase
LTFU	long-term follow-up
MABEL	minimum anticipated biological effect level
MAD	maximum administered dose
mCRPC	metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
Na	Sodium
NCI	National Cancer Institute
NLCB	no longer clinically benefitting
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCWG	Prostate Cancer Working Group
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetics
PR	partial response

PS80	Polysorbate 80
PSMA	prostate-specific membrane antigen
PT	prothrombin time
PTT	partial thromboplastin time
RBC	red blood cell (count)
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SC	subcutaneous(ly)
Sd	single dose; single domain
SFU	safety follow-up
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SOI	start of infusion
Ss	steady state
SSE	symptomatic skeletal event
SSOC	Study Safety Oversight Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
Tc99 MDP	technetium 99m-methyl diphosphonate
TCR	t cell receptor
TDCC	t-cell dependent cellular cytotoxicity
T_{max}	time to maximum concentration after single dose
TNF	tumor necrosis factor
TNM	Tumor, Node, and Metastasis
$T_{ss, max}$	time to maximum concentration at steady state
UK	United Kingdom
ULN	upper limit of normal
US	United States
V_0	initial volume of distribution
Vss	apparent volume of distribution at steady state
WBC	white blood cell (count)

1 INTRODUCTION

1.1 Description of Disease - Metastatic Castrate Resistant Prostate Cancer (mCRPC)

Prostate cancer is the most common non-cutaneous cancer diagnosed in men and the second-highest cause of cancer-related death for men in the United States (Jemal, 2010). An estimated 161,360 new cases of prostate cancer will be diagnosed in 2017, accounting for 19% of new cancer cases in men. While age-adjusted death rates from prostate cancer have declined 51% from 1993 to 2014, researchers estimate prostate cancer to account for 26,730 deaths in 2017, which represent 8% of male cancer deaths (Siegel, 2017). The majority of prostate cancer cases (79.2%) are diagnosed at the local stage, and while fewer patients present with advanced disease because of improved screening, up to 25% of patients will have locally advanced disease and approximately 30% will develop recurrent disease following initial treatment (Bader, 2003; Gupta, 2008; Partin, 1997). However, when the disease has metastasized beyond regional lymph nodes, the 5-year survival rate is only 29.8% (SEER, 2017).

Initial treatment typically includes androgen deprivation therapy (ADT) by surgical orchiectomy or medical therapy. While the majority of patients improve symptomatically, their disease eventually progresses despite a serum testosterone level in the castrate range. Nearly all prostate cancer-specific deaths occur after patients develop castration-resistant prostate cancer (CRPC) (Halabi, 2008). Approximately 90% of prostate cancer patients who develop metastatic castration-resistant prostate cancer (mCRPC) develop bone metastases, which are the primary source of morbidity – including debilitating pain – and mortality in this population (Petrylak, 2004; Tannock, 2004).

1.2 Available Therapies for mCRPC

The current standard of care for symptomatic, chemotherapy-naïve CRPC patients with progressive metastatic disease is the combination of docetaxel and prednisone, which has been demonstrated to prolong survival in two randomized controlled studies (TAX 327 and SWOG-9916 studies). Patients receiving docetaxel every 3 weeks in combination with prednisone had a median survival of 18.9 months compared to 16.5 months with the combination of mitoxantrone and prednisone (Tannock, 2004). The combination of docetaxel-estramustine resulted in a median survival of 17.5 months compared with 15.6 months for mitoxantrone (Petrylak, 2004).

More recently, inhibition of androgen biosynthesis by abiraterone acetate has been demonstrated to prolong survival among patients with metastatic CRPC who previously received chemotherapy (COU-AA-301 study), and abiraterone acetate received regulatory approval as second-line treatment. Patients receiving abiraterone acetate in combination with prednisone had a median survival of 14.8 months compared to 10.9 months with prednisone and placebo (de Bono, 2011).

Inhibition of androgen receptor signaling by MDV3100 (enzalutamide) has also demonstrated prolonged survival in a population of patients with metastatic CRPC who had received prior chemotherapy (AFFIRM study). MDV3100 produced a 4.8-month advantage in median overall survival compared to placebo; the estimated median survival for men treated with MDV3100 was 18.4 months compared with 13.6 months for men treated with placebo (Scher, 2012).

Approximately 90% of CRPC patients develop bone metastases, which are a major cause of morbidity – including debilitating pain – and mortality in CRPC (Petrylak, 2004; Tannock, 2004). Existing therapies for metastatic CRPC that have proven survival benefit have not been associated with resolution of bone lesions on bone scan. A lack of effective therapies for bone-related morbidity and mortality in this bone metastasis-predominant patient population remains a major unmet medical need.

1.3 Scientific Rationale/Role of Target in the Disease

Bispecific antibodies offer a novel immunotherapeutic approach that allows the direct targeting of T cells to mediate tumor cell lysis. These antibodies are engineered with two separate antigen recognition domains; one that recognizes a tumor antigen and another that recognizes CD3 expressed on T cells. Simultaneous binding of CD3 and the tumor antigen initiates a cytotoxic response towards the bound tumor cell. Unlike normal T cell cytotoxicity, bispecific antibody-mediated cytotoxicity is independent of the presence of antigen presenting cells (APCs) and expression of the relevant major histocompatibility complex (MHC) I tumor-associated molecules by the tumor.

HPN424 is a tri-specific recombinant protein containing three humanized antibody-derived binding domains. The three domains of the prostate-specific membrane antigen (PSMA) TriTAC® molecule bind to human CD3ε, human serum albumin (HSA), and human PSMA, respectively. PSMA is a well-validated membrane antigen specific to prostate epithelial cells which is expressed at 100-fold increased levels in human prostate relative to other normal human tissues (Rajasekaran, 2005) and upregulated to an 8-12-fold increase over baseline upon malignant disease of the prostate (Ristau, 2014). HPN424 is intended to redirect human T cells to kill prostate cancer cells in patients with advanced prostate cancer. The binding domains described above were derived from mouse or llama antibodies, and the properties of each domain were optimized using phage display techniques (Dubridge, 2016).

PSMA was discovered in 1987 (Horoszewicz, 1987) and was one of the first prostate cancer biomarkers to be successfully cloned (Israeli, 1993). It is a transmembrane metallopeptidase with folate hydrolase and glutamate carboxypeptidase II activities (Carter, 1996) and its high over-expression in the human prostate and upregulation in prostate cancer make it a very attractive target for therapies aimed at treating advanced prostate cancer. Data on human PSMA expression in the prostate suggest that a PSMA-based therapy will likely be very selective for prostate cancer. As a result, PSMA is being developed as a biomarker for both imaging and therapy for prostate cancer and is the target of several small molecules as well as recombinant protein and antibody-based therapeutics (e.g., see https://clinicaltrials.gov/ct2/results?cond=cancer&term=psma&cntry1=&state1=&recrs=ab). Being an integral membrane type glycoprotein whose expression is widely associated with

prostate cancer, it is a particularly well-suited target for monoclonal antibody therapy, or for therapies with molecules derived from antibody chains and constructs.

The anti-CD3ε portion of the molecule provides a well-established and validated mechanism to specifically engage human effector T cells by binding to CD3ε, an invariant signaling component of the T cell receptor complex (TCR) found on T effector cells (Huehls, 2015). Such an approach has been successful in other tumor settings using single chain bi-specific T cell engagers developed against various differentiation antigens, such as blinatumomab (Blincyto®, developed by Amgen as a bi-specific anti-CD19 T cell engager for B cell acute lymphoblastic leukemia) or an anti-carcinoembryonic antigen (CEA) T cell engager developed by MedImmune, Amgen, and Roche (Tabernero, 2017). Other T cell engagers against solid tumor targets such as epithelial cell adhesion molecule (EpCAM; solitomab) or PSMA are also being evaluated in clinical trials (Frankel, 2013). [redacted] and T cell engagers using a CD3 binding domain tested in cynomolgus monkeys have shown no immunotoxicity in the absence of tumor target engagement in these animals (Kischel, 2016).

The middle section of the TriTAC binds to HSA, a mechanism known to confer prolonged residence time in blood circulation (Larsen, 2016). [redacted] hours when administered intravenously at 0.03-3 mg/kg. By comparison, the half-life of an anti T cell engager that does not have a half-life extender (blinatumomab) is only 1-2 hours (Schlereth, 2006; Wu, 2013).

Harpoon created several prototypes of PSMA-specific TriTAC molecules and selected the PSMA Tri-TAC referred to as HPN424 as a lead candidate for a clinical study, based on its binding and cytotoxicity to human prostate tumor cells.

Additional information can be found in the Investigator's Brochure.

1.4 Description of Drug

HPN424 is a tri-specific recombinant protein containing 3 separate humanized antibody-derived binding domains. HPN424 has a molecular weight of approximately 53 kilodalton (kDa). The N-terminus of HPN424 consists of a humanized llama single domain (sd)Ab specific to human PSMA, also known as folate hydrolase 1 (FOLH1). It is followed by a humanized llama sdAb specific to HSA. A humanized single chain Fv (scFv) specific for human CD3ε is located at the C-terminus of the molecule.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.6 Study Rationale and Potential Risks/Benefits

Therapeutic choices are limited for mCRPC. HPN424 is a tri-specific recombinant protein that offers the potential benefit of highly effective immunotherapy for mCRPC. Nonclinical data suggest that HPN424 has substantial anticancer activity in animal models and *in vitro* studies with human patient specimens. The toxicity profile seen in nonclinical studies of HPN424 is consistent with its target physiological activity, based on clinical experience with other T-cell activating agents (including the approved CD19 × CD3 BiTE, blinatumomab).

Based on available preliminary data, the most common treatment emergent adverse events (TEAEs) include cytokine release syndrome (CRS) and preferred terms consistent with symptoms associated with CRS or infusion related reaction (IRR) (e.g., chills, pyrexia, vomiting, nausea) or associated with prostate cancer (e.g., anemia, constipation, fatigue). Overall, the safety profile of HPN424 as a single agent is consistent with that expected for a recombinant T cell engager specific for PSMA and the CD3 subunit of the T cell receptor. While the risks of this type of immunotherapeutic approach are significant, including potential CRS or other infusion reactions, the potential benefits of anticancer activity justify the evaluation of HPN424 in this FIH trial.

Additional details on available clinical and nonclinical data are provided in the current version of the Investigator's Brochure.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

Dose Escalation: Assess safety and tolerability at increasing dose levels of HPN424 in successive cohorts of patients with metastatic castrate resistant prostate cancer (mCRPC) to estimate the maximum tolerated dose (MTD) or maximum administered dose (MAD) and select the recommended Phase 2 dose(s) (RP2D), and dosing regimen for further investigation.

Dose Expansion: Evaluate preliminary clinical efficacy at RP2D(s)

2.2 Secondary Objectives

The secondary objectives of this study are:

Dose Escalation:

- Evaluate the overall safety profile of HPN424 administered by intravenous (IV) infusion and subcutaneous (SC) injection
- Characterize single dose and multiple dose PK of HPN424
- Evaluate immunogenicity against HPN424
- Evaluate preliminary clinical anti-tumor activity
- Characterize the impact of HPN424 on activation of circulating lymphocytes and systemic soluble immune factors

Dose Expansion:

- Further characterize the safety and tolerability of HPN424 at the RP2D(s)
- Characterize single dose and multiple dose PK of HPN424 at the RP2D(s)
- Evaluate immunogenicity against HPN424
- Characterize the impact of HPN424 on activation of circulating lymphocytes and systemic soluble immune factors

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

HPN424-1001 is a Phase 1/2a, open-label, multicenter, safety and PK study of HPN424 in adults with histologically or cytologically confirmed adenocarcinoma of the prostate with progressive metastatic disease which, in the opinion of the Investigator, requires initiation of new treatment.

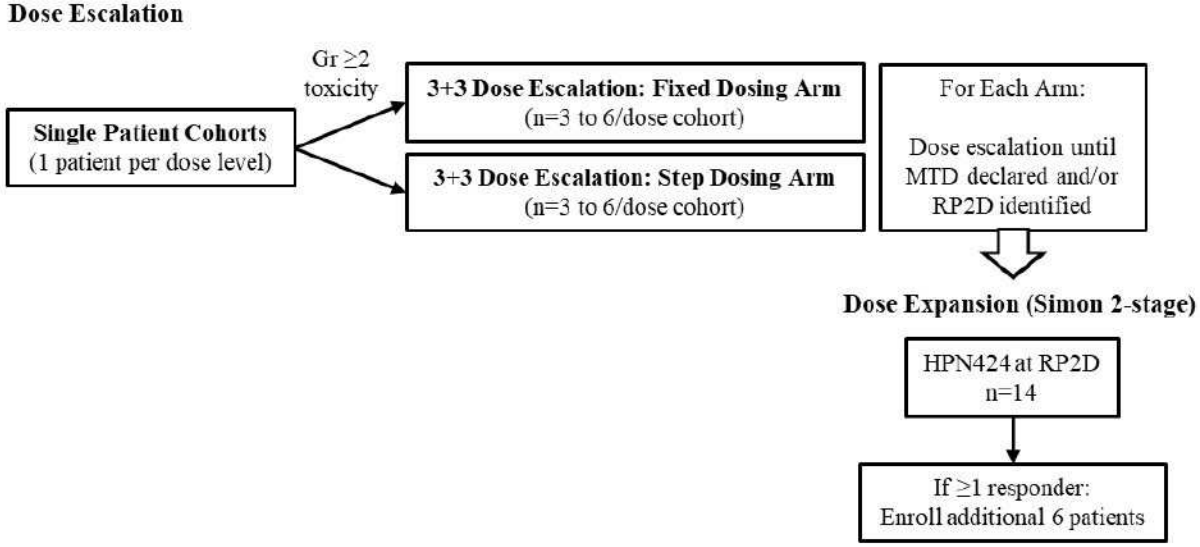
The study will be divided into 2 parts: Dose Escalation and Dose Expansion (Figure 2).

As an added safety measure for this FIH trial, single patient cohorts will initially be enrolled and treated. If toxicity is observed, Dose Escalation will then proceed following a 3+3 design to evaluate 2 treatment arms in parallel:

- Fixed Dosing
- Step Dosing

During single patient dose escalation and in the 3 + 3 dose escalation Fixed Dosing arm, patients will receive the Target Dose (the intended dose for a particular cohort) throughout the treatment period. Patients in the Step Dosing arm will initiate treatment with one (or more) Priming Dose(s) followed by the Target Dose level for the duration of treatment.

Figure 2 Study Design Schema



HPN424 administered weekly by IV infusion or SC injection
Abbreviations: DLT = dose-limiting toxicity (per protocol); MTD = maximum tolerated dose; RP2D = recommended Phase 2 dose; toxicity = AEs related or suspected to be related to HPN424, except those judged not to present safety risk

For each treatment arm, Dose Escalation will continue until the MTD is declared, RP2D(s) are identified, or the Sponsor decides to stop enrollment in one or more arms. A Cohort Review Committee (CRC) comprised of selected Investigators and Sponsor representatives including the Medical Monitor will monitor safety throughout the trial. Following completion of the DLT period for all patients in a given dose cohort, the CRC will review the safety, clinical activity, and any available PK and pharmacodynamic data prior to opening the next higher dose level.

During Dose Escalation, additional patients may be enrolled and treated at dose levels previously determined to be safe by the CRC, i.e., backfilling previously cleared dose levels, after review and approval by the Sponsor (Section 3.1.1.3). For example, these backfill cohorts may explore intermediate or lower dose levels, different priming dose levels, different schedules (e.g., split-dosing), or modified premedication use based on emergent safety and available PK data.

Patients actively receiving therapy may be considered for intra-patient dose escalation to receive a dose level no higher than the highest dose that has previously been deemed safe and tolerable (and thus below the MTD) by the CRC, following review and approval by the Medical Monitor (Section 3.1.1.4).

During Dose Expansion, up to 20 additional evaluable patients will receive HPN424 at the RP2D(s) established in the Dose Escalation stage of the study.

HPN424 will be administered by either intravenous (IV) infusion or subcutaneous (SC) injection. All patients will be administered HPN424 once weekly (QW) during 21-day cycles. Pre-medications will be administered as indicated based on assigned cohort (Section 5.1.4).

Patients may continue to receive HPN424 treatment beyond disease progression provided there is clinical benefit (NLCB, per PCWG3 guidelines, (Scher, 2016) as determined by the Investigator and upon consultation with the Medical Monitor. Disease assessments (PSA, bone scans and CT/MRI) should continue irrespective of whether study treatment is missed or delayed.

3.1.1 Part 1: Dose Escalation Study Design

Dose escalation will be performed initially with single patient cohorts followed by a 3 + 3 design with two parallel arms (Fixed Dosing, Step Dosing) to evaluate tolerability of different dosing regimens:

- During single patient dose escalation and in the 3 + 3 dose escalation Fixed Dosing arm, patients will receive the Target Dose (the intended dose for a particular cohort) starting on Cycle 1 Day 1 and beyond.
- During step dosing, patients will initiate treatment with Priming Dose A on Cycle 1 Day 1. The Target Dose will be administered on Cycle 1 Day 8 and beyond.

- A second priming dose, Priming Dose B, may be implemented in the next cohort on Cycle 1 Day 8. In this case, the Target Dose will be administered on Cycle 1 Day 15 and beyond (Section 3.1.1.2.2).

- Additional Priming Doses may be added (e.g., Priming Dose C) based on the observed safety and tolerability (Section 3.1.1.2.2).

For safety reasons, a staggered start will be employed when a higher dose level cohort is opened. At least 48 hours must elapse between dosing of the first and second patient at any given dose level.

All patients within a dose cohort will be observed for dose-limiting toxicities (DLTs; Section 5.2) through 21 days after the first Target Dose (i.e., the DLT observation period; Table 15). For Step Dosing cohorts, if DLTs are observed between administration of the Priming and Target Doses, the CRC will consider the safety data of all patients treated at the Priming Dose level (including patients who received the priming dose in prior 3+3 cohorts and single patient cohorts) when making decisions regarding cohort expansion (e.g., expand cohort to at least 6 patients if < 6 patients have received the Priming Dose), dose escalation (or de-escalation), and priming regimen.

Subsequent higher dose level cohorts may not be opened until all patients entered in the current dose level cohort have been treated and completed the DLT observation period, and the data have been reviewed by the CRC.

Enrollment in an arm may be stopped following review of the data by the CRC and at the Sponsor's discretion.

3.1.1.1 Single Patient Dose Escalation

During single patient dose escalation, patients will receive the Target Dose as a fixed dose starting on Cycle 1 Day 1.

The initial IV Target Dose of HPN424 will be 1.3 ng/kg/wk, with dose escalation by single-patient cohorts in dose increments of 3-fold until either a Grade ≥2 adverse event [AE] that is related or suspected to be related to HPN424 is observed during Cycle 1 (21-day DLT observation period), or an estimated therapeutic dose level has been reached (Table 5). Should either of these events occur, the 3 + 3 Dose Escalation enrollment plan will be implemented.

Table 5 Dose Escalation Criteria - Single-Patient Cohorts

Cycle 1 Toxicity	Dose Escalation
No Grade >1 AEs or any AEs judged to present a safety risk	Continue single-patient cohorts Up to 3-fold dose increments
Grade ≥2 AEs that are related or suspected to be related to HPN424 (except AEs judged not to present safety risk to the patient)	Switch to 3 + 3 Dose Escalation enrollment plan

3.1.1.2 3+3 Dose Escalation Enrollment Plan

Two arms will be evaluated in parallel: Fixed Dosing and Step Dosing. Each dose cohort within each arm will be enrolled and evaluated independently of the other arm. For each arm, the MTD is defined as the highest Target Dose level associated with the occurrence of DLTs in <33% of DLT-evaluable patients (< 2 patients with DLTs as outlined below).

Enrollment in each cohort will proceed per the following 3 + 3 guidelines:

- Up to 3 patients will be treated in each dose level cohort per arm. Occasionally, due to logistical/clinical reasons, more than 3 but no more than 6 patients may be enrolled in a dose level cohort.
  - If a DLT is observed in 1 of the initial 3 patients treated at the Target Dose level, 3 additional patients up to a total of 6 patients will be enrolled and treated in the same dose level cohort.
  - Patients not evaluable for assessment of DLT may be replaced.

- Dose escalation will continue until DLTs are observed in at least 2 of the patients treated at a Target Dose level, leading to the conclusion that the MTD has been exceeded.
  - When a Target Dose exceeding the MTD has been identified, the next lower dose level may be declared the MTD if 6 patients have already been treated at that dose level. Otherwise, additional patients may be treated at the next lower dose level (for at least 6 patients total at that dose level). If 0 or 1 patient have DLTs, this may be declared the MTD.
  - If 2 or more patients have DLTs, the dose will be further de-escalated according to the same scheme until the MTD is declared.

- An intermediate Target Dose level between the one in which DLTs occurred in 2 patients and the immediate lower level may be explored, if appropriate.
  - If ≥2 patients in the intermediate dose level experience a DLT, no further dose escalation will occur; the MTD would be exceeded, and the next lower dose level may be considered the MTD.

- If dose escalation continues without observation of DLTs in ≥ 33% of patients at any dose level, dose escalation is halted without an MTD estimate. In those circumstances, the MAD may be declared as the RP2D.

3.1.1.2.1 Fixed Dosing Arm

Dose escalation will proceed following 3+3 enrollment plan (Section 3.1.1.2).

Patients enrolled in the Fixed arm will receive the same Target Dose of HPN424 at every treatment visit; use of pre-infusion medications will follow guidance provided in Section 5.1.4.

Dose escalation increments will be determined based on emergent safety data (Table 6, Table 9). The number of Fixed Arm cohorts evaluated will depend on emergent safety data and CRC review and recommendations.

Table 6 Dose Escalation Criteria - 3 + 3 Design for IV Fixed Arm

Cycle 1 Toxicity	Dose Escalation
If 0 DLT in 3 patients	Up to 33% dose increments [a]
If 1 DLT in 3 patients	Cohort expansion up to 6 patients
If 1 DLT in 6 patients	Up to 33% dose increments [a]
If ≥2 DLTs in 3 to 6 patients	Escalation stops, MAD reached and MTD defined at a lower dose level [b]

DLT = dose-limiting toxicity; MAD = maximum administered dose; MTD = maximum tolerated dose

[a] The CRC may decide to escalate to a < 33% dose increment based on review of safety data

[b] Assessment of an intermediate Target Dose lower than the MAD may occur.

3.1.1.2.2 Step Dosing Arm

Dose escalation for the Step Dosing arm will proceed following 3 + 3 enrollment plan (Section 3.1.1.2).

Patients enrolled in the Step Dosing arm will receive an HPN424 Priming Dose A on Cycle 1 Day 1 followed by the Target Dose level at subsequent treatment visits; administration of dexamethasone and other pre-infusion medications will follow guidance provided in Section 5.1.4. The HPN424 dose level administered as Priming Dose A will be less than or equal to the highest dose that has been cleared by the CRC in the Fixed arm at the time the Step Dosing arm is initiated.

If Grade ≥2 CRS occurs after administration of the Target Dose (with no DLT), the CRC may recommend an additional priming dose (Priming Dose B) be added for the next cohort. The dose level of Priming Dose B will be less than or equal to the Target Dose of the cohort resulting in Grade ≥2 CRS. Priming Dose B will be administered on Cycle 1 Day 8. The Target Dose will then be administered on Cycle 1 Day 15 and beyond. The CRC may recommend additional Priming Dose(s) be added (e.g., Priming Dose C) based on the observed safety and tolerability.

A sample step dosing regimen and dose escalation scheme is shown in Table 7. Actual dose escalation increments, and the number of Priming Doses will be determined based on the incidence of DLTs in each dose cohort and overall observed safety data (Table 8). Actual Cycle/Day will be determined by the number of Priming doses for a given regimen (e.g., Priming Dose A will be administered on C1D1, Priming Dose B on C1D8, Priming Dose C

on C1D15). The number of Step Dosing cohorts evaluated will depend on emergent safety data and CRC review and recommendations.

If a Target Dose exceeds the MTD, the CRC may recommend assessment of the same Target Dose with a different Priming Regimen (e.g., additional Priming Doses added prior to administration of the Target Dose). If the same Target Dose assessed with a different Priming Regimen is cleared by the CRC, dose escalation may continue using the modified Priming Regimen.

Table 7 Dose Escalation Example – 3 + 3 Design for Step Dosing Arm

Cohort	C1D1	C1D8	C1D15+
1	Priming Dose A[a] *Example: 100 ng/kg*	Target Dose 1[b] ≤**3x** Priming Dose A *Example: 300 ng/kg*	Maintain Target Dose 1[b] *Example: 300 ng/kg*
2	Priming Dose A[a] *Example: 100 ng/kg*	Target Dose 2[b] ≤**6x** Priming Dose A *Example: 600 ng/kg*	Maintain Target Dose 2[b] *Example: 600 ng/kg*
3	Priming Dose A[a] *Example: 100 ng/kg*	Target Dose 3[b] ≤**9x** Priming Dose A *Example: 900 ng/kg*	Maintain Target Dose 3[b] *Example: 900 ng/kg*
	If ≥Grade 2 CRS occurs with no DLT after administration of Target Dose in any cohort:[c] • Implement Priming Dose B, which is ≤ Target Dose that resulted in Grade ≥2 CRS • Target Dose of first Cohort with Priming Dose B will be ≤2 x Priming Dose B		
4	Priming Dose A[a] *Example: 100 ng/kg*	Priming Dose B [c] ≤Target Dose 3 *Example: 600 ng/kg*	Target Dose 4[d] ≤**2x** Priming Dose B *Example: 1200 ng/kg*
5	Priming Dose A[a] *Example: 100 ng/kg*	Priming Dose B [c] *Example: 600 ng/kg*	Target Dose 5[d] ≤**4x** Priming Dose B *Example: 2400 ng/kg*
6	Priming Dose A[a] *Example: 100 ng/kg*	Priming Dose B [c] *Example: 600 ng/kg*	Target Dose 6[d] ≤**6x** Priming Dose B *Example: 3600 ng/kg*

CRS = cytokine release syndrome; CxDx = Cycle x Day x; DLT = dose limiting toxicity

[a] Priming Dose A is ≤ the highest dose that has been cleared by the CRC in the Fixed arm at the time of initiation of the Step Dosing arm.

[b] Target Dose is up to 3× Priming Dose A in Cohort 1, up to 6x Priming Dose A in Cohort 2, up to 9x Priming Dose A in Cohort 3, etc. until MAD is reached.

[c] If there is ≥Grade 2 CRS at any Target Dose level with no DLT, Priming Dose B may be introduced regardless of the Target Dose level at which the ≥Grade 2 CRS occurred. Priming Dose B will be ≤ Target Dose that resulted in ≥Grade 2 CRS. The CRC may decide to implement Priming Dose B at a threshold lower than a ≥Grade 2 CRS based on a review of the collective safety data.

[d] If Priming Dose B is introduced, the Target Dose of first Cohort with Priming Dose B is up to 2x Priming Dose B, up to 4x Priming Dose B in subsequent cohort, up to 6x Priming Dose B in the subsequent cohort, etc. until MAD is reached.

Table 8 Target Dose Level Escalation – Step Dosing Arm

Cycle 1 Toxicity	Target Dose Escalation
If 0 DLT in 3 patients	Up to 100% or up to 2x dose increments [a]
If 1 DLT in 3 patients	Dose cohort expansion up to 6 patients
If 1 DLT in 6 patients	Up to 100% or up to 2x dose increments [a]
If ≥2 DLTs in 3 to 6 patients	MAD for regimen reached, MTD will be evaluated at a lower Target dose level or with additional priming doses

DLT = dose-limiting toxicity; MAD = maximum administered dose; MTD = maximum tolerated dose
[a] The CRC may decide to escalate to a < 100% dose increment based on review of safety data Assessment of an intermediate Target Dose lower than the MAD may occur.

3.1.1.3 Subcutaneous Dosing

Additional cohorts will be opened to assess SC dosing of HPN424. Enrollment in SC dosing cohorts will follow a 3 + 3 design.

The initial cohort will evaluate 120 ng/kg SC once weekly by Fixed Dosing. The rationale for SC administration and starting SC dose selection are described in Section 3.2.2.

Dose escalation guidelines for fixed dosing SC cohorts will be based on available emergent PK data and the incidence of DLTs and ≥ Grade 2 CRS observed in the fixed dosing SC cohorts as specified in Table 9. Following assessment of the initial SC dose level, dose escalation between successive SC cohorts will be based on observed SC safety and PK data and may exceed IV administered dose levels. If the observed Cmax in a fixed dosing SC cohort is < 25% of the Cmax observed for an HPN424 IV dose of 120 ng/kg and there are no ≥ Grade 2 Treatment Related AEs, the next higher dose increment may be greater than 100% but will not exceed 200% of the previous dose level.

Table 9 Dose Escalation Rules for Subcutaneous Fixed Dosing Cohorts

DLTs	Incidence of ≥Grade 2 CRS	Dose Escalation [a]
0 of 3 patients	0 of 3 patients	Up to 100% dose increments
0 of 3 patients	1 of 3 patients	Up to 33% dose increments
1 of 3 patients	Any	Expand cohort to 6 patients
1 of 6 patients	Any	Up to 33% dose increments
≥2 of 6 pts	Any	Escalation stops, maximum administered dose (MAD) reached and MTD defined at a lower dose level

a. If the observed Cmax in a fixed dosing SC cohort is < 25% of the Cmax observed for an HPN424 IV dose of 120 ng/kg and there are no ≥ Grade 2 Treatment Related AEs, the next higher dose increment may be greater than 100% but will not exceed 200% of the previous dose level.
b. Should tolerability issues arise at the starting dose level (120 ng/kg) a lower dose level (90 ng/kg) may be evaluated

Following initial evaluation of SC Fixed Dose cohorts, SC Step Dosing may be initiated. Step Dosing SC cohorts will follow the same guidelines for dose escalation and priming/target dose regimens as outlined in Section 3.1.1.2.2. Patients will initiate treatment with one (or more) Priming Dose(s) followed by the Target Dose level for the duration of treatment (see dosing examples provided in Table 7).

The HPN424 dose level administered as Priming Dose A will be less than or equal to the highest dose that has been cleared by the CRC in the SC Fixed Dose arm at the time the SC Step Dosing arm is initiated. Dose escalation increments for SC step dosing will be determined based on emergent safety and PK data in the SC dosing cohorts and will not exceed 100% increments from the prior cohort Target Dose level.

The number of SC cohorts evaluated will depend on emergent safety data and CRC review and recommendations.

3.1.1.4 Backfill

Additional patients may be enrolled and treated at dose levels previously determined to be safe by the CRC, i.e., backfilling previously cleared dose levels, after review and approval by the Sponsor. For example, these backfill cohorts may explore intermediate or lower dose levels, different priming dose levels, or different schedules (e.g., split dosing), modified premedication use, or other modifications to step dosing (e.g., Priming Dose levels or additional Priming Doses) based on emergent safety and available PK data. The Schedule of Assessments for backfill cohorts will follow the same schedule as that for the respective 3 + 3 arm (i.e., Fixed or Step Dosing) and route of administration.

3.1.1.5 Intrapatient Dose Escalation

Patients actively receiving therapy may be considered for intrapatient dose escalation to receive a dose level that is no higher than the highest dose that has previously been deemed safe and tolerable (and thus below the MTD) by the CRC, following review and approval by the Sponsor Medical Monitor.

The following criterion must be met to be considered for intrapatient dose escalation:

- Patients must have completed at least 2 cycles (6 doses) at their current dose level without intolerable toxicity.

All patients who undergo intrapatient dose escalation will receive premedication based on discussion between the Investigator and Medical Monitor and be hospitalized for 24-hour inpatient observation following the first of each escalated dose (Section 5.1.4).

See Section 5.1 for provisions where intrapatient transition to a different route of administration may be appropriate.

3.1.2 Part 2: Dose Expansion Study Design

The CRC will determine the RP2D(s) (Priming Dose/Target Dose) regimen and preferred route of administration at or below the MTD. The RP2D(s) will be selected on the basis of available safety, clinical activity, and pharmacokinetics and pharmacodynamics data gathered during Dose Escalation.

Up to 20 evaluable additional patients will receive HPN424 at the RP2D(s) established in the Dose Escalation stage of the study. While the intention is to study a single RP2D, additional

expansion cohorts of up to 20 evaluable patients per expansion cohort may be added at the recommendation of the CRC.

3.2 Rationale for Study Design and Dosing Regimen

[redacted]

3.2.3 Study Design Rationale - Dose Escalation

As HPN424 had not previously been tested in humans before the initiation of this study, an open-label dose escalation design was chosen. The design of the Dose Escalation stage is consistent with other oncology studies used to determine MTD. The initial single-patient dose cohorts allow a relatively low starting dose of 1.3 ng/kg (Section 3.2.1) to minimize safety concerns while rapidly escalating to dose levels in a range expected to be clinically active.

The proposed dose escalation by 3-fold increases before drug-related Grade 2 toxicity is based on first-in-human dose selection and dose escalation modeling conducted on 15 CD3-targeting bispecific constructs and reported by (Saber, 2017). For comparison, dose escalation by 3-fold increments would allow escalation from a starting dose of 0.68 ng/kg to a dose equivalent to the approved fixed maintenance dose of blinatumomab of 28 µg or approximately 400 ng/kg in 6-7 steps (1.3, 4, 12, 36, 108, 324, and 972 ng/kg).

The traditional 3 + 3 dose escalation scheme employs the standard National Cancer Institute definition of MTD (highest dose level tested associated with DLT in <33.3% of patients). After identification of an appropriate dose in the Dose Escalation stage, the larger group of patients in the Expansion stage will allow further elucidation of the safety and preliminary efficacy of HPN424 in mCRPC.

The indication of mCRPC is based on the expected mechanism of action of HPN424, and the poor prognosis and limited treatment choices for patients with mCRPC makes this an appropriate population for this FIH study. Inclusion criteria (Section 4.2), including Eastern Cooperative Oncology Group (ECOG) score 0 or 1, were chosen to permit enrollment of patients who are most likely to benefit from HPN424.

The schedule and nature of assessments in this study, including efficacy assessment based on PCWG3 criteria, are typical of current clinical trials in prostate cancer.

3.2.4 Step Dosing Rationale

Cytokine-mediated adverse events, including CRS, have been associated with multiple CD3 bispecific T cell engaging molecules. CRS is often observed after the first dose administration of CD3 bispecific T cell engaging molecules. This is consistent with the observation that transient cytokine and chemokine increases, particularly IL-6, have been reported, with the highest levels observed after the first dose followed by attenuation of cytokine and chemokine levels upon subsequent doses. Preliminary data from HPN424-1001, has shown transient increases in serum cytokines (e.g., peak levels of IL-6 at 5 – 8 hours post

dose) followed by a trend back to baseline within 24 – 48 hours. Maximum release of serum IL-6 was observed post first dose and attenuated upon subsequent doses. In addition, dexamethasone premedication prior to infusion suppressed the HPN424-mediated cytokine/chemokine spikes following the first dose. Kinetics of serum IL-6 were similar with or without the use of dexamethasone premedication, up to the current cohort of 72 ng/kg and may acclimate patients for subsequent administrations. Consult the Investigator's Brochure for additional details.

Approaches to mitigating CRS have included pretreatment with corticosteroids, and a step dosing regimen in which an initial lower dose (i.e., Priming Dose) is followed by a higher dose on subsequent treatment days. This approach has been effective in mitigating CRS and enabling larger intervals of dose escalation between successive dose cohorts. Two CD3 bispecific T cell engaging molecules currently in development, AMG 330 (anti CD3 /CD33, non-half-life extended) and mosunetuzumab (anti CD3/CD20, half-life extended) have tested both fixed dose and step dose schedules during Phase 1 dose escalation (Bartlett, 2019; Ravandi, 2018). Using the step dosing approach, both agents were able to safely achieve higher target doses than with fixed dose escalation.

Leveraging available data on the kinetics of HPN424-induced serum cytokines and chemokines, an alternate dose escalation scheme in the form of step dosing may expedite dose escalation, mitigate cytokine-mediated AEs, and reduce the number of patients exposed to sub-therapeutic doses.

3.2.5 Dosing Frequency Rationale

The non-GLP single dose PK study (Study 20133857 or HPN424PK-01) and a GLP-compliant toxicity study (Study 2012494 or HPN424TOX-01) as described in Section 1.5, revealed a serum terminal half-life of approximately 3 days for HPN424 in cynomolgus monkeys. These findings support an initial dosing regimen of once weekly in humans.

3.3 Study Duration and Dates

Patient participation includes Screening (28 days), Treatment (ongoing in 21-day cycles), End of Treatment visit (within 7 days after the last dose of HPN424), and Safety Follow-up (SFU; 28 days [+ 7 days] after the last dose of HPN424), after which patients will enter long term follow-up (LTFU) for survival. Patients may continue weekly HPN424 treatment as long as they are receiving clinical benefit (as determined by the Principal Investigator and upon consultation with the Medical Monitor).

For purposes of estimating study duration, patients are expected to remain on treatment for approximately 28 weeks, making total study duration for each patient approximately 32 weeks through the SFU, or 18-24 months total including LTFU for survival. Given that patient recruitment is expected to occur over approximately 36 months, the study as a whole is expected to last approximately 48 months until the last patient completes the SFU.

4 STUDY POPULATION

4.1 Study Population

The study population is comprised of adult patients with histologically or cytologically confirmed adenocarcinoma of the prostate with castrate resistant progressive metastatic disease which, in the opinion of the Investigator, requires initiation of new treatment. Approximately 15-20 centers in the United States (US) and the United Kingdom (UK) are expected to participate.

4.2 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:

1. Male patients ≥18 years of age at the time of signing informed consent
2. Histologically or cytologically confirmed adenocarcinoma of the prostate
3. Progressive metastatic castrate-resistant prostate cancer (mCRPC):
    a. Serum testosterone levels less than 50 ng/dL (or ≤0.50 ng/mL or 1.73 nmol/L) within 28 days prior to start of study drug
    b. Radiographic evidence of metastatic disease
    c. Disease progression on the prior systemic regimen, per Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria (Scher, 2016) described in protocol Appendix 6:
        i. A sequence of at least 2 rising PSA values measured at a minimum of 1 week apart with a 2 ng/mL minimum starting value, or
        ii. Appearance of two or more new lesions on bone scans, or
        iii. Progressive visceral disease, or
        iv. Progressive nodal disease; previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed
4. Must have received at least 2 prior systemic therapies approved for mCRPC
5. Ongoing androgen depletion therapy with a gonadotropin releasing hormone analog or inhibitor, or orchiectomy (surgical or medical castration)
6. For patients previously treated with first generation anti-androgens, discontinuation must have occurred ≥4 weeks (for flutamide or nilutamide) or ≥6 weeks (for bicalutamide) prior to start of study drug, with no evidence of an anti-androgen withdrawal response (i.e., no decline in serum PSA)
7. For patients previously treated with a second-generation anti-androgen (e.g., enzalutamide or equivalent) or with abiraterone acetate, discontinuation must have occurred 2 weeks or 5 half-lives prior to start of study drug

8. For patients previously treated with systemic chemotherapy, targeted therapy, immunotherapy, or treatment with an investigational anticancer agent, discontinuation must have occurred ≥2 weeks, or at least 4 half-lives (up to 4 weeks), whichever is longer, prior to start of study drug.
9. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
10. Adequate bone marrow function, including:
    a. Absolute neutrophil count (ANC) ≥1500/mm^3 or ≥1.5 x 10^9/L
    b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L
    c. Hemoglobin ≥9 g/dL (no transfusions allowed within 1 week prior to screening)
11. Adequate renal function, including:
    a. Estimated creatinine clearance ≥50 mL/min as calculated using the method standard for the institution
12. Adequate liver function, including:
    a. Total serum bilirubin ≤1.5 x upper limit of normal (ULN) unless the patient has documented Gilbert syndrome in which case the maximum total serum bilirubin should be 5 mg/dL
    b. Aspartate and Alanine transaminase (AST and ALT) ≤2.5 x ULN
13. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for adverse events (AEs) not constituting a safety risk per the Investigator
14. If of reproductive potential, willing to use 1 effective method of contraception (as defined in this protocol) during the treatment period, if partner is a female of childbearing potential.
15. Willing to complete all scheduled visits and assessments at the institution administering therapy
16. Able to read, understand and provide written informed consent

4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Previously treated or current brain metastases
2. Untreated spinal cord compression. Participants must be neurologically stable off steroids for at least 4 weeks prior to first dose of study drug
3. Ongoing treatment with anti-tumor necrosis factor (TNF) alpha therapies, systemic corticosteroids (prednisone dose >10 mg per day or equivalent), or other immune suppressive drugs
4. History of or known or suspected autoimmune disease (exception(s): patients with vitiligo, resolved childhood atopic dermatitis, hypothyroidism, or hyperthyroidism that is clinically euthyroid at Screening are allowed)

5. History of clinically significant cardiovascular disease such as symptomatic congestive heart failure (CHF), uncontrolled hypertension defined as sustained BP >150 mmHg systolic, or >100 mmHg diastolic despite optimal antihypertensive treatment (BP must be controlled at screening), unstable angina pectoris, clinically-significant cardiac arrhythmias, history of stroke (including TIA, or other ischemic event) within 6 months before first dose of study drug, myocardial infarction within 6 months before first dose of study drug, history of thromboembolic event within 3 months before first dose of study drug
6. Known active or chronic hepatitis B or hepatitis C as demonstrated by hepatitis B surface antigen (HBsAg) positivity and/or anti-hepatitis C virus (HCV) positivity, respectively, or known history of human immunodeficiency virus (HIV) seropositive status
7. Clinically active liver disease, including liver cirrhosis of Child-Pugh class B or C
8. Second primary malignancy that has not been in remission for greater than 3 years. Exceptions that do not require a 3-year remission: non-melanoma skin cancer, resected melanoma in situ, or non-muscle invasive urothelial carcinoma
9. In the judgment of the Investigator, patient has a clinically significant concurrent illness or psychological, familial, sociological, geographical, or other concomitant condition that would not permit adequate follow-up and compliance with the study protocol
10. Any serious underlying medical or psychiatric condition (e.g., alcohol or drug abuse), dementia or altered mental status or any issue that would impair the ability of the patient to understand informed consent or that in the opinion of the Investigator would contraindicate the patient's participation in the study or confound the results of the study
11. Known hypersensitivity, allergies, or intolerance to immunoglobulins, or to any excipient contained in HPN424 (see Investigator's Brochure)
12. Is a participant or plans to participate in another interventional clinical study, while taking part in this protocol. Participation in an observational study is acceptable

5 STUDY TREATMENT

5.1 Treatment Administered – HPN424

HPN424 will be administered at the assigned dose level, regimen, and route of administration based on the assigned cohort as outlined in Section 3.1. Transition between IV and SC dosing will not occur for individual patients, unless this is recommended by the CRC following review of safety and efficacy data at which point this will be allowed following discussion between the Investigator and Sponsor.

[redacted]

5.1.2 HPN424 for Intravenous Infusion

[redacted]

5.1.2.2 Preparation of HPN424 Solution for Infusion

HPN424 will be administered at the assigned dose level. The Sponsor will provide assigned dose levels (Priming and Target Doses) for a given cohort at the time of cohort opening.

Calculate based on the patient's baseline (Screening) body weight.

HPN424 drug product will be thawed and diluted to the target dose in the provided diluent prior to administration. Sequential dilutions will be performed in the pharmacy to obtain the target dose in a final delivery volume of 10 mL. All dilutions should be performed in a controlled sterile environment. Operators performing the dilutions should follow institutional procedures to avoid contact with HPN424.

Refer to the Pharmacy Manual for detailed instructions regarding handling of HPN424 and diluent and preparation of HPN424 solution for infusion.

5.1.2.3 Pre-Dose Medications

During Dose Escalation, pre- medications should be administered per guidelines described in Table 10.

Table 10 Pre-Medication Guidelines During Dose Escalation

Dosing Regimen	Premedication Regimen
Fixed Dosing Single Patient Cohorts and Fixed Dose 3 + 3 Cohorts	• Premedication with dexamethasone for all patients initiating dosing at HPN424 dose levels ≥ 24 ng/kg [a] • Premedication after C1D1 based on discussion between Investigators and Sponsor at time of cohort opening • Premedication with non-steroidal medication per SOC and/or based on discussion between Investigators and Sponsor at time of cohort opening
Step Dosing Step-dosing 3 + 3 cohorts	• Premedication with dexamethasone for all patients initiating dosing at HPN424 dose levels ≥ 24 ng/kg for each Priming dose (e.g., Priming Dose A, Priming Dose B) and first administration at Target Dose level [a] • Premedication after first administration of Target Dose based on discussion between Investigators and Sponsor at time of cohort opening • Premedication with non-steroidal medication per SOC and/or based on discussion between Investigators and Sponsor at time of cohort opening

CxDx = Cycle number Day number; SOC = standard of care

[a] Dexamethasone dose and schedule based on discussion between Investigators and Sponsor

Changes to pre-medication guidelines are permitted if deemed necessary by the CRC (for a given cohort) or following discussion between the Sponsor and Investigator, and/or according to institutional standards. Changes may include adding additional medications to mitigate CRS risk, adjustment of dose and timing of medications and/or elimination of one or more medications.

Patients who experience symptoms of IRRs or CRS may be prophylaxed with additional medications (e.g., dexamethasone, diphenhydramine, and/or antipyretics prior to subsequent doses. Non-steroidal anti-inflammatory drugs (e.g., indomethacin or ibuprofen) may be used in lieu of acetaminophen if the patient has experienced transaminitis. Infusion duration may also be modified by the Investigator in consultation with the Medical Monitor.

Premedication for patients enrolled in backfill cohorts will be agreed upon between the Investigators and the Sponsor at the time that a cohort is opened and will be based on emergent safety data.

Premedication for patients undergoing intrapatient dose escalation should be agreed upon between the Investigator and the Medical Monitor and will depend on the emergent safety data of the regimen to which the patient is being escalated and the patient's tolerability of prior HPN424 infusions and clinical status.

The premedication regimen for patients in Dose Expansion will be the same as that administered to patients treated at the respective RP2D during Dose Escalation. Adjustments to the premedication regimen for a given RP2D may be made based on review of the available safety data.

5.1.2.4 Administration of HPN424 IV Solution

HPN424 will be administered at the dose level based on the assigned cohort as outlined in Section 3.1. The starting dose of HPN424 will be 1.3 ng/kg/week, with dose escalations by cohorts until MTD and RP2D(s) are determined in Dose Escalation. Patients in Dose Expansion will receive HPN424 at the RP2D(s).

HPN424 will be administered once weekly (–2 days/+1 day), with a minimum of 4 non-dose days between 2 consecutive doses, as a one-hour intravenous infusion. Administration will be done using a 10 mL syringe infusion pump such as the Medfusion® 4000 Wireless Syringe Infusion Pump, Medfusion® 3500 Syringe Infusion Pump, or equivalent. The delivery system must be able to achieve a low enough flow rate to deliver 10 mL of infusion solution in 1 hour. An in-line filter should not be used. HPN424 can be administered via peripheral or central line. Refer to the Pharmacy Manual for further instructions.

The infusion may be slowed or interrupted for patients experiencing infusion-associated symptoms (Section 5.4.1).

5.1.3 HPN424 for Subcutaneous Injection

5.1.3.1 Description of Diluent for Subcutaneous Injection

The same diluent as used for IV infusion is used for SC injection (Section 5.1.2.1).

5.1.3.2 Preparation of HPN424 for Subcutaneous Injection

HPN424 doses will be administered at the assigned dose level based on the assigned cohort as outlined in Section 3.1. The Sponsor will provide assigned dose level(s) and regimen (i.e., Fixed Dosing or Step Dosing) for a given cohort at the time of cohort opening.

HPN424 drug product will be thawed and diluted as necessary to the assigned dose in the provided diluent prior to administration. Dilutions will be performed in the pharmacy to obtain the assigned dose in a final delivery volume of 1.0 mL. All dilutions should be performed in a controlled sterile environment. Operators performing the dilutions should follow institutional procedures to avoid contact with HPN424.

Refer to the Pharmacy Manual for detailed instructions regarding handling of HPN424 and diluent and preparation of HPN424 solution for SC injection.

5.1.3.3 Pre-medications for Subcutaneous Injection

SC dosing cohorts will follow the same premedication guidelines as outlined in Section 5.1.2.3. Additional medications for prophylaxis of CRS and/or injection site reactions, including topical medications and medications administered post-dose may be recommended based on the observed safety data in the cohorts.

5.1.3.4 Administration of Subcutaneous HPN424

HPN424 will be administered at the dose level based on the assigned cohort as outlined in Section 3.1.

HPN424 will be administered once weekly (–2 days/+1 day), with a minimum of 4 non-dose days between 2 consecutive doses, via SC injection. The maximum volume per SC injection site is 1.0 mL. If multiple injections are required to deliver the assigned dose, administer at different injection sites. Injection sites should be rotated with each injection administered at a different anatomic location (i.e., upper arms, upper thighs, buttocks, or any quadrant of abdomen) than the previous injection. Do not inject into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact. Refer to the Pharmacy Manual for further instructions.

5.1.4 Hospitalization and Monitoring

5.1.4.1 Single Patient Cohorts and Fixed Dosing Regimen

All patients enrolled in single-patient cohorts and fixed dose 3 + 3 dose escalation arms will be hospitalized for a 48-hour (± 1 hour) observation following Cycle 1 Day 1 and Cycle 1 Day 8 dosing (administration of first 2 doses).

- If the patient experiences signs or symptoms of CRS/IRR, hospitalization may be extended for monitoring beyond 48 hours until it is confirmed that the patient is symptom free and is stable for discharge.
- If the Cycle 1 Day 1 and Cycle 1 Day 8 doses have been well tolerated, subsequent doses of HPN424 may be administered on an outpatient basis. However, even if administered on an outpatient basis, for Cycles 1, 2, and 3, patients are to remain in the clinic for safety monitoring for at least 4 hours after each HPN424 administration.
- Beginning with Cycle 4 and beyond, the observation period may be reduced to no less than 2 hours after end of HPN424 administration.

Based on emergent safety data and review by the CRC, duration of hospitalization for Cycle 1 Day 1 and Cycle 1 Day 8 may be reduced or omitted. If hospitalization is omitted, outpatient observation following the administration of the first two doses will be for at least 6 hours after the study drug administration.

In the outpatient setting, if the patient experiences signs or symptoms of CRS/IRR, post dose monitoring should be extended until it is confirmed that the patient is symptom free for at least one hour and confirmed by the treating physician that the patient is stable for discharge.

5.1.4.2 Step Dosing Regimen

For patients enrolled in the Step Dosing regimen, hospitalization is as follows:

- Priming Dose(s): Hospitalized a minimum of 48 hours after the administration of each Priming Dose.
    - If the patient experiences signs or symptoms of CRS/IRR, hospitalization may be extended for monitoring beyond 48 hours until it is confirmed that the patient is symptom free and is stable for discharge.
    - After at least 6 patients have initiated treatment with a given priming dose, duration of hospitalization for that priming dose or lower priming dose levels may be reduced or omitted based on CRC review of the safety data.
    - If hospitalization is omitted, observation following first administration of a Priming Dose will be for at least 6 hours after study drug administration.

  In the outpatient setting, if the patient experiences signs or symptoms of CRS/IRR, post dose monitoring should be extended until it is confirmed that the patient is symptom free for at least one hour and confirmed by the treating physician that the patient is stable for discharge.
- Target Dose(s): Hospitalized a minimum of 48 hours after the administration of the first 2 Target Doses.
    - If the patient experiences signs or symptoms of CRS/IRR, hospitalization may be extended for monitoring beyond 48 hours until it is confirmed that the patient is symptom free and is stable for discharge.
    - If the first 2 Target Doses have been well tolerated, subsequent doses of HPN424 may be administered on an outpatient basis. During subsequent Target Doses through Cycle 3, patients are to remain in the clinic for safety monitoring for at least 4 hours after each administration. Beginning with Cycle 4 and beyond, the observation period may be reduced to no less than 2 hours after administration.

Based on emergent safety data and review by the CRC, duration of hospitalization for the first and/or second Target Dose(s) may be reduced or omitted. If hospitalization is omitted, outpatient observation following the administration of the first 2 Target Doses will be for at least 6 hours after the study drug administration.

In the outpatient setting, if the patient experiences signs or symptoms of CRS/IRR, post dose monitoring should be extended until it is confirmed that the patient is symptom free for at least an hour and confirmed by the treating physician that the patients is stable for discharge.

During Dose Expansion, hospitalization and monitoring requirements will be the same as those applied at the respective RP2D during Dose Escalation. The CRC may recommend adjustments to the observation periods based on review of cumulative safety data.

5.1.5 Storage and Stability of HPN424 and Diluent

HPN424 must be kept in a secure limited access area. HPN424 may only be used in patients enrolled specifically in this clinical study and may not be used in other persons or released to any third party, laboratory, or clinic for use in humans, or for *in vivo* or *in vitro* laboratory research, or any other use without prior authorization from Sponsor.

HPN424 vials must be stored frozen upon receipt until preparation for use; vial contents should not be shaken and should be protected from direct sunlight. Diluent must be stored refrigerated. HPN424 and diluent should not be used beyond the expiration date provided by the manufacturer. Consult the vial label, Investigator's Brochure, and Pharmacy Manual for current storage and stability conditions for HPN424 and diluent.

5.1.5.1 Drug Accountability

HPN424 will be supplied directly to the study sites. The individual receiving the shipment must verify the condition and quantity of study drug received. A drug accountability log must be maintained throughout the study to document the receipt, dispensing, return, or destruction of each vial of HPN424.

Used vials will be destroyed according to the site's policy for investigational drug destruction. Unused vials will be either destroyed at the study site or returned to the Sponsor, as agreed between each site and Sponsor. Before disposal/destruction of unused vials, final drug accountability and reconciliation must be performed by the site monitor. Documentation of destruction of vials of HPN424 must be available for review by the monitor.

5.2 Dose-Limiting Toxicity

Severity of adverse events (AEs) will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. During Dose Escalation, any of the following AEs occurring within 21 days after first administration of the Target Dose which are attributable to HPN424 and unrelated to mCRPC, intercurrent illness, or concomitant medications will be classified as DLTs:

Hematological:

- Prolonged myelosuppression, defined as CTCAE Grade ≥3 hematologic parameters (absolute neutrophil count [ANC] <1000/mm^3, platelet count <50,000/mm^3, or hemoglobin [Hgb] <8 g/dL) in a bone marrow with <5% blasts and no evidence of leukemia or abnormal dysplasia, that lasts longer than 21 days from the point of detection
- Grade ≥3 neutropenia with infection
- Grade 4 neutropenia lasting >5 days
- Febrile neutropenia (defined as an ANC <1.0 x 10^9/L with a single temperature of >38.3°C or 101°F, or a sustained temperature of ≥38°C or 100.4°F for more than one hour)
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia

Non-hematological:

- Grade ≥3 non-hematological toxicities are considered DLTs, with the following *exceptions*:
  - Grade 3 nausea/vomiting/diarrhea or Grade 4 vomiting/diarrhea lasting <72 hours in the absence of maximal medical therapy are NOT considered a DLT.
  - Grade 3 fatigue lasting less than 7 days is NOT considered a DLT.
  - Non-hematologic laboratory Grade 3 AE that is asymptomatic and/or rapidly reversible (returned to baseline or to Grade ≤1 within 7 days) unless identified as clinically relevant by the Investigator is NOT considered a DLT
  - Events of increased blood pressure are not considered DLTs if associated with symptoms of CRS/IRR and resolve in concordance with CRS symptom resolution and do not result in additional safety events.
- Dose delay or dose interruption ≥3 weeks is considered a DLT.
- Hy's Law (concomitant ALT or AST elevation of >3 times the upper limit of normal [ULN] and total bilirubin elevation of >2xULN without a clear alternative etiology) is considered a DLT.
- Grade 4 IRR or CRS per ASTCT (Lee, 2019), with or without pre-medication, is considered a DLT.
- Grade 3 IRR or Grade 3 CRS per ASTCT (Lee, 2019) that occurs despite a premedication regimen that includes dexamethasone is considered a DLT.

Clinically important or persistent toxicities (e.g., toxicities responsible for significant dose delay) that are not included in the above criteria may also be considered a DLT following review by the Investigators and Sponsor. To be considered a DLT, the AE must represent a clinically significant shift from baseline and must be considered to be related or suspected to be related to HPN424 by the Investigator or Sponsor.

For Step Dosing cohorts, if DLTs are observed between administration of the Priming and Target Doses, the CRC will consider the safety data of all patients treated at the Priming Dose level (including patients who received the priming dose in prior 3 + 3 cohorts and single patient cohorts) when making decisions regarding cohort expansion (e.g., expand cohort to at least 6 patients if < 6 patients have received the Priming Dose), dose escalation (or de-escalation), and priming regimen.

During Dose Escalation, patients who do not receive at least 3 Target doses of HPN424 for reasons other than DLT (e.g., logistical or technical reasons, non-DLT-related dose delays) may be considered not to be DLT-evaluable and may be replaced, but they can remain on study and receive additional treatment with HPN424 per protocol. Patients in the Dose Escalation stage who withdraw for any reason after Cycle 1 will not be replaced.

Late DLTs

Late DLTs are AEs that meet the same grading criteria as DLT criteria and occur after the DLT period through the 60-day assessment period during Dose Escalation. At the time of the CRC meetings to review a specific cohort, the late DLT events for that cohort will be reviewed by the CRC (Section 11.9), which may decide to:

- Continue enrollment in higher dose level cohorts
- Increase the number of patients at the dose level in which the late DLT occurred to satisfy the 3 + 3 decision rules. All patients will be followed for at least 60 days to reassess safety at this dose level. If the 3 + 3 decision rule of dose-escalation is reached, enrollment in higher dose level cohorts may resume. If, after the enrollment of additional patients, the CRC recommends dose de-escalation, then all patients will be dose-reduced to the recommended dose level.
- Permanently stop enrollment in higher dose level cohorts and declare the dose level to be above MTD. Increase the number of patients at the dose level in which the late DLT occurred satisfy the 3 + 3 decision rules.
- Stop the study

For any patient that is being treated at a dose level that is subsequently considered to be above the MTD, the option to dose-reduce will be discussed. If a patient tolerated the above-MTD dose level well and is benefiting (as determined by the Principal Investigator and upon consultation with the Medical Monitor), continuation of treatment at the above-MTD dose level will require re-consenting.

5.3 Dose Interruptions and Dose Modifications

For patients in all cohorts who do not receive a dose within the protocol scheduled window (–2 days/+1 day) for any reason, the dose will be considered missed. Dosing may resume on the next scheduled visit unless a longer treatment interruption is required for toxicity or other reasons. Considering the length of dose interruption, the Investigator and Medical Monitor will work together to determine hospitalization requirements upon resumption as well as the premedication regimen.

For patients in the Step Dosing arm, resumption of treatment will be with the appropriate priming regimen and should be discussed with the Medical Monitor prior to recommencement of HPN424 Administration.

Dose modifications for toxicities should be independently assessed at each visit. Recommendations for HPN424 dose modifications due to toxicities are provided in Table 11.

Table 11 HPN424 Dose Modification for Toxicity

Toxicity	Action with HPN424	% of Full Dose After Recovery to Grade 1 or Baseline [a]
Grade 1	No change	100%
Grade 2	Hold dose until resolution of toxicity to Grade 1 or Baseline	100%
Grade 3	Hold dose until resolution of toxicity to Grade 1 or Baseline	Reduce 1 dose level [b]
Grade 4	Hold dose until resolution of toxicity to Grade 1 or Baseline	Reduce 1 dose level

[a] If a toxicity is observed in the absence of premedication, the patient may be exposed to same dose level (i.e., no dose modification) following premedication with steroid. The Investigator with consult Medical Monitor prior to resumption of treatment.

[b] Laboratory toxicities that are asymptomatic and/or rapidly reversible and not associated with clinical sequelae may not require a dose modification and should be discussed with the Medical Monitor.

After resolution of a Grade ≥ 3 toxicity considered to be related or suspected to be related to HPN424, patients may be re-started at a lower dose of HPN424, as determined by the Medical Monitor. Once the dose has been reduced for toxicity and found to be well tolerated, re-escalation to the original dose may be permitted, following discussion between the Investigator and Medical Monitor.

If toxicity requiring dose reduction (Grade ≥3 related AE) occurs after administration of a Priming Dose and prior to administration of the Target dose, dose reduction when treatment is resumed will apply to the Priming Dose Level. The reduced Priming Dose must be established to be well tolerated prior to any subsequent dose escalation.

During the Dose Escalation and Expansion stages, dose interruptions of up to 3 weeks are permitted for appropriate resolution of toxicity (as determined by the Investigator). Dose interruptions 3 weeks or longer may be allowed on a case-by-case basis after discussion between the Investigator and Medical Monitor

All reasons for treatment modifications should be fully explained in the patient's medical records.

5.4 Management of Adverse Events

Based on the safety profile of blinatumomab, a bispecific T cell engager that targets CD19 in acute leukemia patients (Blincyto, 2021), activating T cells with a mechanism similar to that expected for HPN424, and from observed adverse events associated with HPN424 to date, the primary anticipated risks related to this Phase 1/2a trial in a prostate cancer population include CRS/IRR, neurological toxicities, and elevated liver enzymes.

5.4.1 Management of Cytokine Release Syndrome and Infusion-Related Reactions

CRS and IRRs have overlapping clinical manifestations and may occur with HPN424 treatment. CRS will be graded using the ASTCT CRS Consensus Grading Criteria (Lee, 2019) (Appendix 8) and managed using the guideline published by Lee (Lee, 2014) and adapted by Neelapu (Neelapu, 2018). Organ toxicities and symptoms occurring as part of a CRS/IRR event will be individually graded according to CTCAE v5.0.

During HPN424 infusion, patients will be clinically monitored at regular intervals for early signs and symptoms indicative of CRS/IRR. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, renal and/or hepatic failure and disseminated intravascular coagulation (DIC). Trained clinical personnel should be prepared to intervene in the event of CRS/IRR. Resources necessary for resuscitation should be readily available.

Patients who experience CRS/IRR should be treated per Investigator discretion and Institutional Guidelines; a general reference is provided in Table 26 (Appendix 8).

If CRS is observed during study treatment, a blood sample for C-reactive protein (CRP) and serum samples for cytokines (specifically IL-6) and PK analysis should be collected and assessed. HPN424 dose modification guidelines are described in Section 5.3.

5.4.2 Management of Injection Site Reactions

Patients should be instructed to notify their health care provider if they experience any pain or discomfort (e.g., warmth, itching, or redness) at the investigational product injection site. Patients who experience any of these symptoms at the injection site should be instructed to apply a cold compress to the area while waiting for further instruction. If injection site reactions become severe, the patient should be evaluated by a dermatologist, and the Investigator should discuss with the Medical Monitor on how to proceed before further injections are administered.

Analgesics for pain, and antihistamines or topical corticosteroids for pruritis and edema may be employed as clinically indicated.

5.4.3 Management of Other Potential Adverse Events

Based on the experience of other T-cell activating agents, severe or serious neurological toxicities could occur with HPN424. Neurotoxicity is a common toxicity observed in adoptive T cell therapy with chimeric antigen receptors. Previously considered in aggregate with CRS, neurotoxicity is now considered and treated as a separate entity (Lee, 2019). If signs and symptoms of neurotoxicity are observed, they should be graded according to CTCAE v5.0. Guidelines for management are provided in Appendix 8. Patients should be monitored for neurological AEs including, but not restricted to, speech disorders, convulsions, and disturbances in consciousness, confusion, disorientation, or coordination and balance disorders. If these or other neurological AEs are observed, administration of HPN424 should be withheld and the Medical Monitor must be consulted as soon as

practically possible. Administration of HPN424 should be withheld for Grade ≥3 neurological AEs and, depending on the nature and severity of the event, the Medical Monitor and Investigator will determine whether administration of HPN424 may recommence after resolution of the event.

High grade transaminitis (Grade 3-4) has been reported with adoptive T Cell therapy and has also been observed in patients treated with HPN424 (Blincyto, 2021). In patients treated with HPN424, these events have not been associated with clinical signs or symptoms of liver dysfunction. The majority of high grade transaminitis events observed with HPN424 treatment have been reported following the initial dose of HPN424 or initial dose increase as part of a step-dosing regimen. Assessment of liver function tests should be done per the appropriate Schedule of Assessments (Appendix 1, Appendix 2, Appendix 3 or Appendix 4). Transaminitis should resolve to Grade ≤ 1 prior to administration of subsequent HPN424 doses. Depending on the extent of elevation and time to resolution, dose reduction may be required. Management and dose modification should be discussed with the Medical Monitor. Bilirubin levels should be monitored in all patients who experience transaminitis. Additional assessments to consider based on the Investigator's discretion and discussion with the Medical Monitor include PT/PTT/INR, albumin, DIC, panel, and platelets. Imaging of the liver and hepatic ducts with ultrasound or MRI/CT should be considered per Investigator's clinical judgement (e.g., for patients who have concurrent elevated bilirubin or signs of liver dysfunction or if the transaminitis is severe and with no indication that it is resolving). Additional assessments should be done per standard of care and Investigator's clinical judgement.

5.5 Selection and Timing of Dose for Each Patient

During Dose Escalation the treatment arm and dose level will be assigned for each patient according to the Dose Escalation scheme in Section 3.1.1.

During Dose Expansion the RP2D(s) will be administered to all patients in a given cohort. While the intention is to study a single RP2D, multiple RP2Ds at or below the MTD or derived from assessment of more than one of the 3 + 3 Dose Escalation arms may be explored in additional expansion cohorts at the recommendation of the CRC.

5.6 Method of Assigning Patients to Treatment Groups

Patients will be assigned to dose level cohorts sequentially as they are enrolled in the study. Sites must contact the Sponsor or designee to obtain approval for enrollment and confirmation of cohort assignment for each patient prior to initiation of study treatment.

If both a SC cohort and an IV cohort are open simultaneously, then enrollment in the SC cohort will be prioritized unless emergent data indicates that enrollment into the IV cohort should be prioritized. There is no intention to make formal comparisons of the different routes of administration under investigation.

5.7 Blinding

There is no blinding in this open-label study.

5.8 Concomitant Therapy

5.8.1 Permitted Medications

In addition to premedications (Section 5.1.4), the following medications may be administered during the study:

- Palliative and supportive care for disease related symptoms
- Granulocyte colony stimulating factors after first dose
- Primary prophylaxis of diarrhea, nausea, and vomiting after first dose
- Anti-inflammatory or narcotic analgesic
- Acute emergency and short-term administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids
- Limited palliative radiotherapy
- Caution with any surgical procedures during the study (i.e., if there is clinical indication for surgical procedure during the study this should be discussed with the Sponsor Medical Monitor)

5.8.2 Prohibited Medications

The following medications are prohibited during the study:

- Anticancer treatment including chemotherapy, hormonal therapy initiated during the course of the study, radiotherapy, or experimental anticancer medications. Palliative external radiation (e.g., to bone metastasis) is allowed if medically unavoidable. If radiation therapy is required, interruption and/or continuation of study treatment should be discussed with the Medical Monitor
- Chronic, systemic corticosteroid use (prednisone >10 mg/day or equivalent) for palliative or supportive purposes. If treatment with high dose corticosteroids is required for management of AE, interruption and/or continuation of study treatment should be discussed with the Medical Monitor.
- Live vaccine administration during the study, including the treatment period, and until recovery of B lymphocytes to normal ranges following last treatment cycle

5.9 Treatment Compliance

Treatment compliance will be monitored via study documentation including patient records and the drug accountability logs. Treatment compliance will also be reflected in the HPN424 levels measured in PK assessments.

6 DESCRIPTION OF STUDY PROCEDURES

Study procedures are to be performed on the appropriate schedule outlined in the Schedule of Assessments in Appendix 1, Appendix 2, Appendix 3, or Appendix 4. Additional details for selected study procedures are provided in the sections below.

6.1 Informed Consent

Before the performance of any protocol-specific procedures that would not otherwise be done for a patient as part of standard of care, a written and signed informed consent form (ICF) must be obtained from the patient.

6.2 Confirmation of Inclusion/Exclusion Criteria and Enrollment

The patient must be confirmed to meet all inclusion and exclusion criteria within 28 days prior to the start of study treatment (Day 1) unless otherwise specified.

Sites must contact the Sponsor or designee to obtain approval for enrollment and confirmation of patient identification number and dose level assignment for each patient prior to initiation of study treatment.

6.3 Demography and Medical History

A complete medical history should be collected through review of medical records and by interview. Disease history should include the date and Tumor, Node and Metastasis (TNM) stage at initial diagnosis. Dates of treatment should be recorded for prior treatment including androgen deprivation therapy (ADT), anticancer systemic treatment, surgical procedures, and radiotherapy. Response and type of progression on prior treatment should be recorded: PSA only, bone only ± nodal disease, nodal disease only (no bone disease present), visceral (lung, liver, adrenal, central nervous system) disease ± other sites, and/or clinical (e.g., pain escalation). History of symptomatic skeletal events (SSEs) including symptomatic fracture, radiation, or surgery to bone, or spinal cord compression should be recorded.

6.4 ECOG Performance Status

The grading scale for ECOG Performance Status is shown in Appendix 5. ECOG will be recorded on Day 1 of each cycle.

6.5 Height, Weight, and Physical Examination

The screening physical examination should include, at a minimum, height (screening only) and weight, the general appearance of the patient, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams should be done at subsequent visits as indicated per appropriate Schedule of Assessments.

6.6 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the patient has rested in the sitting position.

6.7 12-Lead Electrocardiogram

Routine 12-lead ECG should be performed pre-dose at the designated visits in the appropriate Schedule of Assessments. Patients should be resting in a supine or sitting position for ≥10 minutes prior to an ECG collection. If cardiac abnormalities are detected or suspected, two additional ECGs must be performed to further evaluate and each reading should be obtained at least 3 minutes apart.

6.8 Pulse Oximetry

Pulse oximetry will be assessed at rest prior to each dose of HPN424.

6.9 Clinical Laboratory Tests

Clinical laboratory tests including hematology, chemistry, and urinalysis will be performed at local laboratory facilities at each site, on Day 1 of each cycle and at additional visits (unless otherwise specified) per the appropriate Schedule of Assessments.

If the required lab samples are not collected at the protocol-specified study visit, sites should attempt to collect samples at the next study visit.

Table 12 Clinical Laboratory Parameters

Hematology:
- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential

Coagulation:
- Prothrombin time (PT)/ international normalized ratio (INR)
- Activated partial thromboplastin time (PTT)

Urinalysis:
- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Nitrite
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen

Serum Chemistry:
- Albumin (ALB)
- Alkaline phosphatase, total (ALK-P)[a]
- Alkaline phosphatase, bone specific (BAP)
- Alanine aminotransferase (ALT; SGPT)[a]
- Amylase
- Aspartate aminotransferase (AST; SGOT)[a]
- Blood urea nitrogen (BUN) or Urea
- Calcium (Ca)
- Carbon dioxide (CO_2)
- Chloride (Cl)
- Creatinine
- C-Reactive protein (CRP)[b]
- Globulin
- Glucose
- Lactate dehydrogenase (LDH)
- Lipase
- Magnesium
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin [a]
- Direct bilirubin
- Total protein
- Uric acid

[a] Additional assessments for alkaline phosphatase (total), alanine aminotransferase, aspartate aminotransferase, and total bilirubin will be assessed at end of HPN424 administration and 5 hours [± 1 hour] after HPN424 administration. Consult appropriate Schedule of Assessments for specified visits/timepoints.

[b] Consult appropriate Schedule of Assessments for specified visits/timepoints. Collect additional samples for CRP when signs of CRS are observed (Section 5.4.1).

6.10 Testosterone

Testosterone is to be tested using testosterone assays at local laboratories per the appropriate Schedule of Assessments.

6.11 Serum Cytokines

Serum specimens will be collected for cytokine analysis per the appropriate Schedule of Assessments. Additional samples should be collected during treatment if signs of CRS or neurotoxicity are observed. Additional serum samples may be collected as needed (e.g., following CRS, Grade ≥3 IRR, HPN424 dose modification, dose schedule modification, steroid [i.e., dexamethasone] use/dose modification, etc.). Patients who partake in intrapatient dose escalation should have additional samples collected 5 hours and 24 hours post- first HPN424 administration at the increased dose level.

Evaluations will include (but are not limited to): IL-2, IL-4, IL-6, IL-10, IFN-γ, and TNF-α. Instructions for submitting specimens to the central lab are provided in the Laboratory Manual.

If CRS occurs (or is observed, regardless of the grade), the site should draw a cytokine panel (specifically IL-6) using their local lab.

6.12 Immunophenotyping of Circulating Lymphocytes

Whole blood samples (5 mL) for immunophenotyping of circulating lymphocytes will be evaluated by flow cytometry per the appropriate Schedule of Assessments to assess post-treatment margination and treatment-induced lymphocyte activation. Instructions for submitting specimens to the central lab are provided in the Laboratory Manual.

6.13 Circulating Tumor Cells (CTC)

Whole blood samples (10 mL) for CTCs will be assessed per the appropriate Schedule of Assessments. CTCs, as an exploratory disease biomarker, will be evaluated for morphological phenotypes, biochemical analyses, and genomic profiling. Instructions for submitting specimens to the central lab are provided in the Laboratory Manual.

6.14 Pharmacokinetics Assessments

Serum samples will be collected to evaluate the serum levels of HPN424 per the appropriate Schedule of Assessments. Samples should be drawn from a vein in the opposite arm of that used for HPN424 infusion or from a separate vein if HPN424 was administered through a central line.

Additional serum samples may be collected as needed (e.g., following CRS, Grade ≥3 IRR, HPN424 dose modification, dose schedule modification, steroid [i.e., dexamethasone] use/dose modification, etc.). Patients who partake in intrapatient dose escalation should have additional samples collected 5 hours and 24 hours post- first HPN424 administration at the increased dose level.

Details for collection, handling, and shipment of specimens are provided in the Laboratory Manual.

6.15 Anti-Drug Antibodies

Serum samples will be collected to evaluate the levels of antibodies to HPN424 (anti-drug antibodies, ADA) per the appropriate Schedule of Assessments. Details for collection, handling, and shipment of specimens are provided in the Laboratory Manual.

6.16 Exploratory Research

No additional specimens will be collected for exploratory research, but any available unused or leftover tissue, plasma, serum, and/or whole blood collected for required study assessments may be banked for exploratory research purposes such as serum PSMA levels and cytokines determination beyond treatment Cycle 1.

6.17 Tissue Specimens for PSMA Expression and Biomarker Studies

Archival tissue specimens may be collected, if available, for testing of PSMA expression, morphologies of the prostate cancer cells, and other biomarkers of immune cell infiltration and activation, by immunohistochemistry if the sample meets the specifications in the Laboratory Manual. If appropriate archival specimens are not available, a fresh specimen may be collected via biopsy prior to the start of study treatment, provided the patient provides consent. Tissue may be from the primary tumor or a metastatic site. Documentation of PSMA expression is not required for study entry; tissue specimens will be batched and tested while the study is ongoing.

During the study, if additional biopsies or relevant biological samples (e.g., pleural fluid) are collected by the Investigator for clinically indicated assessment, a sample should be retained, if possible, for Sponsor research evaluation.

Detailed instructions for tissue collection, processing, and shipment are provided in the Laboratory Manual.

6.18 Disease Assessments

Patients will be assessed for disease status by the Investigator, according to the PCWG3 recommendations (Scher, 2016) (Appendix 6). The Investigator will record Biochemical Response (based on PSA) and Radiographic Response (based on bone scans and, for those with soft tissue disease, CT or MRI results) at timepoints as outlined in the appropriate Schedule of Assessments and at other times if clinically indicated.

Key disease assessments (PSA, bone scans and CT/MRI) are to be performed per the appropriate Schedule of Assessments irrespective of whether treatment is delayed or missed. In other words, the schedule for these items is calendar-based and fixed relative to C1D1.

Note: in patients who show evidence of clinical benefit, PCWG3 advises continuing therapy until the patient is no longer clinically benefitting (NLCB), not strictly at the first sign of

disease progression. PCWG3 draws the distinction between documenting progression for consistency of reporting (e.g., recording the date of documented progression in a site of disease such as a lymph node that is unlikely to adversely affect prognosis) versus the decision to stop therapy. In this study, patients may continue weekly HPN424 treatment as long as they are receiving clinical benefit (as determined by the Principal Investigator and upon consultation with the Medical Monitor).

Disease assessments are to continue (unless the patient withdraws consent or is lost to follow-up), until discontinuation of study treatment and prior to initiation of new anticancer therapy.

6.19 Prostate Specific Antigen (PSA)

Prostate specific antigen (PSA) will be measured per the appropriate Schedule of Assessments. Timepoints are fixed based on the calendar, regardless of treatment delays. PSA response and progression will be defined per modified PCWG3 guidelines (Appendix 6). PSA progression does not warrant discontinuation of tumor assessments or study treatment.

6.20 Radiological Imaging

Radiological imaging, including bone scans and CT/MRI for all known or suspected disease sites, is required during Screening and repeated using the same imaging techniques during study treatment, as indicated in the appropriate Schedule of Assessments. Timepoints are fixed based on the calendar, regardless of treatment delays. Tumor assessments are to continue regardless of discontinuation of study treatment or initiation of subsequent systemic anticancer therapy unless there is withdrawal of consent or permanent loss to radiographic follow-up (including hospice admission).

Imaging techniques are to follow PCWG3 guidelines (Scher, 2016) as summarized in Appendix 6 and details below.

6.20.1 Tumor Assessment Criteria

Radiologic tumor assessments including bone scans and CT or MRI scans should be performed according to the appropriate Schedule of Assessments irrespective of whether study treatment is delayed or missed. Brain scans will be performed at baseline and on study if disease is suspected, and on study as appropriate to follow disease. Analysis of tumor assessments for the purpose of this study will be by Investigator assessment and will be collected on case report forms (CRFs).

6.20.2 Image Acquisition Parameters

The following image acquisition parameters must be recorded as applicable: tomographic slice thickness and reconstruction interval, pulse sequence, contrast agent (including brand name), contrast agent dose and route of administration, contrast agent injection start and stop times, and contrast agent injector type (e.g., manual or power/auto injector).

6.20.3 Soft Tissue Disease Assessment

CT scans should include full coverage of chest, abdomen, and pelvis at all specified timepoints. If MRI is performed for the abdomen and pelvis examinations, then at least a non-contrast CT chest must be performed as well. Baseline central nervous system (CNS) imaging is not required with the exception of symptomatic patients to rule out CNS metastases. The same method of radiological assessment must be used throughout the study. In particular, the same modality and imaging protocol used at baseline should be used at all subsequent imaging timepoints. For at least the baseline imaging examination, both pre-contrast CT (or MRI) scans of the abdomen (liver at minimum) and post contrast CT (or MRI) scans of the chest, abdomen, and pelvis must be obtained. For the abdomen and pelvis at least single phase (equilibrium or IVC phase) should be obtained. For all scheduled follow-up imaging examinations, post contrast CT (or MRI) scans of the chest, abdomen, and pelvis must be obtained. Volume acquisition CT reconstructed every 3-5 mm contiguously with a soft tissue filter should be performed. MRI scans should be performed using a body coil and reconstruction every 3-5 mm without gap.

Soft tissue disease response and progression will be defined per modified PCWG3 guidelines (Appendix 6). Soft tissue disease progression does not warrant discontinuation of tumor assessments or study treatment (Table 24). Nodes ≥1.5 cm in the short axis are considered measurable; nodes ≥ 1.0 and less than 1.5 cm in the short axis are considered pathologic according to clinical discretion, and nontarget; nodes less than 1.0 cm in the short axis are nonpathologic.

6.20.4 Bone Scan Assessment

Whole body anterior and posterior bone scans should be acquired using 25 mCi (± 10%) technetium 99m-methyl diphosphonate (Tc99 MDP) administered intravenously, with imaging performed 3 hours post injection. For all follow-up bone scans, the same dose of Tc99 MDP and the same delay from injection to scanning and bed speed must be used and be recorded on source documents.

For patients with symptoms of spinal compression, MRI of the spine and base of the skull should also be performed.

Worsening bone scan does not warrant discontinuation of bone scans or study treatment (Table 24).

6.21 PSMA PET

PSMA-targeted PET scans may be performed as an exploratory disease assessment at selected sites. The Sponsor may collect the PSMA PET and associated scans for possible central review and analysis.

6.22 Prior and Concomitant Medication Data

All prior medications (within 28 days prior to Day 1) and any ongoing or concomitant medications from Day 1 through the SFU (28 days [+ 7 days] after the last study treatment) are to be recorded.

6.23 Adverse Event Assessments

Adverse events will be monitored and recorded throughout the study.

6.23.1 Definition of Adverse Event

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

Medical conditions that are present at baseline (i.e., before the patient receives any HPN424) are not AEs and are not recorded on AE CRFs; they should be documented on the Medical History CRFs. However, medical conditions present at baseline that worsen in intensity or frequency during the AE reporting period must be reported as AEs.

Abnormal laboratory results or vital signs with physical symptoms or that require intervention are to be recorded as AEs (e.g., lightheadedness secondary to anemia), as are complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).

6.23.2 Adverse Event Reporting Requirements

6.23.2.1 Adverse Event Reporting Period

After informed consent has been obtained but prior to initiation of study drug, all AEs/SAEs assessed as attributable to a protocol-mandated intervention (e.g., biopsies, discontinuation of medications) must be reported to the Sponsor. Starting from the first dose of study drug and through SFU (28 days [+ 7 days] after the last dose of study drug) all AEs/SAEs must be reported to the Sponsor. If during the SFU period the patient has initiated another systemic treatment, information regarding the treatment should be recorded, including treatment and date of initiation.

After the SFU period, any AE or SAE assessed as related to HPN424 must be reported to the Sponsor.

6.23.2.2 Adverse Event Follow-up

AEs assessed as not related to study drugs or procedure, including clinically significant laboratory tests, ECGs, or physical examination findings, must be followed until the event

resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first and as judged by the Investigator.

AEs and SAEs assessed as related to study drugs or procedure will be followed for as long as necessary to adequately evaluate the patient's safety, or until the event stabilizes, or the patient is lost to follow-up. If resolved, a resolution date should be provided, and for SAEs, a follow-up SAE report must be submitted indicating the resolution date. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and causality of the AE. This may include additional clinical laboratory testing or investigations, examinations, histopathological examinations, or consultation with other health care professionals as is practical.

6.23.2.3 Post Study Reporting Requirements

Any AE or SAE assessed by the Investigator as being related to study drug or procedures must be reported regardless of time after study termination.

6.23.3 Severity

The Investigator will record the maximum intensity (or severity) of the AE using the NCI CTCAE version 5.0. If the CTCAE does not have grading criteria for the event, the event should be graded by the Investigator using the following scale in Table 13:

Table 13 Adverse Event Severity Scale

Grade	CTCAE v5.0 Guideline
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE

* Instrumental activities of daily living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.23.3.1 Severity Assessment of Cytokine Release Syndrome

The AE of CRS should be graded using the ASTCT CRS Consensus Grading Criteria (Lee, 2019) (Appendix 8). AEs that are organ toxicities and symptoms occurring as part of a CRS event will be individually graded according to CTCAE v5.0.

6.23.4 Causal Relationship

The Investigator's assessment of an AE's relationship to study drug (HPN424) or study procedure is required. The relationship or association of the study drug or procedure in causing or contributing to the AE will be characterized using the classification and criteria in Table 14. Refer to the Investigator's Brochure for Reference Safety Information which lists the adverse reactions expected for the study drug, their frequency of occurrence, and which provides guidance for assessing expectedness and determining the expedited reporting requirements of any suspected unexpected serious adverse reactions (SUSARs).

Table 14 Adverse Event Relationship Criteria

Related or Suspected to be Related to Study Drug or Procedure	Some temporal relationship exists between the event and the administration of the study drug(s) or procedure, and the event is unlikely to be explained by the patient's medical condition, other therapies, or accident. The AE follows a reasonable temporal sequence from administration of the study drug or procedure and at least one of the following instances of clinical evidence: • Follows a known or suspected response pattern to the study drug or procedure. • Is confirmed by improvement upon stopping the study drug or procedure or decreasing the dose (dechallenge). • Reappears upon repeated exposure (rechallenge) if medically appropriate. There is a reasonable possibility that the study drug or procedure caused the event — i.e., there is evidence to suggest a causal relationship.
Not Related to Study Drug or Procedure	Event can be readily explained by other factors such as the patient's underlying medical conditions, concomitant therapy, or accident; or there is no temporal relationship between study drug or procedure and the event. A reasonable possibility or clinical evidence that the study drug(s) or procedure caused the event is lacking.

6.23.5 Serious Adverse Events

6.23.5.1 Definition of Serious Adverse Event

A serious adverse event (SAE) is an AE that fulfills any of the following criteria, as per Title 21 CFR 312.32 and International Council for Harmonisation (ICH) E2A.II.B. Events meeting the following seriousness criteria must be reported within 24 hours of the site being notified of the event, using the expedited reporting procedures described in Section 6.23.7. The event must also be entered on the AE CRF.

- Is fatal (results in death)
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe). If either the

Investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.

- Requires inpatient hospitalization or prolongs existing hospitalization
- Results in persistent or significant incapacity or disability, defined as substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one of the outcomes listed above
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition of an SAE.

  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, and the development of drug dependency or drug abuse.

Hospitalization is NOT considered an SAE if:

- It is planned prior to patient entering trial
- It is for social reasons and respite care in the absence of any deterioration in the patient's general condition
- It is elective in nature and not related to worsening of an underlying condition

Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.

"Inpatient hospitalization" means the patient has been formally admitted to a hospital for medical reasons, for any length of time. Emergency room care without admission to a hospital is considered outpatient care.

Overdose, medication errors, inadvertent or accidental exposure to study drug and drug misuse/abuse of the study drug are SAEs only if any of the seriousness criteria are met. Details of signs and symptoms, clinical management, and outcome should be reported.

For medical questions regarding an SAE, contact the Medical Monitor.

6.23.6 Other Experiences Immediately Reportable to the Sponsor

The following immediately reportable experiences should always be assessed for seriousness criteria first, and if those criteria are not met, then they must be entered on the AE CRF and SAE form and reported within 24 hours of first knowledge of the event by study personnel, using the expedited reporting procedures described in Section 6.23.7.

- ALT or AST with a 3-fold or greater elevation above the upper limit of normal (ULN) in addition to an elevation of serum total bilirubin greater than two times the ULN, with no other identifiable etiology
- Liver enzyme (ALT or AST) value greater than or equal to 5 times the ULN

In addition, if a patient's partner becomes pregnant any time after the first dose of study drug through the end of the required contraception period, the pregnancy must be immediately reported on a Pregnancy Report Form to the Sponsor or its designee. The pregnancy must be followed until the outcome of the pregnancy or for a minimum of 6 months following the birth of the child. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae must be provided to the Sponsor.

6.23.7 Expedited Reporting Procedures

All SAEs and other immediately reportable events, regardless of relationship to HPN424 or expectedness, that occur during the AE reporting period are to be reported to the Sponsor or designated representative as soon as possible, and no more than 24 hours after first becoming aware of the SAE. Contact information and reporting procedures will be detailed in the Study Manual.

SAE reports should be completed as thoroughly as possible and reviewed by the Investigator or his/her designee before transmittal. The Investigator must provide his/her assessment of causality to study drug or procedure at the time of the initial report. Where the Investigator does not provide causality assessment of the event at the time of the initial report, the event by default will be presumed "Related." If the Investigator's assessment of causality changes, and if additional relevant information becomes available, then follow-up SAE reports must be submitted.

The Sponsor may request additional information from the Investigator, e.g., hospital admission or discharge notes, laboratory results, or consultation reports.

The Investigator is responsible for reporting SAEs to the institutional review board (IRB) or independent ethics committee (IEC) per applicable guidelines. SAEs will be reported by Harpoon Therapeutics or designee to the Regulatory Authorities, per local regulations.

6.23.8 Progression of Underlying Malignancy

Progressive disease may be recorded as a reason for discontinuing study treatment but is not considered an AE per se and it should not be reported as an AE.

Clinical manifestations of progressive disease may be reported as AEs if they occur during the study and through the SFU (28 days [+ 7 days] after the last dose of HPN424). If clinical manifestations of disease progression meet serious criteria (Section 6.23.5), the event should be reported to the Sponsor as an SAE.

6.23.9 Death

Death is an outcome and not an AE per se. The event or condition that led to the patient's death should be recorded as an SAE with an outcome of fatal. If the cause of death is unknown, then "unknown cause of death" should be recorded as the SAE. If the cause of death becomes available, then the term "unknown cause of death" should be replaced with the appropriate term.

If the death can only be attributed to progression of the underlying malignancy, "progression of pre-existing cancer" should be recorded as the SAE with an outcome of fatal.

All deaths that occur after the SFU (28 days [+ 7 days] should be reported to the Sponsor.

6.24 End of Treatment Visit

The End of Treatment visit will occur within 7 days after the last dose of HPN424.

If the patient withdraws or is lost to follow-up and does not complete the End of Treatment visit per protocol, the Investigator will report any known AEs that occurred up to 28 days after the end of the last HPN424 infusion (i.e., through the SFU).

If scheduled study assessments have been performed within the following windows, the assessments need not be repeated for the End of Treatment visit, unless recent clinical changes have contributed to the decision to end treatment: safety assessments (ECOG, physical exams, vital signs, ECGs, clinical laboratories) within 7 days; specialty labs (CTCs, ADA) within 3 weeks; PSA within 9 weeks; radiological imaging within 9 weeks.

6.25 Safety Follow-up

Safety Follow-up (SFU) will occur at least 28 days (+ 7 days) after the end of the last dose of HPN424, regardless of whether the patient starts another anticancer therapy. The Investigator will report any known concomitant medications that the patient received and any known AEs that occurred through 28 days after the end of the last HPN424 infusion.

Any AEs that are considered to be related to HPN424 and any SAEs (regardless of relationship to HPN424) that are ongoing at the time of the SFU should be followed until the AE resolves, stabilizes, or is considered irreversible. Any SAEs that occur more than 28 days after end of the last HPN424 infusion and are considered by the Investigator to be related to HPN424 must be reported to the Sponsor or designee.

6.26 Long-term Follow-up for Survival

After the SFU, patients are to be contacted via telephone or during routine clinic visits to determine survival. These long-term follow-up (LTFU) telephone calls or visits are to occur monthly (±7 days) for 6 months following the SFU, then every 3 months (±1 month) until death, lost to follow-up or withdrawal from study.

6.27 Contraception

Patients of reproductive potential with female partners of childbearing potential, must be willing to use 1 effective method of contraception (as defined below) during the treatment period, if partner is a female of childbearing potential.

- Methods Considered Highly Effective (defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly)
  - Vasectomy
  - Partner with bilateral tubal occlusion
  - Abstinence - defined as refraining from heterosexual intercourse for the entire period of risk associated with the study treatments. Periodic abstinence is not acceptable (calendar, symptothermal, post ovulation methods), nor is the withdrawal method (coitus interruptus). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.
- Methods Not Considered Highly Effective (defined as methods that result in a failure rate of more than 1% per year)
  - Condom plus spermicide

Contraception must be effective at the first administration of study treatment and throughout the treatment period.

It should be explained to the patient that if his partner is pregnant or breastfeeding when he is enrolled on the trial, the patient should use barrier method contraception (condom plus spermicidal gel) to prevent the unborn fetus or the baby being exposed to investigational product.

7 STUDY DISCONTINUATION

The Investigator must make every reasonable effort to keep each patient on study for the whole duration of the trial, including post-treatment follow-up after completion or discontinuation of study treatment until death, lost to follow-up, consent withdrawal, or study end (as determined by Sponsor), whichever occurs first.

7.1 Discontinuation of Study Treatment

Patients may continue HPN424 treatment beyond disease progression until they are no longer clinically benefiting (NLCB, per PCWG3 guidelines, (Scher, 2016)) as determined by the Principal Investigator and upon consultation with the Medical Monitor. For example, continuation of treatment is encouraged if a rising PSA or worsening of an isolated disease site that was not clinically significant is the sole indicator of disease progression and the patient is otherwise tolerating therapy well.

Patients (or legally acceptable representatives) may decline to continue receiving study drug at any time during the study. The primary consideration in any determination to discontinue study drug treatment is the patient's health and welfare. Patients who withdraw from study drug during the treatment period should be encouraged to return for an End of Treatment visit for evaluation of safety within 7 days of the decision to end study treatment.

The following are acceptable reasons for discontinuation of study treatment:

- Death
- Adverse event that in the Investigator's or Sponsor's judgement warrants withdrawal of study treatment
- Withdrawal of consent
- Serious violation of the study protocol (including persistent patient attendance failure or persistent non-compliance)
- Sponsor's decision to terminate the study
- Withdrawal by the Investigator for clinical reasons not related to HPN424
- Documented progressive disease; or clinical deterioration and patient is no longer clinically benefiting (NLCB) as determined by the Principal Investigator

7.2 Withdrawal from Study Participation

Patients have the right to withdraw from the study at any time and for any reason without prejudice to future medical care. Patient data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data may be included after withdrawal of consent. The Investigator is to discuss with the patient the appropriate

procedures for withdrawal from the study. The Investigator or Sponsor has the right to discontinue any patient from study participation.

Reasons for withdrawal from study participation may include, but are not limited to, the following:

- Death
- Patient's request (withdrawal of consent), with or without a stated reason
- Noncompliance
- Sponsor's discretion
- Lost to follow-up

7.3 Study Termination

The Sponsor reserves the right to terminate the study at any time. Both the Sponsor. and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The Investigator is to notify the IRB/IEC in writing of the study's completion or early termination and send a copy of the notification to the Sponsor.

7.4 Safety Oversight and Stopping Rules

Safety will be monitored throughout the trial by the CRC. In addition, a Study Safety Oversight Committee (SSOC; Section 11.9) will monitor safety on an ongoing basis and will review safety data periodically (as defined by charter), including the identification of any DLT as well as safety events beyond the 60- day DLT/Late DLT window.

During Dose Escalation, patients will be monitored for DLTs and late DLTs (Section 5.2). Decisions on whether to enroll additional patients or proceed with dose escalation will be based on Dose Escalation criteria (Section 3.1.1).

During Dose Expansion, the observation of unacceptable toxicities (e.g., AEs that meet DLT criteria) in more than 33% of patients (with at least 6 patients enrolled) at any time will trigger temporary stopping of patient enrollment and SSOC review of cumulative safety data. Findings will be shared with the CRC. Should this occur, modification of the RP2D may be recommended as an added safety measure, or the SSOC/CRC may recommend amending the protocol, discontinuing additional enrollment, or stopping the trial.

7.5 Replacement of Study Patients

Patients in the Dose Escalation stage who do not receive at least 3 Target doses of HPN424 for reasons other than DLT at the Target Dose (e.g., logistical or technical reasons, non-DLT-related dose delays, or toxicity at a Priming Dose level which inhibits escalation to the Target Dose) may be replaced for DLT evaluation purposes but can remain on study and receive

additional treatment with HPN424 per protocol. Patients in Dose Escalation who withdraw for any reason after the DLT period will not be replaced.

Patients in Dose Expansion who withdraw due to documented disease progression or unacceptable treatment-related toxicity will not be replaced. Patients withdrawing for other reasons may be replaced, on a case by case basis, after discussion with the Medical Monitor.

8 STUDY PROCEDURES BY PERIOD

Schedules of visits and assessments conducted throughout the study are dependent on the assigned dosing regimen (i.e., Fixed Dosing or Step Dosing) and the route of administration and are detailed in the following Appendices:

- Appendix 1: Fixed Dosing Intravenous Regimen
- Appendix 2: Step Dosing Intravenous Regimen
- Appendix 3: Fixed Dosing Subcutaneous Regimen
- Appendix 4: Step Dosing Subcutaneous Regimen

8.1 Screening Period (Day -28 to Day -1)

Before the performance of any protocol-specific procedures that would not otherwise be done for a patient, a written and signed ICF must be obtained from the patient.

Results of screening assessments will be reviewed in the context of eligibility criteria to confirm that the patient meets all inclusion (Section 4.2) and exclusion criteria (Section 4.3) for the study.

If the patient meets all inclusion/exclusion criteria, contact the Sponsor to obtain approval for enrollment and assignment of dose level/cohort (see Study Manual for specific procedures).

8.2 Treatment Period

Cycle 1 Day 1 predose assessments must be completed within 72 hours prior to the start of the Cycle 1 Day 1 dose of HPN424, unless otherwise indicated. If screening assessments were done within this window, they need not be repeated on Cycle 1 Day 1.

The timing of dose administration, hospitalization schedule (Section 5.1.4), and DLT observation period for each cohort is dependent on the assigned dosing regimen and treatment arm and detailed in Table 15.

Table 15 Cycle 1 Treatment and Monitoring Schedule

	Fixed Dose Regimen	One Priming Dose Regimen (Prime A)	Two Priming Dose Regimen (Prime A + Prime B)	Three Priming Dose Regimen (Prime A + Prime B + Prime C)[b]
Priming Dose A	--	C1D1	C1D1	C1D1
Priming Dose B	--	--	C1D8	C1D8
Priming Dose C	--	--	--	C1D15
Target Dose	C1D1	C1D8	C1D15	C2D1
DLT Period	D1-D21	D1-D28	D1-D35	D1- D42
Hospitalization	C1D1, C1D8	C1D1[a], C1D8, C1D15	C1D1[a], C1D8[a], C1D15, C2D1	C1D1[a], C1D8[a], C1D15, C2D1, C2D8

[a] Hospitalization for Priming and Target dose(s) may be reduced or omitted based on CRC review of the emergent safety data at a particular dose level (Section 5.1.4).

[b] If additional Prime Doses are added (e.g., Prime Dose D) Cycle/Day for Prime Dose and first Target dose will be determined by the number of Priming doses for a given regimen (e.g., Priming Dose A will be administered on C1D1, Priming Dose B on C1D8, Priming Dose C on C1D15, and Priming Dose D on C2D1 and so on. The DLT period for all patients in a given cohort will be through 21 days after the first Target Dose.

The patient will be asked to complete scheduled visits and assessments per assigned dose regimen.

During the Treatment Period, disease assessments (including PSA and radiological imaging) are to be performed as indicated irrespective of whether treatment is delayed or missed. In other words, the schedule for these items is calendar-based and fixed relative to C1D1.

8.3 End of Treatment

The End of Treatment visit will occur within 7 days after the end of the last dose of HPN424.

If scheduled study assessments have been performed within the following windows, the assessments need not be repeated for the End of Treatment visit, unless recent clinical changes have contributed to the decision to end treatment: safety assessments (ECOG, physical exams, vital signs, ECGs, clinical laboratories) within 7 days; specialty labs (CTCs, ADA) within 3 weeks; PSA within 9 weeks; radiological imaging within 9 weeks.

8.4 Safety Follow-up

Safety Follow-up (SFU) visit will occur at least 28 days (+ 7 days) after the end of the last dose of HPN424, regardless of the reason for stopping treatment and should occur even if the patient starts another anticancer therapy.

8.5 Long Term Follow-up Visits and End of Study Participation

After the SFU, patients are to be contacted via telephone or during routine clinic visits to determine survival. These long-term follow-up (LTFU) telephone calls or visits are to occur monthly (±7 days) for 6 months following the SFU, then every 3 months (±1 month) until death, lost to follow-up or withdrawal from study.

9 QUALITY CONTROL AND ASSURANCE

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Training of site personnel on all protocol procedures during site initiation visits
- Routine study site monitoring (Section 11.6)
- CRF review against source documents (Section 11.8)
- Data management quality control checks (Section 11.10)

In addition, the Sponsor or designee may conduct periodic site audits.

10 PLANNED STATISTICAL METHODS

10.1 General Considerations

Descriptive statistics will be used to summarize data including baseline patient characteristics, treatment with HPN424, safety variables and preliminary efficacy. Categorical or nominal variables will be summarized by frequency and percentage. Continuous variables will be summarized using standard summary statistics (n, mean, standard deviation, median, minimum, and maximum). Where appropriate, 95% confidence intervals around point estimates will be presented. Details of endpoints analyses will be described in the Statistical Analysis Plan.

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Patients who withdraw or are lost to follow-up will be included in statistical analyses to the point of their last evaluation.

10.2 Determination of Sample Size

Up to 150 patients with mCRPC may be enrolled. The number of cohorts and patients will depend on data observed during Dose Escalation.

Dose Escalation may include up to 130 patients, depending on the dose at which the MTD and RP2D(s) are determined. The sample size and design of the Dose Escalation portion of the study are consistent with those in other oncology studies used to determine MTD. The traditional 3 + 3 dose escalation scheme employs the standard NCI definition of MTD (highest dose associated with DLT in <33.3% of patients) for each arm.

Dose Expansion will include up to 20 evaluable patients using a Simon 2-stage design to assess preliminary clinical efficacy of HPN424 at the RP2D(s). Power calculations based on a Simon 2-stage minimax design (Simon, 1989) test the null hypothesis that overall response rate (ORR) $\leq$0.01 versus the alternative hypothesis that ORR $\geq$0.15, with a Type 1 error rate of 0.05 and power of 80%. This design would allow identification of a target response rate of 15% or better in a population of patients who have failed standard available therapy and would not be expected to have any responders.

A sample size of 14 evaluable patients will be enrolled in the first stage. If the total number responding (defined as partial response [PR] or complete response [CR] is $\geq$ 1, an additional 6 evaluable patients will be enrolled in the second stage for a total of 20 evaluable patients. If the total number responding is $\leq$ 1, the effectiveness of treatment based on ORR will be rejected. If treatment is actually not effective and ORR 0.01, then the expected sample size is 14.8 evaluable patients with a 0.869 probability of early termination and there is a 0.016 probability of incorrectly concluding the treatment is effective (the target for this Type 1 error rate was 0.05 or less). If the treatment is actually effective, there is a 0.199 probability of incorrectly concluding it is not effective (the target for this Type 2 error rate was 0.20 or less).

While the intention is to study a single RP2D, additional expansion cohorts of up to 20 patients per expansion cohort may be added at the recommendation of the CRC. If the CRC recommends multiple RP2Ds, each will be evaluated with independent Simon 2-stage designs of up to 20 evaluable patients per RP2D.

10.3 Analysis Populations

Safety analyses will be based on the Safety Population, defined as all patients who have received any amount of HPN424.

Efficacy analyses will be performed based on the Efficacy Evaluable Population, defined as all patients who have received any amount of HPN424 at the assigned RP2D and who have any evaluable post baseline disease assessment. Patients who withdraw from study treatment due to clinical progression or death without post baseline assessments will be considered non-responders.

PK analyses will be based on the PK Evaluable Population, defined as all patients who have received any amount of HPN424 and who have any evaluable post baseline PK assessment.

10.4 Study Endpoints

10.4.1 Primary Endpoints

Dose Escalation:

- Number and severity of DLTs following treatment with escalating doses of HPN424.

Dose Expansion:

- Overall response rate (ORR), as assessed by PCWG3 criteria for response.

10.4.2 Secondary Endpoints

- Adverse events (NCI CTCAE version 5.0).
- Laboratory abnormalities (NCI CTCAE version 5.0).
- Progression-free survival (PFS) using PCWG3 criteria.
- Duration of response (DOR) using PCWG3 criteria.
- Overall survival (OS).
- Change from baseline in PSA over time
- Change from baseline in CTCs over time
- Pharmacokinetic parameters of HPN424:

- Single dose - maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the single dose concentration-time curve over dosing interval τ ($AUC_{sd, \tau}$), area under the concentration-time curve extrapolated to infinity (AUC_{inf}), terminal elimination half-life ($t_{1/2}$), and clearance (CL) as data permit.
- Multiple dose (assuming steady state is achieved) - maximum concentration at steady state ($C_{ss, max}$), time to maximum concentration ($T_{ss, max}$), area under the steady state concentration-time curve over dosing interval τ ($AUC_{ss, \tau}$), $t_{1/2}$, minimum concentration ($C_{ss, min}$), CL, volume of distribution (V_{ss}), and accumulation ratio ($AUC_{ss, \tau}/AUC_{sd, \tau}$) as data permit.

- Incidence and titers of anti-drug antibodies against HPN424.
- Pre- and post-dose quantification of soluble cytokines in serum.
- Assessment of biomarkers and characterization of immune cell infiltration and activation in the tumor microenvironment

10.5 Analysis of Demographics and Baseline Characteristics

Demographics and baseline characteristics, including diagnosis and treatment history, will be summarized descriptively for all patients.

10.6 Analysis of Pharmacokinetics, Pharmacodynamics, and Immunogenicity

Noncompartmental analysis of HPN424 PK will include the following parameters after a single dose (sd) or at steady state (ss) with multiple doses, as applicable to the route of administration and as data permit:

- maximum concentration (C_{max}, $C_{ss, max}$)
- time to maximum concentration (T_{max}, $T_{ss, max}$)
- area under the concentration-time curve over dosing interval τ ($AUC_{sd, \tau}$, $AUC_{ss, \tau}$)
- area under the concentration-time curve extrapolated to infinity (AUC_{inf})
- terminal elimination half-life ($t_{1/2}$)
- clearance (CL, CL/F)
- apparent volume of distribution at steady state (V_{ss}, V_{ss}/F)
- accumulation ratio ($AUC_{ss, \tau}$ / $AUC_{sd, \tau}$)

Pharmacodynamics parameters including cytokine release and immunophenotyping will be summarized descriptively.

Immunogenicity parameters including the incidence of ADA (antibodies to HPN424) will be summarized descriptively.

10.7 Analysis of Safety

Safety summaries will include summaries in the form of tables and listings. For all patients, AE data will be listed by dose level cohort. The frequency (number and percentage) of treatment-emergent AEs will be summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). Summaries will also be presented by the severity of the AE and by relationship to study treatment. In addition, DLTs and all SAEs, including deaths, will be listed separately and summarized.

Laboratory shift tables containing counts and percentages based on NCI CTCAE (version 5.0) grade will be prepared by dose level cohort, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Changes in vital signs, ECGs, and ECOG scores will be tabulated and summarized.

Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary and listed.

10.8 Analysis of Efficacy

Preliminary analysis of efficacy of HPN424 will be based on radiographic response per Prostate Cancer Working Group 3 (PCWG3) criteria (see the guidelines in Appendix 6).

Efficacy Endpoint Definitions:

- Objective Response Rate (ORR), defined as the proportion of patients who achieve a CR or PR determined by the investigator according to the PCWG3 criteria
- Progression-free Survival (PFS), defined as the time from first receipt of HPN424 to documented disease progression or death due to any cause, whichever occurs first (summarized descriptively using Kaplan Meier method)
- Duration of Response (DOR), defined as the time from the first observed response (CR or PR) to documented disease progression or death due to any cause (summarized descriptively using Kaplan Meier method)
- Overall Survival (OS), defined as the time from first receipt of HPN424 to death due to any cause (summarized descriptively using Kaplan Meier method)

Primary efficacy analyses will measure overall response rate. Secondary efficacy analyses will include PFS, DOR, and OS. Exploratory analyses will be summarized descriptively and relationships between clinical outcomes and safety may be explored.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Compliance with Laws and Regulations

This study will be conducted in compliance with the protocol; Title 21 of the US Code of Federal Regulations (CFR), Good Clinical Practice (GCP) guidelines, ICH guidelines, the Declaration of Helsinki, the requirements of other regulatory agencies as necessary, and local legal and ethical requirements. If there is any discrepancy between US Food and Drug Administration (FDA), ICH, and local requirements, the most stringent standard shall apply.

11.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

This protocol, the informed consent, Investigator's Brochure, and any other relevant supporting information (e.g., all advertising materials) must be reviewed and approved by an appropriate IRB or IEC before study initiation. A letter confirming IRB/IEC approval of the protocol and informed consent, and a statement that the IRB/IEC is organized and operates according to GCP guidelines and the applicable laws and regulations, must be provided to Sponsor before screening patients for the study. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study.

The Investigator is responsible for informing the IRB/IEC of the progress of the clinical study as appropriate and updating the IRB/IEC at least annually. Investigators are required to promptly submit Safety Reports or other updated safety information (e.g., amended Investigator's Brochure) to the IRB/IEC.

The IRB/IEC may have other specific reporting requirements with which the Investigator is expected to comply.

11.3 Ethical Conduct of the Study

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

11.4 Patient Information and Consent

The IRB/IEC-approved informed consent form (ICF) and Patient Information Sheet (PIS), if required, must be provided to the Sponsor. The Investigator or designee must explain to the patient the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in 21 CFR Part 50 and other applicable national and local regulations governing informed consent form.

Before the performance of any protocol-specific procedures that would not otherwise be done for a patient, a written and signed ICF must be obtained from the patient. The form must be signed and dated by the patient or by the patient's legally authorized representative if the patient is unable to sign. A copy of the ICF must be provided to the patient. If applicable, it can be provided in a certified translation into the local language. Signed ICFs must remain in

each patient's study file and must be available for verification by study monitors or regulatory agencies at any time.

In the US, patients must also sign a Health Insurance Portability and Accountability Act (HIPAA)-compliant authorization containing the mandated core elements and requirements prior to participating in a clinical study.

11.5 Patient Confidentiality

The patient's medical information obtained in this clinical study is confidential, and disclosure to third parties other than those noted below is prohibited. This information is protected as mandated by HIPAA (45 CFR Subpart E) for patients in the US. Further, each patient is assigned a unique identification number to correspond to data entered into computer databases and used in reports.

Because of the experimental nature of this treatment, the Investigator agrees to allow the IRB/IEC, representatives of the Sponsor, its designated agents and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all patients enrolled into this study. This includes providing de-identified copies of radiology, pathology, or laboratory results when requested by the Sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

With the patient's permission, medical information may be given to the patient's personal physician or other appropriate medical personnel responsible for the patient's welfare.

11.6 Study Monitoring

Representatives designated by the Sponsor will monitor the clinical study in accordance with current FDA, ICH, national and local regulations and guidelines. During the clinical study, site monitors will visit the study sites on a regular basis to assess and assure satisfactory enrollment rates, data recording, maintenance of required regulatory documentation, and protocol compliance. The Investigator must ensure that all requested materials, including patient charts, CRFs, source documents, laboratory records, and study drug inventory records are available to the site monitor. The Investigator must also ensure that he/she and other qualified personnel are available at each study site visit to discuss and resolve any study-related issues.

As stipulated by 21 CFR 312.58 and ICH guidelines for GCP, representatives of the Sponsor, the FDA, or other regulatory agencies may conduct periodic study site audits. These representatives must have access to all requested materials, including patient charts, CRFs, source documents, laboratory records, and study drug inventory records.

11.7 Case Report Forms

Authorized site personnel will complete electronic CRFs designed for this study and provided by the Sponsor. The Investigator will ensure that the CRFs are accurate, complete,

legible, and completed in a timely fashion. CRF completion guidelines and instructions for transmitting the CRFs to the Sponsor or designee will be provided.

11.8 Source Documentation

As stipulated by 21 CFR 312.57 and ICH guidelines for GCP, source documentation for this clinical study must be maintained to document the treatment and study course of patients, and to substantiate the integrity of the clinical study data submitted for review to the regulatory agencies. Source documentation for clinical studies includes, but is not limited to, the following:

- Hospital, clinic, or office records documenting patient visits, including treatments with HPN424 and other treatments or procedures
- Medical history and physical examination information
- Laboratory and special assessments results
- Patient diaries, if applicable
- Medical consultations

The Investigator must ensure that source documents that are required to verify the validity and completeness of data transcribed on the CRFs are never obliterated or destroyed. Refer to Section 11.11 for record retention requirements.

The Investigator must ensure that source documentation is accessible to appropriate study personnel listed in Section 11.5 (Patient Confidentiality) for purposes of study monitoring and site audits as described in Section 11.6.

11.9 Study Safety Oversight Committee (SSOC) and Cohort Review Committee (CRC)

A Study Safety Oversight Committee (SSOC), comprised of selected Sponsor representatives including the Medical Monitor, will monitor safety on an ongoing basis and will review safety data periodically, including the identification of any DLT. The SSOC will make recommendations to the Cohort Review Committee (CRC) who will then decide on further actions.

The CRC, comprised of selected Investigators and Sponsor Representatives include the Medical Monitor, will review the safety, clinical activity, and any available PK and pharmacodynamics data at the identification of any DLT and at the completion of each dose level cohort, and will make a recommendation as to whether escalation to the next scheduled dose level should occur. The CRC may also recommend an intermediate dose level be explored, within the range of dose levels specified in the protocol. The CRC may also make recommendations regarding premedication.

All CRC decisions will be communicated to Investigators and documented in the study files.

11.10 Data Generation and Analysis

Data will be collected on CRFs as described in Section 11.7, entered into a clinical database, reviewed for data quality and protocol compliance, and analyzed by the Sponsor and its designated representatives.

11.11 Retention of Data

The Investigator is responsible for maintaining all essential documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information transmitted to the Sponsor, patient files (including source documentation described in Section 11.8) that substantiate entries in CRFs, all relevant correspondence, and other documents pertaining to the conduct of the study.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of HPN424. However, these documents may be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor.

11.12 Publication and Disclosure Policy

Sponsor may use the results of this clinical study in registration documents for regulatory authorities in the US or abroad. Publication of any study results in papers, abstracts, posters or other material presented at scientific meetings or published in professional journals must be approved by Sponsor.

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Appendix 1 Schedule of Assessments: Fixed Dose Intravenous Regimen

Study Period	Screen	Treatment Period																				Post-treatment		
		Cycle 1								Cycle 2						C3+						EOT	SFU	LTFU[a]
Study Day	-28 to -1	1[b]	2[c]	3[c]	5	8[b]	9[c]	10	15[b]	1[b]	8[b]	15[b]	16	17	19	1[b]	2	3	5	8[b]	15[b]	≤7d post last dose	≥28d post last dose	
Window					±1d	±1d			±1d	±1d	±1d	±1d				±1d				±1d	±1d	+7d	+7d	
Informed Consent[d]	X																							
Inclusion/Exclusion	X																							
Enrollment /Dose Assignment	X																							
Demography/Medical History	X																							
ECOG	X									X						X						X		
Weight, Height[e]	X	X								X						X								
Physical Examination[f]	X[f]	X								X						X						X		
Vital Signs[g]	X	X[g]	X[g]	X[g]		X[g]			X[g]	X[g]	X[g]	X[g]				X[g]				X[g]	X[g]	X		
12-Lead ECG[w]	X	X								X						X						X		
Pulse Oximetry[x]	X	X				X			X	X	X	X				X				X	X	X		
Hematology[h]	X	X[h]	X	X		X[h]	X	X	X[h]	X[h]		X[h]				X[h]						X		
Chemistry[i]	X	X[i]	X	X		X[i]	X	X	X[i]	X[i]						X[i]						X		
C-reactive protein[v]		X	X			X				X						X								
Coagulation[j]	X	X								X						X								
Urinalysis[k]		X								X						X						X		
Testosterone[l]	X																							
Research sample collection		Refer to Research Sample Collection Table 16																						
Tissue (optional) for PSMA[m]	X																							
Disease Assessment[n]	X															Q9wk						X		
PSA[o]	X															Q9wk						X		
Radiological Imaging[p]																								
– Bone Scan[q]	X															Q9wk						X		
– CT/MRI[r]	X															Q9wk						X		
PSMA PET[s]	X															Q9wk								
HPN424 IV[t]		**X**				**X**			**X**	**X**	**X**	**X**				**X**				**X**	**X**			
Hospital Admission[c]		X				X																		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival[a]																								X

Abbreviations: C(x)D(y) = Cycle(x) Day(y); CT = computed tomography; CTC = circulating tumor cells; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetics; PSMA = prostate-specific membrane antigen; PET = positron emission tomography; Q(x)w = every (x) weeks; SFU = safety follow-up.

Footnotes for Fixed Dose IV Schedule of Assessments:

[a] Long-term follow-up telephone calls or visits to occur monthly (±7 d) for 6 months, then every 3 months (±1 month) until death, lost to follow-up, or withdrawal from study.

[b] Predose assessments are to be done on the day of, and prior to, the start of infusion, unless otherwise indicated. C1D1 predose assessment must be completed within 72 hours prior to start of the C1D1 dose of HPN424, unless otherwise indicated. If Screening assessments were not done within this window, they need to be repeated on C1D1. C1D8+ predose assessments may be completed within 24 hours prior to the start of HPN424 infusion, provided it is after the previous dose.

[c] Hospital admission: 48-hour inpatient admission required following C1D1 and C1D8 dosing for all patients treated at each specific dose level. All patients who undergo intrapatient dose escalation will be hospitalized for 24-hour inpatient observation following the first of each escalated dose. Please refer to Section 5.1.4 Hospitalization and Monitoring for additional instruction on requirements for hospitalization.

[d] Informed Consent form must be signed before any study–related procedures are performed.

[e] Height is measured at Screening only.

[f] Full physical examination at Screening; symptom-directed exams at indicated visits thereafter.

[g] Vital signs: blood pressure, heart rate, respiratory rate, and temperature at the following timepoints during treatment, or more often if clinically indicated: during each HPN424 dose, predose (within 1 hour prior to the start of infusion), every 15 minutes (± 10 min) during the infusion (i.e., 15, 30, 45, 60 minutes), and at 4 hours (± 1 h) after the end of infusion (EOI). For inpatients at C1D1, vital signs are to be recorded every 4 hours (± 1 h) until discharge. Beginning with Cycle 4 and beyond, the Investigator may have the option to reduce the observation period from 4 hours to ≥2 hours after EOI. If the observation period is reduced to ≥2 hours, collect vital signs 2 hours (± 30 minutes) after EOI.

[h] Hematology: complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential. C1D1 samples to be collected within 72 hours prior to dose. C1D8+ samples to be collected within 24 hours prior to dose.

[i] Chemistry: albumin (ALB), alkaline phosphatase (ALK-P), bone specific alkaline phosphatase (BAP), alanine aminotransferase (ALT; SGPT), amylase, aspartate aminotransferase (AST; SGOT), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO2), chloride (Cl), creatinine, globulin, glucose, lactate dehydrogenase (LDH), lipase, magnesium, phosphorus, potassium (K), sodium (Na), total bilirubin, direct bilirubin, total protein, uric acid. C1D1 samples to be collected within 72 hours prior to dose. C1D8+ samples to be collected within 24 hours prior to dose. Additional ALK-P, ALT, AST, and total bilirubin samples to be collected at C1D1, C1D8, and C1D15—within 15 minutes after EOI and 5(± 1 h) after EOI.

[j] Coagulation: prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (PTT). C1D1 samples to be collected within 72 hours prior to dose. C2+ Day 1 samples to be collected within 24 hours prior to dose.

[k] Urinalysis: appearance, bilirubin, color, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, urobilinogen. C1D1 samples to be collected within 72 hours prior to dose; all subsequent Day 1 samples to be collected within 24 hours prior to dose.

[l] Testosterone: tested via local laboratories

[m] Pre-study tissue specimens are optional for all patients; if archival specimens meeting the requirements in the Laboratory Manual are not available, a fresh biopsy specimen may be collected prior to the start of study treatment.

[n] The Investigator is to perform disease assessments with supporting blood and imaging evaluations and when clinically indicated, including at Early Termination if patient withdraws from study due to disease progression.

[o] PSA: Baseline (on or within 14 days prior to Cycle 1 Day 1), every 9 weeks (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.), and at EOT visit if not collected in the prior 9 weeks.

[p] Imaging Tumor assessments are fixed relative to C1D1, irrespective of missed or delayed study treatments.

[q] Bone scan: 99mTc-methylene diphosphonate radionuclide bone scintigraphy every 9 weeks (±7 days) (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.). Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form Appendix 7.

[r] CT/MRI imaging may include chest, abdomen, and pelvis CT or MRI scans (the same method should be used throughout the study). Brain scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. CT or MRI scans to be done every 9 weeks (±7 days) (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.). Tumor assessments should be repeated at the EOT visit if more than 9 weeks have passed since the last evaluation. Patients should have confirmatory scans for response or progression and should remain on treatment if they are receiving clinical benefit (as determined by the Principal Investigator and upon consultation with the Medical Monitor).

[s] PSMA PET to be performed at selected sites only.

[t] HPN424 IV will be administered via 1-hour infusion. HPN424 will be administered once weekly (–2 days/+1 day) with a minimum of 4 non-dose days between 2 consecutive doses). Doses are to be calculated based on the patient's baseline (Screening) body weight, not adjusted each cycle for weight at Day 1 of each cycle. Please refer to Section 5.1.4. Hospitalization and Monitoring for additional instruction on requirements for post-dose monitoring.

[u] Adverse events (including serious AEs [SAEs]) recorded from signing of informed consent form through the SFU (≥28 days [+7 days] after last dose of HPN424).

[v] C-reactive protein (CRP): at C1D1—predose (-72 h), 5 h (± 1 h) after end of infusion (EOI), C1D2—24 h (± 1 h) after EOI; C1D8—predose (-24 h); once per cycle (predose [- 24 h] starting with Cycle 2), and when signs of cytokine release syndrome (CRS) are observed.

[w] 12-Lead ECG: Patients should be resting in a supine or sitting position for ≥10 minutes prior to electrocardiogram (ECG) collection. Obtain 1 ECG pre-dose at each of the following timepoints: Screening; D1 of each cycle; EOT visit. If cardiac abnormalities are detected or suspected, two additional ECGs must be performed to further evaluate and each reading should be obtained at least 3 minutes apart.

[x] Pulse oximetry: Within 1 hour prior to each dose.

Table 16 Intravenous Fixed Dosing Regimen: Research Specimen Collection

Cycle	Study Day	Cytokines[a]	Immuno-phenotyping	CTC	PK[b]	Anti-Drug Antibodies
Cycle 1	C1D1-Pre dose	X	X	X	X	X
	C1D1-EOI				X	
	C1D1-2 h Post EOI				X	
	C1D1-5 h Post EOI	X	X		X	
	C1D2	X	X		X	
	C1D3	X	X		X	
	C1D5				X	
	C1D8-Pre dose	X			X	
	C1D8-EOI				X	
	C1D8-5 h Post EOI	X			X	
	C1D15-Pre dose	X		X	X	X
	C1D15-EOI				X	
	C1D15-5 h Post EOI	X			X	
Cycle 2	C2D1-Pre dose				X	X
	C2D1-EOI				X	
	C2D8-Pre dose				X	
	C2D8-EOI				X	
	C2D15-Pre dose	X	X		X	X
	C2D15-EOI				X	
	C2D15-2 h Post EOI				X	
	C2D15-5 h Post EOI	X	X		X	
	C2D16				X	
	C2D17				X	
	C2D19				X	
C3	C3D1-Pre dose			X	X	X
	C3D1-EOI				X	
C4	C4D1-Pre dose	X	X		X	X
	C4D1-EOI				X	
	C4D1-5 h Post EOI	X	X		X	
C5	C5D1-Pre dose				X	X
	C5D1-EOI				X	
	C5D8-Pre dose			X		
C6	C6D1-Pre dose	X	X		X	X
	C6D1-EOI				X	
	C6D1-5 h Post EOI	X	X		X	
C7	C7D1-Pre dose				X	
	C7D1-EOI				X	
C8	C8D1-Pre dose				X	X
	C8D1-EOI				X	

Cycle	Study Day	Cytokines[a]	Immuno-phenotyping	CTC	PK[b]	Anti-Drug Antibodies
	C8D1-2 h Post EOI				X	
	C8D1-5 h Post EOI				X	
	C8D2				X	
	C8D3				X	
	C8D5				X	
	C8D8				X	
C9	C9D1-Pre dose			X	X	
	C9D1-EOI				X	
C10+	CYD1-Pre dose				X	X
	CYD1-EOI				X	
EOT	≤7d Post last dose				X	X

All samples: Specimen handling is described in the Laboratory Manual.

[a] Cytokine sample: Serum specimens will be collected during treatment if signs of CRS or neurotoxicity are observed. Additional serum samples may be collected as needed (e.g., following CRS, Grade ≥3 IRR, HPN424 dose modification, dose schedule modification, steroid [i.e., dexamethasone] use/dose modification, etc.). If CRS occurs (or is observed, regardless of the grade), the site should draw a cytokine panel (specifically IL-6) using their local lab or the central laboratory.

[b] PK sample: Additional serum samples may be collected as needed (e.g., following CRS, Grade ≥3 IRR, HPN424 dose modification, dose schedule modification, steroid [i.e., dexamethasone] use/dose modification, etc.).

Appendix 2 Schedule of Assessments: Step Dosing Intravenous Regimen

Study Period	Screen	Treatment Period													Post-treatment		
		Cycle 1							Cycle 2			C3+			EOT	SFU	LTFU[a]
Study Day	-28 to -1	1[b]	2[c]	3	8[cb]	9	10	15[b]	1[b]	8[b]	15[b]	1[b]	8[b]	15[b]	≤7d post last dose	≥28d post last dose	
Window					±1d			±1d	±1d	±1d	±1d	±1d	±1d	±1d	+7d	+7d	
Informed Consent[d]	X																
Inclusion/Exclusion	X																
Enrollment /Dose Assignment	X																
Demography/Medical History	X																
ECOG	X								X			X			X		
Weight, Height[e]	X	X							X			X					
Physical Examination[f]	X[f]	X			X			X	X			X			X		
Vital Signs[g]	X	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X		
12-Lead ECG[w]	X	X							X			X			X		
Pulse Oximetry[x]	X	X			X			X	X	X	X	X	X	X	X		
Hematology[h]	X	X[h]	X	X	X[h]	X	X	X[h]	X[h]	X[h]	X[h]	X[h]			X		
Chemistry[i]	X	X[i]	X	X	X[i]	X	X	X[i]	X[i]	X[i]	X[i]	X[i]			X		
C-reactive protein[v]		X	X		X	X		X	X			X					
Coagulation[j]	X	X							X			X					
Urinalysis[k]		X							X			X			X		
Testosterone[l]	X																
Research sample collection		Please refer to Research Sample Collection Table 17															
Tumor Tissue (optional) [m]	X																
Disease Assessment[n]	X											Q9wk			X		
PSA[o]	X											Q9wk			X		
Radiological Imaging[p]																	
– Bone Scan[q]	X											Q9wk			X		
– CT/MRI[r]	X											Q9wk			X		
PSMA PET[s]	X											Q9wk					
HPN424 IV [t]		**P**			**P or T**			**P or T**	**P or T**	**P or T**	**P or T[y]**	**T**	**T**	**T**			
Hospital Admission[c]		X			X			X									
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival [a]																	X

Abbreviations: C(x)D(y) = Cycle(x) Day(y); CT = computed tomography; CTC = circulating tumor cells; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetics; PSMA = prostate-specific membrane antigen; PET = positron emission tomography; Q(x)w = every (x) weeks; SFU = safety follow-up, A = Priming Dose A, T = Target Dose.

Footnotes for Intravenous Step Dosing Regimen:

[a] Long-term follow-up telephone calls or visits to occur monthly (±7 d) for 6 months, then every 3 months (±1 month) until death, lost to follow-up, or withdrawal from study.

[b] Predose assessments are to be done on the day of, and prior to, the start of infusion, unless otherwise indicated. C1D1 predose assessment must be completed within 72 hours prior to start of the C1D1 dose of HPN424, unless otherwise indicated. If Screening assessments were not done within this window, they need to be repeated on C1D1. C1D8+ predose assessments may be completed within 24 hours prior to the start of HPN424 infusion, provided it is after the previous dose.

[c] Hospital admission: Please refer to section 5.1.4 Hospitalization and Monitoring for additional instruction on requirements for hospitalization and outpatient monitoring.

[d] Informed Consent form must be signed before any study–related procedures are performed.

[e] Height is measured at Screening only.

[f] Full physical examination at Screening; symptom-directed exams at indicated visits thereafter.

[g] Vital signs: blood pressure, heart rate, respiratory rate, and temperature at the following timepoints during treatment, or more often if clinically indicated: during each HPN424 dose, predose (within 1 hour prior to the start of infusion), every 15 minutes (± 10 min) during the infusion (i.e., 15, 30, 45, 60 minutes), and at 4 hours (± 1 h) after the end of infusion (EOI). For inpatients at C1D1 and C1D8, vital signs are to be recorded every 4 hours (± 1 h) until discharge. Beginning with Cycle 4 and beyond, the Investigator may have the option to reduce the observation period from 4 hours to ≥2 hours after EOI. If the observation period is reduced to ≥2 hours, collect vital signs 2 hours (± 30 minutes) after EOI.

[h] Hematology: complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential. C1D1 samples to be collected within 72 hours prior to HPN424 administration. C1D8+ samples to be collected within 24 hours prior to HPN424 administration. During 48-hour inpatient hospitalization, should be drawn once within 24-hour period after HPN424 administration, and once during 24-48-hour period after HPN424 administration.

[i] Chemistry: albumin (ALB), alkaline phosphatase (ALK-P), bone specific alkaline phosphatase (BAP), alanine aminotransferase (ALT; SGPT), amylase, aspartate aminotransferase (AST; SGOT), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO2), chloride (Cl), creatinine, globulin, glucose, lactate dehydrogenase (LDH), lipase, magnesium, phosphorus, potassium (K), sodium (Na), total bilirubin, direct bilirubin, total protein, uric acid. C1D1 samples to be collected within 72 hours prior to HPN424 administration. C1D8+ samples to be collected within 24 hours prior to HPN424 administration. Additional ALK-P, ALT, AST, and total bilirubin samples to be collected at C1D1, C1D8, and C1D15—within 15 minutes after HPN424 administration and 5 hours (± 1 h) after HPN424 administration. During 48-hour inpatient hospitalization, should be drawn once within 24-hour period after HPN424 administration, and once during 24-48-hour period after HPN424 administration.

[j] Coagulation: prothrombin time/ international normalized ratio (PT/INR), activated partial thromboplastin time (PTT). C1D1 samples to be collected within 72 hours prior to HPN424 administration. C2+ Day 1 samples to be collected within 24 hours prior to HPN424 administration

[k] Urinalysis: appearance, bilirubin, color, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, urobilinogen. C1D1 samples to be collected within 72 hours prior to HPN424 administration; all subsequent Day 1 samples to be collected within 24 hours prior to HPN424 administration

[l] Testosterone: tested via local laboratories

[m] Pre-study tissue specimens are optional for all patients; if archival specimens meeting the requirements in the Laboratory Manual are not available, a fresh biopsy specimen may be collected prior to the start of study treatment.

[n] The Investigator is to perform disease assessments with supporting blood and imaging evaluations and when clinically indicated, including at Early Termination if patient withdraws from study due to disease progression.

[o] PSA: Baseline (on or within 14 days prior to Cycle 1 Day 1), every 9 weeks (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.), and at EOT visit if not collected in the prior 9 weeks.

[p] Imaging Tumor assessments are fixed relative to C1D1, irrespective of missed or delayed study treatments.

[q] Bone scan: 99mTc-methylene diphosphonate radionuclide bone scintigraphy every 9 weeks (±7 days) (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.). Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form Appendix 7.

[r] CT/MRI imaging may include chest, abdomen, and pelvis CT or MRI scans (the same method should be used throughout the study). Brain scans and bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. CT or MRI scans to be done every 9 weeks (±7 days) (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.). Tumor assessments should be repeated at the EOT visit if more than 9 weeks have passed since the last evaluation. Patients should have confirmatory scans for response or progression and should remain on treatment if they are receiving clinical benefit (as determined by the Principal Investigator and upon consultation with the Medical Monitor).

[s] PSMA PET to be performed at selected sites only.

[t] HPN424 IV will be administered via 1-hour infusion. HPN424 will be administered once weekly (–2 days/+1 day with a minimum of 4 non-dose days between 2 consecutive doses) as a 1-hour infusion. Doses of HPN424 are to be calculated based on the patient's baseline (Screening) body weight, not adjusted each cycle for weight at Day 1 of each cycle. Please refer to section 5.1.4 Hospitalization and Monitoring for additional instruction on requirements for post-dose monitoring.

[u] Adverse events (including serious AEs [SAEs]) recorded from signing of informed consent form through the SFU (≥28 days [+7 days] after last dose of HPN424).

[v] C-reactive protein (CRP): at C1D1—predose (-72 h), 5 h (± 1 h) after HPN424 administration; C1D2—24 h (± 1 h) after HPN424 administration; C1D8—predose (-72 h), 5 h (± 1 h) after HPN424 administration; C1D9—24 h (± 1 h) after HPN424 administration; once per cycle (predose [- 24 h] beginning with first Target dose), and when signs of cytokine release syndrome (CRS) are observed

[w] 12-Lead ECG: Patients should be resting in a supine or sitting position for ≥10 minutes prior to electrocardiogram (ECG) collection. Obtain 1 ECG pre-dose at each of the following visits: Screening; D1 of each cycle; EOT visit. If cardiac abnormalities are detected or suspected, two additional ECGs must be performed to further evaluate and each reading should be obtained at least 3 minutes apart.

[x] Pulse oximetry: Within 1 hour prior to each dose

[y] Additional Priming doses of HPN424 may be administered after C2D15, after discussion with Medical Monitor

Table 17 Intravenous Step Dosing Regimen: Research Specimen Collection

Cycle	Study Day	Cytokines[b]	Immuno-phenotyping[c]	CTCs[d]	PK[e]	Anti-Drug Antibodies
Cycle 1	C1D1-Pre dose[a]	X	X	X	X	X
	C1D1-EOI[a]				X	
	C1D1-5 h Post EOI[a]	X	X		X	
	C1D8-Pre dose	X	X		X	
	C1D8-EOI				X	
	C1D8-5 h Post EOI	X	X		X	
	C1D9	X	X		X	
	C1D10		X		X	
	C1D12				X	
	C1D15-Pre dose	X			X	X
	C1D15-EOI				X	
	C1D15-5 h Post EOI	X			X	
Cycle 2	C2D1-Pre dose	X		X	X	X
	C2D1-EOI				X	
	C2D1-5 h Post EOI	X			X	
	C2D8-Pre dose				X	
	C2D8-EOI				X	
	C2D15-Pre dose	X	X		X	X
	C2D15-EOI				X	
	C2D15-5 h Post EOI	X	X		X	
C3	C3D1-Pre dose			X	X	X
	C3D1-EOI				X	
C4	C4D1-Pre dose	X	X		X	X
	C4D1-EOI				X	
	C4D1-5 h Post EOI	X	X		X	
C5	C5D1-Pre				X	X
	C5D1-EOI				X	
	C5D15-Pre dose			X		
C6	C6D1-Pre dose	X	X		X	X

Cycle	Study Day	Cytokines[b]	Immuno-phenotyping[c]	CTCs[d]	PK[e]	Anti-Drug Antibodies
	C6D1-EOI				X	
	C6D1-5 h Post EOI	X	X		X	
C7	C7D1-Pre dose				X	
	C7D1-EOI				X	
C8	C8D1-Pre dose				X	X
	C8D1-EOI				X	
	C8D1-2 h Post EOI				X	
	C8D1-5 h Post EOI				X	
	C8D2				X	
	C8D3				X	
	C8D5				X	
	C8D8				X	
C9	C9D8-Pre dose			X		
C10+even	CYD1-Pre dose				X	X
	CYD1-EOI				X	
EOT	≤7d Post last dose				X	X

All samples: Specimen handling is described in the Laboratory Manual.

[a] If a priming dose is administered on C1D8, or other subsequent dosing days (e.g., C1D15, C2D1, etc), repeat the scheduled sample collections for C1D1 for each priming dose. EXCEPT CTC and ADA samples, which are drawn only at C1D1 and where otherwise indicated. Actual Cycle/Day will be determined by the number of Priming doses for a given regimen (e.g., Priming Dose will be administered on C1D1, C1D8, C1D15, and so on).

[b] Cytokine Samples: If more than one priming dose is required and the target dose is after C1D8, do not collect cytokine samples on C1D9; At first target dose, collect samples predose, 5 h (± 1 h) post EOI and 24 h (± 1 h) post EOI. Serum specimens will be collected during treatment if signs of CRS or neurotoxicity are observed. Additional serum samples may be collected as needed (e.g., following CRS, Grade ≥3 IRR, HPN424 dose modification, dose schedule modification, steroid [i.e., dexamethasone] use/dose modification, etc.). If CRS occurs (or is observed, regardless of the grade), the site should draw a cytokine panel (specifically IL-6) using their local lab or the central laboratory.

[c] Immunophenotyping samples: If more than one priming dose is required and the target dose is after C1D8, do not collect immunophenotyping samples on C1D9 nor C1D10. At first target dose, collect samples predose, 5 h (± 1 h) post EOI, 24 h (± 1 h) post EOI, and 48 h (± 1 h) post EOI.

[d] CTC samples: Collected at C1D1, and 2, 13, and 24 weeks after the first target dose. For example, if first target dose is C1D8, follow collection in table. If first target dose is C1D15, draw CTCs at C2D8, C6D1, and C9D15. Sample on C3D1 should always be collected regardless of when the first target dose occurs.

[e] PK Samples: If more than one priming dose is required and the target dose is after C1D8, do not collect PK samples on C1D9, C1D10, nor C1D12. At first target dose, collect samples predose, within 15 minutes after EOI, 2 h (± 1 h) post EOI, 5 h (± 1 h) post EOI, 24 h (± 1 h) post EOI, 48 h (± 1 h) post EOI, and 96 h (± 24 h) post EOI. The 96 hour timepoint will require subjects to return to clinic for PK blood draw. Additional serum samples may be collected as needed (e.g., following CRS, Grade ≥3 IRR, HPN424 dose modification, dose schedule modification, steroid [i.e., dexamethasone] use/dose modification, etc.).

Appendix 3 Schedule of Assessments: Fixed Dosing Subcutaneous Regimen

Study Period	Screen	Treatment Period																	Post-treatment			Section #
		Cycle 1								Cycle 2			C3+						EOT	SFU	LTFU[a]	
Study Day	-28 to -1	1[b]	2[c]	3[c]	5	8[b]	9[c]	10	15[b]	1[b]	8[b]	15[b]	1[b]	2[c]	3	5[c]	8[b]	15[b]	≤7d post last dose	≥28d post last dose		
Window					±1d	±1d			±1d	±1d	±1d	±1d	±1d				±1d	±1d	+7d	+7d		
Informed Consent[d]	X																					
Inclusion/Exclusion	X																					
Enrollment /Dose Assignment	X																					
Demography/Medical History	X																					
ECOG	X									X			X						X			
Weight, Height[e]	X	X								X			X									
Physical Examination[f]	X[f]	X								X			X						X			
Vital Signs[g]	X	X[g]	X[g]	X[g]		X[g]			X[g]	X[g]	X[g]	X[g]	X[g]				X[g]	X[g]	X			
12-Lead ECG[w]	X	X								X			X						X			
Pulse Oximetry[x]	X	X				X			X	X	X	X	X				X	X	X			
Hematology[h]	X	X[h]	X	X		X[h]	X	X	X[h]	X[h]		X[h]	X[h]						X			
Chemistry[i]	X	X[i]	X	X		X[i]	X	X	X[i]	X[i]			X[i]						X			
C-reactive protein[v]		X				X				X			X									
Coagulation[j]	X	X								X			X									
Urinalysis[k]		X								X			X						X			
Testosterone[l]	X																					
Research sample collection		Please refer to Research Sample Collection Table 18																				
Tissue (optional) for PSMA[m]	X																					
Disease Assessment[n]	X												Q9wk						X			
PSA[o]	X												Q9wk						X			
Radiological Imaging[p]																						
– Bone Scan[q]	X												Q9wk						X			
– CT/MRI[r]	X												Q9wk						X			
PSMA PET[s]	X												Q9wk									
HPN424 SC[t]		X				X			X	X	X	X	X				X	X				
Hospital Admission[c]		X				X																
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Survival[a]																					X	

Abbreviations: C(x)D(y) = Cycle(x) Day(y); CT = computed tomography; CTC = circulating tumor cells; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetics; PSMA = prostate-specific membrane antigen; PET = positron emission tomography; Q(x)w = every (x) weeks; SFU = safety follow-up.

Footnotes for Fixed Dose SC:

[a] Long-term follow-up telephone calls or visits to occur monthly (±7 d) for 6 months, then every 3 months (±1 month) until death, lost to follow-up, or withdrawal from study.

[b] Predose assessments are to be done on the day of, and prior to, the start of infusion, unless otherwise indicated. C1D1 predose assessment must be completed within 72 hours prior to start of the C1D1 dose of HPN424, unless otherwise indicated. If Screening assessments were not done within this window, they need to be repeated on C1D1. C1D8+ predose assessments may be completed within 24 hours prior to the start of HPN424 infusion, provided it is after the previous dose.

[c] Hospital admission: Please refer to section 5.1.4 Hospitalization and Monitoring for additional instruction on requirements for hospitalization and outpatient monitoring.

[d] Informed Consent form must be signed before any study–related procedures are performed.

[e] Height is measured at Screening only.

[f] Full physical examination at Screening; symptom-directed exams at indicated visits thereafter.

[g] Vital signs: blood pressure, heart rate, respiratory rate, and temperature at the following timepoints during treatment, or more often if clinically indicated: during each HPN424 dose, predose (within 1 hour prior to the start of infusion), every 15 minutes (± 10 min) during the infusion (i.e., 15, 30, 45, 60 minutes), and at 4 hours (± 1 h) after the end of infusion (EOI). For inpatients at C1D1, vital signs are to be recorded every 4 hours (± 1 h) until discharge. Beginning with Cycle 4 and beyond, the Investigator may have the option to reduce the observation period from 4 hours to ≥2 hours after EOI. If the observation period is reduced to ≥2 hours, collect vital signs 2 hours (± 30 minutes) after EOI.

[h] Hematology: complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential. C1D1 samples to be collected within 72 hours prior to dose. C1D8+ samples to be collected within 24 hours prior to dose.

[i] Chemistry: albumin (ALB), alkaline phosphatase (ALK-P), bone specific alkaline phosphatase (BAP), alanine aminotransferase (ALT; SGPT), amylase, aspartate aminotransferase (AST; SGOT), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO2), chloride (Cl), creatinine, globulin, glucose, lactate dehydrogenase (LDH), lipase, magnesium, phosphorus, potassium (K), sodium (Na), total bilirubin, direct bilirubin, total protein, uric acid. C1D1 samples to be collected within 72 hours prior to dose. C1D8+ samples to be collected within 24 hours prior to dose. Additional ALK-P, ALT, AST, and total bilirubin samples to be collected at C1D1, C1D8, and C1D15—within 15 minutes after EOI and 5(± 1 h) after EOI.

[j] Coagulation: prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (PTT). C1D1 samples to be collected within 72 hours prior to dose. C2+ Day 1 samples to be collected within 24 hours prior to dose

[k] Urinalysis: appearance, bilirubin, color, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, urobilinogen. C1D1 samples to be collected within 72 hours prior to dose; all subsequent Day 1 samples to be collected within 24 hours prior to dose

[l] Testosterone: tested via local laboratories

[m] Pre-study tissue specimens are optional for all patients; if archival specimens meeting the requirements in the Laboratory Manual are not available, a fresh biopsy specimen may be collected prior to the start of study treatment.

[n] The Investigator is to perform disease assessments with supporting blood and imaging evaluations and when clinically indicated, including at Early Termination if patient withdraws from study due to disease progression.

[o] PSA: Baseline (on or within 14 days prior to Cycle 1 Day 1), every 9 weeks (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.), and at EOT visit if not collected in the prior 9 weeks.

[p] Imaging Tumor assessments are fixed relative to C1D1, irrespective of missed or delayed study treatments.

[q] Bone scan: 99mTc-methylene diphosphonate radionuclide bone scintigraphy every 9 weeks (±7 days) (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.). Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form Appendix 7.

[r] CT/MRI imaging may include chest, abdomen, and pelvis CT or MRI scans (the same method should be used throughout the study). Brain scans and bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. CT or MRI scans to be done every 9 weeks (±7 days) (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.). Tumor assessments should be repeated at the EOT visit if more than 9 weeks have passed since the last evaluation. Patients should have confirmatory scans for response or progression and should remain on treatment if they are receiving clinical benefit (as determined by the Principal Investigator and upon consultation with the Medical Monitor).

[s] PSMA PET to be performed at selected sites only.

[t] HPN424 SC will be administered via subcutaneous injection. HPN424 will be administered once weekly (–2 days/+1 day) with a minimum of 4 non-dose days between 2 consecutive doses). Doses are to be calculated based on the patient's baseline (Screening) body weight, not adjusted each cycle for weight at Day 1 of each cycle. Please refer to section 5.1.4 Hospitalization and Monitoring for additional instruction on requirements for post-dose monitoring.

[u] Adverse events (including serious AEs [SAEs]) recorded from signing of informed consent form through the SFU (≥28 days [+7 days] after last dose of HPN424).

[v] C-reactive protein (CRP): at C1D1—predose (-72 h), 5 h (± 1 h) after administration, 24 h (± 1 h) after administration; C1D8—predose (-24 h); once per cycle (predose [- 24 h] starting with Cycle 2), and when signs of cytokine release syndrome (CRS) are observed

[w] 12-Lead ECG: Patients should be resting in a supine or sitting position for ≥10 minutes prior to electrocardiogram (ECG) collection. Obtain 1 ECG pre-dose at each of the following timepoints: Screening; D1 of each cycle; EOT visit. If cardiac abnormalities are detected or suspected, two additional ECGs must be performed to further evaluate and each reading should be obtained at least 3 minutes apart.

[x] Pulse oximetry: Within 1 hour prior to each dose

Table 18 Subcutaneous Fixed Dosing Regimen: Research Specimen Collection

Cycle	Study Day	Cytokines[a]	Immuno-phenotyping	CTC	PK[b]	ADA
Cycle 1	C1D1-Pre dose	X	X	X	X	X
	C1D1-5 h Post dose	X			X	
	C1D2	X	X		X	
	C1D3	X	X		X	
	C1D5	X	X		X	
	C1D8-Pre dose	X			X	
	C1D9	X			X	
	C1D10	X			X	
	C1D15-Pre dose			X	X	X
Cycle 2	C2D1-Pre dose				X	X
	C2D8-Pre dose				X	
	C2D15-Pre dose				X	X
Cycle 3	C3D1-Pre dose	X	X	X	X	X
	C3D1-5 h Post dose	X			X	
	C3D2	X	X		X	
	C3D3	X	X		X	
	C3D5	X	X		X	
	C3D8-Pre dose				X	
Cycle 4	C4D1-Pre dose				X	X
Cycle 5	C5D1-Pre dose				X	X
Cycle 5	C5D8-Pre dose			X		
Cycle 6	C6D1-Pre dose				X	X
Cycle 7	C7D1-Pre dose				X	
Cycle 8	C8D1-Pre dose				X	X
Cycle 9	C9D1-Pre dose			X		
Cycle 10+even	CYD1-Pre dose				X	X
EOT	≤7d Post last dose				X	X

All samples: Specimen handling is described in the Laboratory Manual.

[a] Cytokine samples: Serum specimens will be collected during treatment if signs of CRS or neurotoxicity are observed. Additional serum samples may be collected as needed (e.g., following CRS, Grade ≥3 IRR, HPN424 dose modification, dose schedule modification, steroid [i.e., dexamethasone] use/dose modification, etc.). If CRS occurs (or is observed, regardless of the grade), the site should draw a cytokine panel (specifically IL-6) using their local lab or the central laboratory.

[b] PK samples: Additional serum samples may be collected as needed (e.g., following CRS, Grade ≥3 IRR, HPN424 dose modification, dose schedule modification, steroid [i.e., dexamethasone] use/dose modification, etc.).

Appendix 4 Schedule of Assessments: Step Dosing Subcutaneous Regimen

Study Period	Screen	Treatment Period																Post-treatment		
		Cycle 1							Cycle 2			C3+						EOT	SFU	LTFU[a]
Study Day	-28 to -1	1[b]	2[c]	3	8[b]	9	10	15[b]	1[b]	8[b]	15[b]	1[b]	2	3	5	8[b]	15[b]	≤7d post last dose	≥28d post last dose	
Window					±1d			±1d	±1d	±1d	±1d	±1d				±1d	±1d	+7d	+7d	
Informed Consent[d]	X																			
Inclusion/Exclusion	X																			
Enrollment /Dose Assignment	X																			
Demography/Medical History	X																			
ECOG	X								X			X						X		
Weight, Height[e]	X	X							X			X								
Physical Examination[f]	X[f]	X			X			X	X			X						X		
Vital Signs[g]	X	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]				X[g]	X[g]	X		
12-Lead ECG[w]	X	X							X			X						X		
Pulse Oximetry[x]	X	X			X			X	X	X	X	X				X	X	X		
Hematology[h]	X	X[h]	X	X	X[h]	X	X	X[h]	X[h]	X[h]	X[h]	X[h]						X		
Chemistry[i]	X	X[i]	X	X	X[i]	X	X	X[i]	X[i]	X[i]	X[i]	X[i]						X		
C-reactive protein[v]		X	X		X	X		X	X			X								
Coagulation[j]	X	X							X			X								
Urinalysis[k]		X							X			X						X		
Testosterone[l]	X																			
Research sample collection		Please refer to Research Sample Collection Table 19																		
Tumor Tissue (optional) [m]	X																			
Disease Assessment[n]	X											Q9wk						X		
PSA[o]	X											Q9wk						X		
Radiological Imaging[p]																				
-- Bone Scan[q]	X											Q9wk						X		
-- CT/MRI[r]	X											Q9wk						X		
PSMA PET[s]	X											Q9wk								
HPN424 SC[t]		**P**			**P or T**			**P or T**	**P or T**	**P or T**	**P or T[y]**	**T**				**T**	**T**			
Hospital Admission[c]		X			X			X												
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events[u]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival[a]																				X

Abbreviations: C(x)D(y) = Cycle(x) Day(y); CT = computed tomography; CTC = circulating tumor cells; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PK = pharmacokinetics; PSMA = prostate-specific membrane antigen; PET = positron emission tomography; Q(x)w = every (x) weeks; SFU = safety follow-up, A = Priming Dose A, T = Target Dose.

Footnotes for SC Step Priming Dose:

[a] Long-term follow-up telephone calls or visits to occur monthly (±7 d) for 6 months, then every 3 months (±1 month) until death, lost to follow-up, or withdrawal from study.

[b] Predose assessments are to be done on the day of, and prior to, the start of infusion, unless otherwise indicated. C1D1 predose assessment must be completed within 72 hours prior to start of the C1D1 dose of HPN424, unless otherwise indicated. If Screening assessments were not done within this window, they need to be repeated on C1D1. C1D8+ predose assessments may be completed within 24 hours prior to the start of HPN424 infusion, provided it is after the previous dose.

[c] Hospital admission: Please refer to section 5.1.4 Hospitalization and Monitoring for additional instruction on requirements for hospitalization and outpatient monitoring. [d]. Informed Consent form must be signed before any study–related procedures are performed.

[e] Height is measured at Screening only.

[f] Full physical examination at Screening; symptom-directed exams at indicated visits thereafter.

[g] Vital signs: blood pressure, heart rate, respiratory rate, and temperature at the following timepoints during treatment, or more often if clinically indicated: during each HPN424 dose, predose (within 1 hour prior to HPN424 administration), every 15 minutes (± 10 min) during first hour after HPN424 administration (i.e., 15, 30, 45, 60 minutes), and at 4 hours (± 1 h) after HPN424 administration. For inpatients at C1D1 and C1D8, vital signs are to be recorded every 4 hours (± 1 h) until discharge. Beginning with Cycle 4 and beyond, the Investigator may have the option to reduce the observation period from 4 hours to ≥2 hours after HPN424 administration. If the observation period is reduced to ≥2 hours, collect vital signs 2 hours (± 30 minutes) after HPN424 administration.

[h] Hematology: complete blood count (CBC), including platelet count and white blood cell count (WBC) with differential. C1D1 samples to be collected within 72 hours prior to dose. C1D8+ samples to be collected within 24 hours prior to dose. During 48-hour inpatient hospitalization, should be drawn once within 24-hour period after HPN424 administration, and once during 24-48 hour period after HPN424 administration.

[i] Chemistry: albumin (ALB), alkaline phosphatase (ALK-P), bone specific alkaline phosphatase (BAP), alanine aminotransferase (ALT; SGPT), amylase, aspartate aminotransferase (AST; SGOT), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO2), chloride (Cl), creatinine, globulin, glucose, lactate dehydrogenase (LDH), lipase, magnesium, phosphorus, potassium (K), sodium (Na), total bilirubin, direct bilirubin, total protein, uric acid. C1D1 samples to be collected within 72 hours prior to dose. C1D8+ samples to be collected within 24 hours prior to HPN424 administration. Additional ALK-P, ALT, AST, and total bilirubin samples to be collected at C1D1, C1D8, and C1D15—within 15 minutes after HPN424 administration and 5 hours(± 1 h) after HPN424 administration. During 48-hour inpatient hospitalization, should be drawn once within 24-hour period after HPN424 administration, and once during 24-48 hour period after HPN424 administration.

[j] Coagulation: prothrombin time/ international normalized ratio (PT/INR), activated partial thromboplastin time (PTT). C1D1 samples to be collected within 72 hours prior to dose. C2+ Day 1 samples to be collected within 24 hours prior to dose

[k] Urinalysis: appearance, bilirubin, color, glucose, ketones, nitrite, occult blood, pH, protein, specific gravity, urobilinogen. C1D1 samples to be collected within 72 hours prior to dose; all subsequent Day 1 samples to be collected within 24 hours prior to dose

[l] Testosterone: tested via local laboratories

[m] Pre-study tissue specimens are optional for all patients; if archival specimens meeting the requirements in the Laboratory Manual are not available, a fresh biopsy specimen may be collected prior to the start of study treatment.

[n] The Investigator is to perform disease assessments with supporting blood and imaging evaluations and when clinically indicated, including at Early Termination if patient withdraws from study due to disease progression.

[o] PSA: Baseline (on or within 14 days prior to Cycle 1 Day 1), every 9 weeks (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.), and at EOT visit if not collected in the prior 9 weeks.

[p] Imaging Tumor assessments are fixed relative to C1D1, irrespective of missed or delayed study treatments.

[q] Bone scan: 99mTc-methylene diphosphonate radionuclide bone scintigraphy every 9 weeks (±7 days) (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.). Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form Appendix 7.

[r] CT/MRI imaging may include chest, abdomen, and pelvis CT or MRI scans (the same method should be used throughout the study). Brain scans and bone scans will be performed at baseline if disease is suspected and on study as appropriate to follow disease. CT or MRI scans to be done every 9 weeks (±7 days) (e.g., Day 1 of Cycles 4, 7, 10, 13, etc.). Tumor assessments should be repeated at the EOT visit if more than 9 weeks have passed since the last evaluation. Patients should have confirmatory scans for response or progression and should remain on treatment if they are receiving clinical benefit (as determined by the Principal Investigator and upon consultation with the Medical Monitor).

[s] PSMA PET to be performed at selected sites only.

[t] HPN424 SC will be administered via subcutaneous injection. HPN424 will be administered once weekly (–2 days/+1 day with a minimum of 4 non-dose days between 2 consecutive doses) as a subcutaneous injection. Doses of HPN424 are to be calculated based on the patient's baseline (Screening) body weight, not adjusted each cycle for weight at Day 1 of each cycle. Please refer to section 5.1.4 Hospitalization and Monitoring for additional instruction on requirements for post-dose monitoring.

[u] Adverse events (including serious AEs [SAEs]) recorded from signing of informed consent form through the SFU (≥28 days [+7 days] after last dose of HPN424).

[v] C-reactive protein (CRP): at C1D1—predose (-72 h), 5 h (± 1 h) after HPN424 administration; C1D2—24 h (± 1 h) after HPN424 administration; C1D8—predose (-72 h), 5 h (± 1 h) after HPN424 administration; C1D9—24 h (± 1 h) after HPN424 administration; once per cycle (predose [- 24 h] beginning with first Target dose), and when signs of cytokine release syndrome (CRS) are observed

[w] 12-Lead ECG: Patients should be resting in a supine or sitting position for ≥10 minutes prior to electrocardiogram (ECG) collection. Obtain 1 ECG pre-dose at each of the following visits: Screening; D1 of each cycle; EOT visit. If cardiac abnormalities are detected or suspected, two additional ECGs must be performed to further evaluate and each reading should be obtained at least 3 minutes apart.

[x] Pulse oximetry: Within 1 hour prior to each dose

[y] Additional Priming doses of HPN424 may be administered after C2D15, after discussion with Medical Monitor

Table 19 Subcutaneous Step Dosing Regimen: Research Specimen Collection

Cycle	Study Day	Cytokines[b]	Immuno-phenotyping[c]	CTC[d]	PK[e]	ADA
Cycle 1	C1D1-Pre dose[a]	X	X	X	X	X
	C1D1-5 h Post dose[a]	X			X	
	C1D2[a]	X	X		X	
	C1D3[a]	X	X		X	
	C1D8-Pre dose	X	X		X	
	C1D8-5 h Post dose	X			X	
	C1D9	X	X		X	
	C1D10	X	X		X	
	C1D12	X	X		X	
	C1D15-Pre dose	X			X	X
	C1D16	X			X	
	C1D17	X			X	
Cycle 2	C2D1-Pre dose			X	X	X
	C2D8-Pre dose				X	
	C2D15-Pre dose				X	X
Cycle 3	C3D1-Pre dose	X	X	X	X	X
	C3D1-5 h Post dose	X			X	
	C3D2	X	X		X	
	C3D3	X	X		X	
	C3D5	X	X		X	
	C3D8-Pre dose				X	
Cycle 4	C4D1-Pre dose				X	X
Cycle 5	C5D1-Pre dose				X	X
	C5D15-Pre dose			X		
Cycle 6	C6D1-Pre dose				X	X
Cycle 7	C7D1-Pre dose				X	
Cycle 8	C8D1-Pre dose				X	X
Cycle 9	C9D8-Pre dose			X		
Cycle 10+even	CYD1-Pre dose				X	X
EOT	≤7d Post last dose				X	X

All samples: Specimen handling is described in the Laboratory Manual.

[a] If a priming dose is administered on C1D8, or other subsequent dosing days (e.g., C1D15, C2D1, etc), repeat the scheduled sample collections for C1D1 for each priming dose. EXCEPT CTC and ADA samples, which are drawn only at C1D1 and where otherwise indicated. Actual Cycle/Day will be determined by the number of Priming doses for a given regimen (e.g., Priming Dose will be administered on C1D1, C1D8, C1D15, and so on).

[b] Cytokine samples: At first target dose (e.g., C1D8, C1D15, C2D1, etc), collect samples predose, 5 h (± 1 h) post dose, 24 h (± 1 h) post dose, 48 h (± 1 h) post dose, and 96 h (± 24 h) post dose. If target dose is not on C1D8 (e.g., C1D15, C2D1, etc), do not collect C1D12. Serum specimens will be collected during treatment if signs of CRS or neurotoxicity are observed. Additional serum samples may be collected as needed (e.g., following CRS, Grade ≥3 IRR, HPN424 dose modification, dose schedule modification, steroid [i.e., dexamethasone] use/dose modification, etc.). If CRS occurs (or is

observed, regardless of the grade), the site should draw a cytokine panel (specifically IL-6) using their local lab or the central laboratory.

[c] Immunophenotyping samples: At first target dose (e.g., C1D8, C1D15, C2D1, etc), collect samples predose, 24 h (± 1 h) post dose, 48 h (± 1 h) post dose, and 96 h (± 24 h) post dose. If target dose is not on C1D8 (e.g., C1D15, C2D1, etc), do not collect C1D12.

[d] CTC samples: Collected at C1D1, and 2, 13, and 24 weeks after the first target dose. For example, if first target dose is C1D8, follow collection in table. If first target dose is C1D15, draw CTCs at C2D8, C6D1, and C9D15. Sample on C3D1 should always be collected regardless of when the first target dose occurs.

[e] PK samples: At first target dose (e.g., C1D8, C1D15, C2D1, etc), collect samples predose, 5 h (± 1 h) post dose, 24 h (± 1 h) post dose, 48 h (± 1 h) post dose, and 96 h (± 24 h) post dose. The 96 hour timepoint will require subjects to return to clinic for PK blood draw. If target dose is not on C1D8 (e.g., C1D15, C2D1, etc), do not collect C1D12. Additional serum samples may be collected as needed (e.g., following CRS, Grade ≥3 IRR, HPN424 dose modification, dose schedule modification, steroid [i.e., dexamethasone] use/dose modification, etc.).

Appendix 5 ECOG Performance Status

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655. Available at http://ecog-acrin.org/resources/ecog-performance-status. Accessed on 19 March 2016.

Appendix 6 Tumor Response Assessment Guidelines (per PCWG3)

The following guidelines for assessment of response are based on the recommendations of the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria (Scher, 2016).

SOFT TISSUE RESPONSE CRITERIA

Adapted from (Eisenhauer, 2009) (RECIST v1.1) and (Scher, 2016)(PCWG3).

a. Categorizing Lesions at Baseline

Measurable Lesions: Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm). Record individual sites of spread (lung, liver, adrenal, CNS) separately; up to 5 lesions per site.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT or MRI. Nodes ≥1.5 cm in the short axis are considered measurable; nodes ≥ 1.0 and less than 1.5 cm in the short axis are considered pathologic according to clinical discretion, and nontarget; nodes less than 1.0 cm in the short axis are nonpathologic. Record pelvis and extrapelvis (retroperitoneal, mediastinal, thoracic, other) nodal disease separately; up to five nodes in total.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Nonmeasurable Disease

Nonmeasurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly nonmeasurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, and lymphangitic involvement of skin or lung.

- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is nonmeasurable unless it has progressed since completion of treatment.

Normal Sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or nontarget disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or nonmeasurable disease.

b. Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target Lesions

All measurable lesions up to a maximum of 5 lesions per site, and 5 lymphatic lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise, a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

Nontarget Disease

All nonmeasurable disease is nontarget. All measurable lesions not identified as target lesions are also included as nontarget disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED.

c. Objective Response Status at Each Evaluation

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for

target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable Disease (SD): Does not qualify for CR, PR, or progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Objective Progression: 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate: Progression has not been documented, and
  - one or more target measurable lesions have not been assessed
  - or assessment methods used were inconsistent with those used at baseline
  - or one or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure)
  - or one or more target lesions were excised or irradiated and have not reappeared or increased.

Nontarget disease

- CR: Disappearance of all nontarget lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any nontarget lesions and/or tumor marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in nontarget disease should be rare.
- Indeterminate: Progression has not been determined and one or more nontarget sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Record all new lesions and the sites of all new lesions.

Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Subjective Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as progressive disease (PD) on tumor assessment CRFs. This should be indicated on the CRF as discontinuation of treatment due to Global Deterioration of Health Status.

Every effort should be made to document objective progression even after discontinuation of treatment.

ASSESSMENT OF RADIOGRAPHIC RESPONSE AND PROGRESSION IN PATIENTS WITH METASTATIC CRPC

Radiographic imaging for patients with CRPC is categorized as soft tissue or bone. Soft tissue imaging may include CT scans of the chest, abdomen and pelvis or MRIs of the abdomen and pelvis. Bone imaging must be whole body radionuclide bone scan.

The Investigator will assess response of soft tissue disease as described above. However, bone disease is not to be considered as nontarget lesions.

Bone disease will be assessed for progressive disease only by PCWG3. The documentation required for the determination of radiographic progression is shown in Table 20.

Table 20 Criteria for Evidence of Radiographic Progression

Date Progression Detected [a]	Criteria for Progression	Criteria to Confirm Progression	Criteria to Document Disease Progression on Confirmatory Scan
Week 9	Bone lesions: 2 or more new lesions compared to screening bone scan by PCWG3	Timing: At least 9 weeks after progression identified or at Week 18 visit [b]	2 or more new bone lesions on bone scan compared to Week 9 scan
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	Confirmatory scan required for soft tissue disease progression	No confirmatory scan required for soft tissue disease progression
Week 18 or later	Bone lesions: 2 or more new lesions on bone scan compared to Week 9 bone scan	Timing: At least 9 weeks after progression identified or at next imaging timepoint [b]	Persistent or increase in number of bone lesions on bone scan compared to prior scan [c]
	Soft tissue lesions: Progressive disease on CT or MRI by RECIST v1.1	Confirmatory scan required for soft tissue disease progression	Confirmatory scan required for soft tissue disease progression

Abbreviations: CR=complete response, PD=progressive disease, PR=partial response, SD=stable disease, NE=nonevaluable.

a. Progression detected by bone scan at an unscheduled visit either before Week 9 or between scheduled visits will require a confirmatory scan at least 9 weeks later and should follow confirmation criteria outlined in the table for the next scheduled scan.
b. Confirmation must occur at the next available scan.
c. For confirmation, at least 2 of the lesions first identified as new must be present at the next available scan (confirmation scan).

Disease progression in bone must be confirmed at least 9 weeks later, as per PCWG3. See Table 21 below for the timing of confirmatory imaging requirements.

Table 21 Confirmatory Imaging Requirements for Patients with CRPC Based on RECIST v1.1 and PCWG3

Disease Site	Response	Progression [a]
Soft tissue	Must be confirmed at least 9 weeks later	Confirmation required
Bone	Not applicable	Must be confirmed at least 9 weeks later

a. To inform permanent treatment discontinuation

Radiographic progression-free survival (PFS) is defined as the time from enrollment to documentation of radiographic progression in soft tissue by Investigator's assessment according to RECIST v1.1 (Table 22, Table 23), in bone by Investigator's assessment according to PCWG3, or death, whichever occurs first.

Table 22 Objective Response Status at Each Evaluation

Target Lesions	Nontarget Disease	New Lesions	Objective Status
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/non-PD, indeterminate, or missing	No	PR
SD	Non-CR/non-PD, indeterminate, or missing	No	Stable
Indeterminate or missing	Non-PD	No	Indeterminate
PD	Any	Yes or No, including bone determination	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
Abbreviations: CR=complete response, PD=progressive disease, PR=partial response			

If there is a protocol deviation and a patient has been enrolled with only nontarget disease, Table 23 will be used.

Table 23 Objective Response Status at Each Evaluation for Patients with Nontarget Disease Only

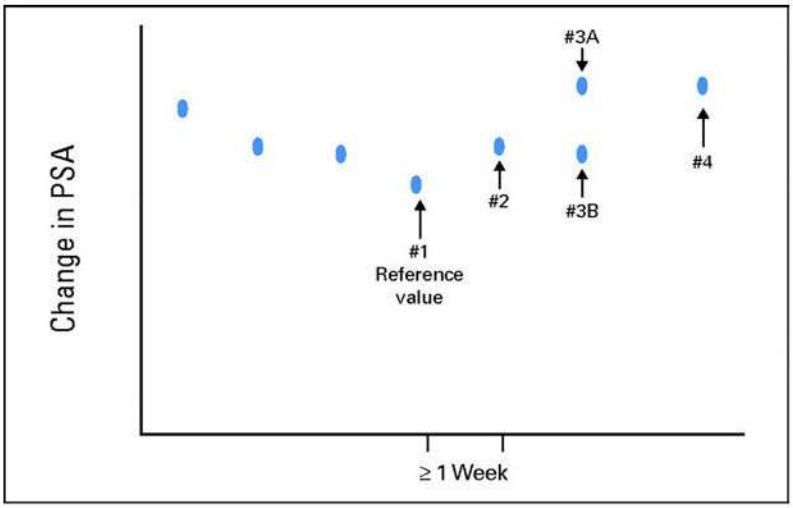
Nontarget Disease	New Lesions	Objective Status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD
Abbreviations: CR=complete response, PD=progressive disease		

EVIDENCE OF PD TO DETERMINE CRPC FOR TRIAL ELIGIBILITY

Patients being considered for trial entry should have evidence of disease progression by PCWG3 criteria to be eligible.

PSA: PSA evidence of disease progression based on the PCWG2 criteria consist of a minimum PSA level 1.3 ng/mL that has risen on at least 2 successive occasions, at least 1 week apart. The reference value #1 (Figure 3) is the last value before the rise in PSA was observed. If the confirmatory PSA value (#3A) is greater than the screening value, then progression by PSA is met and the patient is eligible for trial enrollment on the basis of PSA alone. If the confirmatory PSA (#3B) value is less than the screening PSA (#2) value, then an additional test for rising PSA (#4) will be required to document progression before the patient can be enrolled.

Figure 3 Example PSA Values for Determination of Disease Progression for Trial Eligibility



Target lesion/measurable disease: Patients are not required to have evidence of disease progression by measurable disease if they meet the criteria for disease progression on the basis of PSA or bone scan. Evidence of nodal or visceral disease RECIST 1.1 progression however is sufficient for trial entry independent of PSA readings. Because lymph nodes may be enlarged due to benign pathology, only lymph nodes that are ≥2.0 cm should be used for disease evaluation.

Bone scan: Evidence of disease progression based on bone scan appearance is sufficient for trial entry independent of PSA readings. If the appearance of the bone scan is the only indicator of progression, then there must be ≥2 new bone lesions compared with the prior bone scans. If there is ambiguity about the appearance of the bony lesions such as traumatic in nature or secondary to a flare reaction, then it is recommended that an alternative imaging modality such as MRI or fine-cut CT be used to evaluate these lesions further.

OUTCOME MEASURES OF RESPONSE / PROGRESSION POST STUDY TREATMENT

Procedures for Assessing PSA Response / Progression Post Study Treatment

Increases and decreases in PSA measurements will be tracked in order to assess disease response. The PSA reading on its own will not be used to define progression in this protocol. PSA response and PSA progression will be defined according to the consensus guidelines of the PCWG3:

- PSA partial response is defined as a ≥50% decline in PSA from Cycle 1 Day 1 (baseline) PSA value. This PSA decline must be confirmed to be sustained by a second PSA value obtained 3 or more weeks later.

- PSA progression date is defined as the date that a ≥25% increase and an absolute increase of ≥2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained four or more weeks later.

Table 24 Radiological Criteria for Ascribing Disease Progression

Evidence of Progression	Confirmation	Action
Bone Disease Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment ≤13 weeks from Cycle 1 Day 1 compared with baseline; must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should show an additional 2 new lesions compared to the first post treatment scan (i.e., a total of ≥ 4 new lesions compared with the baseline bone scan).	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Appearance of two or more new bone lesions on bone scan	≥ 2 new lesions at the first scheduled reassessment >13 weeks from Cycle 1 Day 1 compared with baseline; must be confirmed by a second scan performed 6 or more weeks later. Confirmatory scans should confirm the presence of the 2 new lesions compared the baseline scan. (i.e., a total of ≥ 2 new lesions compared with the baseline bone scan).	Investigators are highly encouraged to maintain the patient's treatment with study medication unless progression is confirmed.
Soft Tissue Disease as defined by RECIST on CT/MRI	Progression at any scheduled reassessment should be confirmed.	Investigators are highly encouraged to maintain the patient's treatment with study medication unless radiological progression is confirmed.

Appendix 7 Bone Scan Assessment Tool (PCWG3)

The bone scan case report form for this study is adapted from (Scher, 2016) (below). The CRF will be completed for each bone scan.

Prostate Cancer Clinical Trials Consortium (PCCTC) Bone Scan Assessment Tool (4 pp.)

PCCTC Bone Scan Assessment Tool			
BASELINE Scan Date: (_____/_____/_____)			
Patient Identifier:			
Protocol Number:		Protocol Start Date:	
Is tracer uptake related to metastatic disease? ❑ Yes ❑ No *NOTE: If "NO", do not fill out the form below*			
If yes, indicate total number of lesions related to metastatic disease (select one) ❑ 1 ❑ 2-4 ❑ 5-9 ❑ 10-20 ❑ >20			
Comments		Investigator's Signature	
Version 1.0			© 2010, MSKCC

PCCTC Bone Scan Assessment Tool

8 Week Scan Date: (_____/_____/_____)

Patient Identifier:	
Protocol Number:	Protocol Start Date:

Is tracer uptake related to metastatic disease?

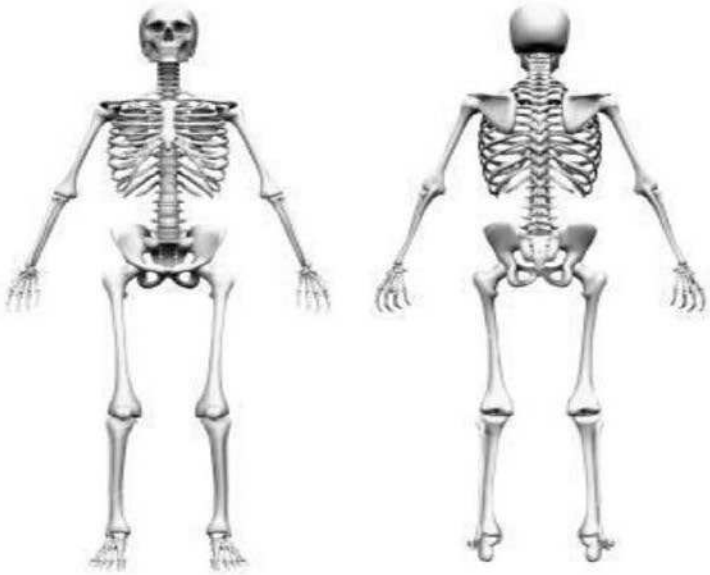
❑ Yes ❑ No

NOTE: If "NO", do not fill out the form below

Draw site(s) of NEW lesion(s) on skeleton

Check Region(s) of NEW Disease:

- ❑ **Skull**
- ❑ **Thorax**
- ❑ **Spine**
- ❑ **Pelvis**
- ❑ **Extremities**



If yes, indicate total number of NEW lesions compared to Baseline Scan (Date:___/___/___)
(select one)

❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ >5

*Presence of new lesions at this time does not confirm progression *

Clinical Impression (circle one)

❑ Improved ❑ Stable ❑ Progression

Comments		Investigator's Signature	

Version 1.0

PCCTC Bone Scan Assessment Tool

_____ Week Scan Date: (_____/_____/_____)

****To be compared to 8 Week Scan****

Patient Identifier:	
Protocol Number:	**Protocol Start Date:**

Is tracer uptake related to metastatic disease?

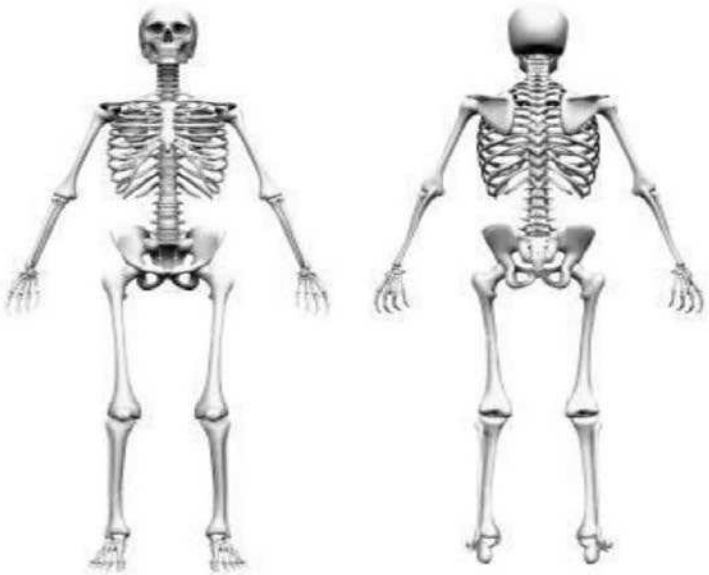
❑ Yes ❑ No

NOTE: If "NO", do not fill out the form below

Draw site(s) of NEW lesion(s) on skeleton

Check Region(s) of NEW Disease:

- ❑ **Skull**
- ❑ **Thorax**
- ❑ **Spine**
- ❑ **Pelvis**
- ❑ **Extremities**



If yes, indicate total number of NEW lesions compared to 8 Week Scan (Date:___/___/___)

(select one)

❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ >5

Clinical Impression (circle one)

❑ Improved ❑ Stable ❑ Progression

Comments		**Investigator's Signature**	

Version 1.0

PCCTC Bone Scan Assessment Tool

Assessment Worksheet

Patient Identifier:	
Protocol Number:	Protocol Start Date:

Date of Scan: _____/ _____/_____

1. Are there 2 or more new lesions compared to the WEEK 8 SCAN?

❑ Yes ❑ No

If YES, proceed to question 2.
If NO, the patient does not have radiographic progression by bone scan.

2. Is this the first scan performed POST the WEEK 8 SCAN?

❑ Yes ❑ No

If YES, proceed to question 3A. If NO, proceed to question 3B.

3A. Were there 2 or more new lesions at the WEEK 8 SCAN compared to the BASELINE SCAN?	3B. Does this scan confirm the presence of 2 or more new lesions seen since the WEEK 8 SCAN?
❑ Yes ❑ No	❑ Yes ❑ No

If YES, patient has met conditions for radiographic progression by bone scan.
If NO, the patient does not have radiographic progression by bone scan.

Comments		Investigator's Signature	

Version 1.0

Appendix 8 Cytokine Release Syndrome (CRS) and Neurotoxicity Mitigation and Management

Cytokine Release Syndrome (CRS) is a non-antigen-specific cytokine-associated toxicity that occurs as a result of high-level immune activation. CRS is a potentially life-threatening toxicity that has been observed following administration of immune-based therapies for cancer (antibodies and adoptive T-cell therapies). CRS can be managed through supportive care and anti-cytokine interventions.

Early intervention should be undertaken at the first sign of CRS; signs may include pyrexia, tachycardia, tachypnea and/or hypotension that are temporally related to HPN424 infusion, in the absence of alternative etiologies. The following are treatment guidelines (which may be modified as needed by the responsible Investigator according to the best practices at their institution) based on the American Society for Transplant and Cellular Therapy (ASTCT) grading scale for CRS proposed by Lee (Lee, 2019) and management of CRS proposed by Lee (Lee, 2014) and adapted by Neelapu (Neelapu, 2018). This grading scale allows for more intensive supportive care and treatment of the underlying cause of the CRS (excessive cytokine production) before the event must be considered Grade 3 or Grade 4 severity.

Serum C-reactive protein (CRP) levels are a useful marker to monitor in patients undergoing cellular immunotherapy because IL-6 induces the production of CRP by hepatocytes. Thus, an increase in serum CRP level is typically detected after the onset of CRS and correlates with increased levels of IL-6. Moreover, the return of CRP levels to baseline indicates that the CRS phase of the therapy has ended, and the patient can be considered for discharge from the hospital, assuming other toxicities that require monitoring and/or intervention have resolved. Of note, the correlation between CRP levels and CRS is variable, and is not observed in all patients.

CRS events will be graded according to the definitions described in Table 25. Organ toxicities and symptoms occurring as part of a CRS event will be individually graded according to CTCAE version 5.0 but do not influence CRS grading.

Table 25 ASTCT Consensus Grading for Cytokine Release Syndrome

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever [1]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		and/or [2]		
Hypoxia	None	Requiring low-flow nasal cannula[3] or blow-by	Requiring high-flow nasal cannula[3], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS must be graded according to CTCAE v5.0 but they do not influence CRS grading

[1] Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

[2] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

[3] Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Adapted from Lee et al. 2019 (Lee, 2019); BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure;

CRS should be managed per Investigator discretion and according to Institutional Guidelines. A reference guideline is provided in Table 26. This guideline is adapted from Neelapu 2018 (Neelapu, 2018) which summarizes recommendations from the CAR-T-cell-therapy-associated toxicity working group (CARTOX). These recommendations focus on assessment and management of toxicities associated with CAR-T therapies but can be applied to other types of therapies that activate T cell with a mechanism similar to HPN424.

Table 26 Management of Cytokine Release Syndrome

CRS Grade	Symptom or Sign	Management
Grade 1	Fever or organ toxicity	• Acetaminophen[¥] and hypothermia blanket for the treatment of fever • Ibuprofen can be used as second treatment option for fever, if not contraindicated • Assess for infection using blood and urine cultures, and chest radiography • Empiric broad-spectrum antibiotics and filgrastim if neutropenic • Maintenance intravenous (IV) fluids for hydration • Symptomatic management of constitutional symptoms and organ toxicities • Consider tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV for persistent (lasting >3 days) and refractory fever
Grade 2	Hypotension	• IV fluid bolus of 500–1,000 ml of normal saline • Can give a second IV fluid bolus if systolic blood pressure (SBP) remains <90 mmHg • Tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV for the treatment of hypotension that is refractory to fluid boluses; tocilizumab can be repeated after 6 h if needed • If hypotension persists after two fluid boluses and anti-IL-6 therapy, start vasopressors, consider transfer to intensive-care unit (ICU), obtain echocardiogram, and initiate other methods of haemodynamic monitoring • In patients at high-risk[‡] or if hypotension persists after 1–2 doses of anti-IL-6 therapy, dexamethasone can be used at 10 mg IV every 6 h • Manage fever and constitutional symptoms as in Grade 1
	Hypoxia	• Supplemental oxygen • Tocilizumab or siltuximab ± corticosteroids and supportive care, as recommended for the management of hypotension
	Organ toxicity	• Symptomatic management of organ toxicities, as per standard guidelines • Tocilizumab or siltuximab ± corticosteroids and supportive care, as indicated for hypotension
Grade 3	Hypotension	• IV fluid boluses as needed, as recommended for the treatment of Grade 2 CRS • Tocilizumab and siltuximab as recommended for Grade 2 CRS, if not administered previously; • Vasopressors as needed • Transfer to ICU, obtain echocardiogram, and perform haemodynamic monitoring as in the management of Grade 2 CRS • Dexamethasone 10 mg IV every 6 h; if refractory, increase to 20 mg IV every 6 h • Manage fever and constitutional symptoms as indicated for Grade 1 CRS
	Hypoxia	• Supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above
	Organ toxicity	• Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above
Grade 4	Hypotension	• IV fluids, anti-IL-6 therapy, vasopressors, and haemodynamic monitoring as defined for the management of Grade 3 CRS • Methylprednisolone 1 g/day IV • Manage fever and constitutional symptoms as in Grade 1 CRS
	Hypoxia	• Mechanical ventilation • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above
	Organ toxicity	• Symptomatic management of organ toxicities as per standard guidelines • Tocilizumab or siltuximab plus corticosteroids and supportive care, as described above

All medication doses indicated are for adults.
[¥] Consider another antipyretic if liver toxicity and/or transaminitis is observed or is a concern.
* Maximum amount of tocilizumab per dose is 800 mg.
‡ High-risk patients include those with bulky disease, those with comorbidities, and those who develop early onset CRS within 3 days of CAR-T-cell infusion.

Along with CRS, another common toxicity observed after CAR-T cell therapy is neurotoxicity. Previously considered in aggregate with CRS, neurotoxicity is now considered and treated as a separate entity. Immune effector cell-associated neurotoxicity syndrome (ICANS) may manifest as delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremor, seizures, and, rarely, cerebral edema (Lee, 2019). The term CAR-related encephalopathy syndrome (CRES) has been proposed to describe neurotoxicity associated with CAR T cell therapy (Neelapu, 2018). Although encephalopathy is a dominant feature of the neurologic changes that occur as neurotoxic complications of CAR-T therapy, the term ICANS is to be inclusive of other symptoms (Lee, 2019).

Although symptoms can be more diverse than those of CRS, many patients with neurotoxicity have a stereotypic evolution of a specific set of symptoms. The earliest manifestations of ICANS are tremor, dysgraphia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy. Headache is a nonspecific symptom, frequently occurring during fever or after chemotherapy in patients without other neurologic dysfunction. Thus, headache alone is not a useful marker of ICANS (Lee, 2019).

If signs and symptoms of neurotoxicity are observed, they should be graded according to CTCAE v5.0. Guidelines for work-up and management of ICANS are provided in Table 27, Table 28, and Table 29 [adapted from (Neelapu, 2018)]. These recommendations focus on assessment and management of toxicities associated with CAR-T therapies but may be applied to neurotoxicity from other types of therapies that activate T cell with a mechanism similar to that of HPN424.

Table 27 Recommendations for Management of CAR-T Cell Related Encephalopathy Syndrome (CRES)

Grade	Management
Grade 1	• Vigilant supportive care; aspiration precautions; intravenous (IV) hydration • Withhold oral intake of food, medicines, and fluids, and assess swallowing • Convert all oral medications and/or nutrition to IV if swallowing is impaired • Avoid medications that cause central nervous system depression • Low doses of lorazepam (0.25–0.5 mg IV every 8 h) or haloperidol (0.5 mg IV every 6 h) can be used, with careful monitoring, for agitated patients • Neurology consultation • Fundoscopic exam to assess for papilloedema • MRI of the brain with and without contrast; diagnostic lumbar puncture with measurement of opening pressure; MRI spine if the patient has focal peripheral neurological deficits; CT scan of the brain can be performed if MRI of the brain is not feasible • Daily 30 min electroencephalogram (EEG) until toxicity symptoms resolve; if no seizures are detected on EE.G., continue levetiracetam 750 mg every 12 h • If EEG shows non-convulsive status epilepticus, treat as per algorithm in Table 28 Consider anti-IL-6 therapy with tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV, if CRES is associated with concurrent cytokine-release syndrome (CRS)
Grade 2	• Supportive care and neurological work-up as described for Grade 1 CRES • Tocilizumab 8 mg/kg* IV or siltuximab 11 mg/kg IV if associated with concurrent CRS • Dexamethasone 10 mg IV every 6 h or methylprednisolone 1 mg/kg IV every 12 h if refractory to anti-IL-6 therapy, or for CRES without concurrent CRS • Consider transferring patient to intensive-care unit (ICU) if CRES associated with Grade ≥2 CRS
Grade 3	• Supportive care and neurological work-up as indicated for Grade 1 CRES • ICU transfer is recommended • Anti-IL-6 therapy if associated with concurrent CRS, as described for grade 2 CRES and if not administered previously • Corticosteroids as outlined for Grade 2 CRES if symptoms worsen despite anti-IL-6 therapy, or for CRES without concurrent CRS; continue corticosteroids until improvement to grade 1 CRES and then taper • Stage 1 or 2 papilloedema with cerebrospinal fluid (CSF) opening pressure <20 mmHg should be treated as per algorithm presented in Table 29 • Consider repeat neuroimaging (CT or MRI) every 2–3 days if patient has persistent Grade ≥3 CRES
Grade 4	• Supportive care and neurological work-up as outlined for Grade 1 CRES • ICU monitoring; consider mechanical ventilation for airway protection • Anti-IL-6 therapy and repeat neuroimaging as described for Grade 3 CRES • High-dose corticosteroids continued until improvement to Grade 1 CRES and then taper; for example, methylprednisolone IV 1 g/day for 3 days, followed by rapid taper at 250 mg every 12 h for 2 days, 125 mg every 12 h for 2 days, and 60 mg every 12 h for 2 days • For convulsive status epilepticus, treat as per algorithm in Table 28 • Stage ≥3 papilloedema, with a CSF opening pressure ≥20 mmHg or cerebral oedema, should be treated as per algorithm in Table 29

Table 28 Recommendations for the Management of Status Epilepticus After CAR-T Cell Therapy

Type	Management
Non-convulsive status epilepticus	• Assess airway, breathing, and circulation; check blood glucose • Lorazepam* 0.5 mg intravenously (IV), with additional 0.5 mg IV every 5 min, as needed, up to a total of 2 mg to control electrographical seizures • Levetiracetam 500 mg IV bolus, as well as maintenance doses • If seizures persist, transfer to intensive-care unit (ICU) and treat with phenobarbital loading dose of 60 mg IV • Maintenance doses after resolution of non-convulsive status epilepticus are as follows: lorazepam 0.5 mg IV every 8 h for three doses; levetiracetam 1,000 mg IV every 12 h; phenobarbital 30 mg IV every 12 h
Convulsive status epilepticus	• Assess airway, breathing, and circulation; check blood glucose • Transfer to ICU • Lorazepam* 2 mg IV, with additional 2 mg IV to a total of 4 mg to control seizures • Levetiracetam 500 mg IV bolus, as well as maintenance doses • If seizures persist, add phenobarbital treatment at a loading dose of 15 mg/kg IV • Maintenance doses after resolution of convulsive status epilepticus are: lorazepam 0.5 mg IV every 8 h for three doses; levetiracetam 1,000 mg IV every 12 h; phenobarbital 1–3 mg/kg IV every 12 h • Continuous electroencephalogram monitoring should be performed, if seizures are refractory to treatment

All indicated doses of medication are for adult patients. CAR, chimeric antigen receptor.
* Lorazepam is the recommended benzodiazepine because it is short-acting, compared with diazepam, and has been widely used in the management of seizures.

Table 29 Recommendation for Management of Raised Intracranial Pressure (ICP) After CAR-T Cell Therapy

Type	Management
Stage 1 or 2 papilloedema* with cerebrospinal fluid (CSF) opening pressure of <20 mmHg without cerebral oedema	• Acetazolamide 1,000 mg intravenously (IV), followed by 250–1,000 mg IV every 12 h (adjust dose based on renal function and acid–base balance, monitored 1–2 times daily)

Stage 3, 4, or 5 papilloedema*, with any sign of cerebral oedema on imaging studies, or a CSF opening pressure of ≥20 mmHg	• Use high-dose corticosteroids with methylprednisolone IV 1 g/day, as recommended for grade 4 CAR-T-cell-related encephalopathy syndrome
	• Elevate head end of the patient's bed to an angle of 30 degrees
	• Hyperventilation to achieve target partial pressure of arterial carbon dioxide ($PaCO_2$) of 28–30 mmHg, but maintained for no longer than 24 h
	• Hyperosmolar therapy with either mannitol (20 g/dl solution) or hypertonic saline (3% or 23.4%, as detailed below)
	  ○ Mannitol: initial dose 0.5–1 g/kg; maintenance at 0.25–1 g/kg every 6 h while monitoring metabolic profile and serum osmolality every 6 h, and withhold mannitol if serum osmolality is ≥320 mOsm/kg, or the osmolality gap is ≥40
	  ○ Consider neurosurgery consultation and IV anaesthetics for burst-suppression pattern on electroencephalography
	  ○ Metabolic profiling every 6 h and daily CT scan of head, with adjustments in usage of the aforementioned medications to prevent rebound cerebral oedema, renal failure, electrolyte abnormalities, hypovolemia, and hypotension

All indicated doses of medication are for adult patients. CAR, chimeric antigen receptor.
* Papilloedema grading should be performed according to the modified Frisén scale (Frisén, 1982).