Official Title:	A Parallel Arm Phase 1b/2a Study of DKN-01 as Monotherapy or in Combination With Docetaxel for the Treatment of Advanced Prostate Cancer With Elevated DKK1
NCT Number:	NCT03837353
Study Number:	17-01747
Document Type:	Study Protocol and Statistical Analysis Plan
Date of the Document:	• July 13, 2021

A Parallel Arm Phase 1b/2a Study of DKN-01 as Monotherapy or in Combination With Docetaxel for the Treatment of Advanced Prostate Cancer

Protocol Version: DKN-01-Prostate Version 1.5

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

Study Sponsor and

Principal Investigator: David R. Wise, MD, PhD
Medical Oncologist
Perlmutter Cancer Center at NYU Langone
160 E 34TH Street, 10th Fl, Suite 1009
New York, NY 10016

Biostatistician: Andrea Troxel, PhD

Protocol No: s17-01747

IND: 140254

Coordinating Center: NYU Langone Health
Perlmutter Cancer Center
Clinical Trials Office
PCC-QAU@nyulangone.org

Document Version: Original Protocol dtd 2018 May 22
Protocol v1.2 dtd 2018 Aug 05
Protocol v1.3 dtd 2019 May 21
Protocol v1.4 dtd 2020 June 30
Protocol v1.5 dtd 2021 April 19

SIGNTURE PAGE

Protocol Title: A Parallel Arm Phase 1b/2a Study of DKN-01 as Monotherapy or in Combination With Docetaxel for the Treatment of Advanced Prostate Cancer

Protocol Number: s17-01747

REVIEWED/APPROVED BY:

David R. Wise, MD, PhD

Signature Date

INVESTIGATOR STATEMENT

I understand that all documentation provided to me by the Sponsor or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator's Brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board or Ethics Committee. No changes will be made to the study protocol without the prior written approval of the Sponsor and the Institutional Review Board or Ethics Committee, except where necessary to eliminate an immediate hazard to the patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Name	Investigator Signature	Date

Name and address of investigational site / institution
(please print)

STATEMENT OF COMPLIANCE

This study will be conducted in accordance with the Code of Federal Regulations (CFR) on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable United States government research regulations, and institutional research policies and procedures. The International Council for Harmonization ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with Food and Drug Administration (FDA) and Department of Health and Human Services regulations. The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

CLINICAL STUDY SYNOPSIS

Name of Sponsor:	Perlmutter Cancer Center at NYU Langone Medical Center
Name of Investigational Product:	DKN-01
Protocol Title:	A Parallel-Arm Phase 1b/2a Study of DKN-01 as Monotherapy or in Combination With Docetaxel for the Treatment of Advanced Prostate Cancer
Protocol Number:	s17-01747
Summary	This is a non-randomized multi-center Phase 1b/2a dose escalation and dose expansion study involving up to 84 patients testing DKN-01 as monotherapy or in combination with docetaxel in metastatic castration-resistant prostate cancer. Biopsies for correlative studies are encouraged but not mandatory. Pharmacokinetic (PK) testing of one pre-treatment blood sample and one post-treatment blood sample will be mandatory on Day 1 of every cycle.
Study Phase:	1b/2a
Objectives:	**Primary Objectives:** Part 1: Dose Escalation: To determine the safety, tolerability, dose-limiting toxicities (DLTs), and maximum tolerated dose (MTD) of DKN-01 administered alone and in combination with docetaxel in patients with advanced prostate cancer with elevated DKK1. Part 2: Dose Expansion: To evaluate the anti-tumor activity of DKN-01 in combination with docetaxel in patients with advanced prostate cancer with elevated DKK1. **Secondary Objectives:** 1. To determine the anti-tumor activity of DKN-01 as monotherapy using immune-related response criteria (iRECIST) guidelines. 2. To characterize the pharmacodynamics effects of DKN-01 administered as monotherapy or in combination with docetaxel. 3. To characterize the PK of DKN-01 administered as monotherapy or in combination with docetaxel. 4. To characterize the immunogenicity of DKN-01 administered as monotherapy or in combination with docetaxel. 5. To determine the concordance between anti-tumor activity and DKK1 expression in the monotherapy and combination cohorts. **Exploratory Objectives:** 1. To determine the effect of DKN-01 monotherapy on peripheral and intratumoral immune cell abundance and activation.

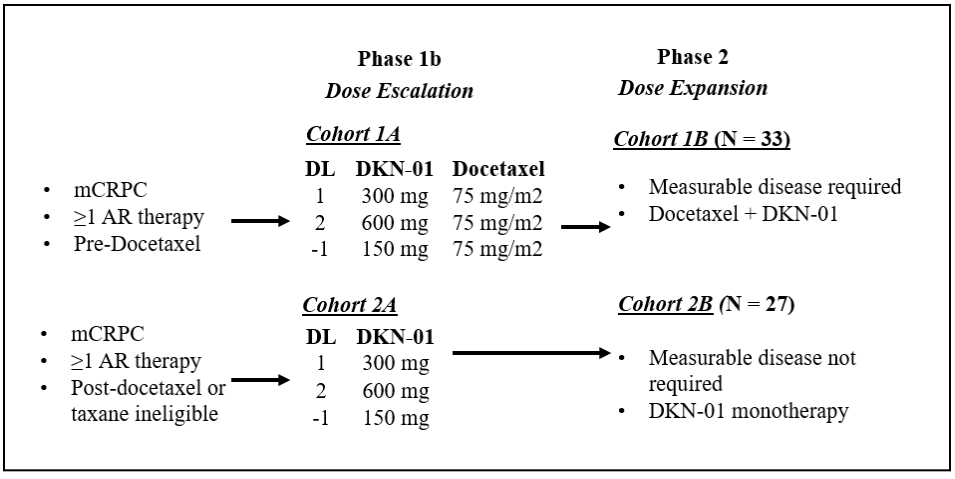
	2. To explore the association between DKN-01 exposure, peripheral and intratumoral immune cell abundance and activation, anti-tumor activity, and key safety measures. 3. To determine the impact of docetaxel on peripheral and intratumoral immune cell abundance and activation. 4. To determine the concordance between plasma and intratumoral DKK1 levels and determine the association between DKK1 level, Wnt pathway, FGF, and, cell cycle gene alterations, and anti-tumor activity 5. To determine the effect of DKN-01 as monotherapy or in combination with docetaxel on ex-vivo intratumoral immune cell abundance and activation in a 3-dimensional organotypic culture model. 6. To explore the association between response to study drug treatment and clinical evidence of "prostate-specific antigen (PSA)-high" (concordant radiographic and PSA progression) and "PSA-low" (radiographic evidence in the absence of PSA progression) prostate cancer.
Endpoints:	**Primary Endpoints:** Phase 1b, Cohort 1A and Cohort 2A: DLT observed during the DLT evaluation period (starting from Cycle 1, Day 1 [C1D1] until C2D1). Phase 2, Cohort 1B: Best overall response, based on iRECIST v1.1 soft tissue response. **Secondary efficacy endpoints (apply to all cohorts):** • Radiographic progression-free survival (PFS). • PSA PFS. • Overall survival (OS). • Duration of response (DR). • Time-to-tumor response (TTR). • ≥50% decline in PSA. • Percentage change in PSA from baseline to 12 weeks post-treatment. • Maximal decline in PSA after treatment initiation. • CTC conversion from unfavorable (5 or greater CTC/7.5 mL) to favorable (4 or fewer CTC/7.5 mL) at 13 weeks • CTC ≥1 at baseline and 0 at 13 weeks (CTC0). • BOR stratified by tumoral DKK1 expression, Wnt pathway, FGF pathway, and/or cell cycle gene alteration

	Exploratory Endpoints: • Baseline (for tumor tissue and peripheral blood) and on treatment (for tumor and peripheral blood) measurements related to genomic events that might predict outcome, including Wnt pathway alterations, genome scarring and mutational load, neoantigen analysis, ribonucleic acid (RNA) sequencing, and whole exome sequencing. Genomic studies will be done on tumor tissue and when feasible on cell-free deoxyribonucleic acid (DNA). • Baseline and on-treatment measurement of the viability of pre-treatment patient-biopsy-derived 3-dimensional organotypic cultures as well as the number and phenotype of the immune cells present within these cultures incubated ex-vivo with DKN-01 and docetaxel. • Baseline (for tumor tissue and peripheral blood) and on treatment (for tumor and peripheral blood) measurements related to target modulation and immune function that may include, but not be limited to, the number and phenotype of immune cells, gene expression profile, abundance and diversity of tumor infiltrating and peripheral blood T cell clones by high throughput T-cell receptor (TCR) sequencing, variation in proteomic signatures within peripheral blood and presence or absence of key driver mutations and quantitation of mutational load within tumor tissue. • Overall response stratified by "PSA-high" (concordant radiographic and PSA progression) and "PSA-low" (radiographic evidence in the absence of PSA progression) prostate cancer status. • Overall response stratified by plasma DKK1 "high" and "low" defined as above or below the DKK1 plasma level reference range in a cohort of healthy men.
Study Design:	This is a 2-arm, non-randomized, phase 1b/2a, multicenter, open-label study of DKN-01 as monotherapy or in combination with docetaxel in patients with advanced treatment-refractory prostate cancer. This study will be conducted in two parts: dose escalation and expansion. The dose escalation and expansion parts will each consist of cohorts in which DKN-01 is combined with docetaxel (Cohorts 1A, 1B) and in which DKN-01 is administered as monotherapy (Cohorts 2A, 2B). Dose escalation (Part 1) will apply exclusively to the dose of DKN-01 in both cohorts. In dose escalation Cohort 1A, the dose of docetaxel 75 mg/m^2 will remain fixed. The DKN-01 dose level will start with 300 mg and be escalated to 600 mg or de-escalated to 150 mg depending on the absence or presence of identified DLTs. DKN-01 will be administered in combination with docetaxel on Day 1 and as monotherapy on Day 15 of each 21-day cycle. The DLT monitoring period will start with C1D1 and end on C2D1, but may be longer in the setting of a treatment delay. The maximum treatment delay is 28 days prior to necessitating withdrawal from study. The MTD or highest dose tested of DKN-01 in combination with docetaxel will be the dose used Dose Expansion Cohort 1B.

In dose escalation Cohort 2A, DKN-01 dose level will start with 300 mg and be escalated to 600 mg or de-escalated to 150 mg depending on the absence or presence of identified DLTs. DKN-01 will be administered as monotherapy on Days 1 and 15 of the 28-day cycle 1. The DLT monitoring period will start with C1D1 and end on C2D1, but may be longer in the setting of a treatment delay. The maximum treatment delay is 28 days prior to necessitating withdrawal from study. The MTD or highest dose tested of DKN-01 monotherapy will be the dose used Dose Expansion Cohort 2B.

Doses of DKN-01 higher than 600 mg will not be tested because of the PK and pharmacodynamic data described Section 2.2.

Dose expansion (Part 2) will include two cohorts. The dose of DKN-01 chosen for dose expansion cohorts 1B will be the MTD or highest dose tested in dose escalation cohort 1A. The dose of DKN-01 chosen for dose expansion cohorts 2B will be the MTD or highest dose tested in dose escalation cohort 2A. Cohorts 1B will be restricted to patients who have had 1 or more prior 2nd generation AR targeting therapies (enzalutamide/abiraterone/apalutamide/darolutamide) and no prior docetaxel exposure. Cohort 1B will include patients with RECIST v1.1 measurable disease. Cohort 2B will be restricted to patients who have had 1 or more prior 2nd generation AR targeting therapies and have had progression on 1 or more prior taxane chemotherapies or are intolerant of taxane-based chemotherapy or refusing taxane-based chemotherapy. In either cohort, Patients with pure neuroendocrine carcinoma do not need to have been previously treated with androgen receptor (AR) signaling inhibitors (abiraterone or enzalutamide or apalutamide or darolutamide) but must have castrate testosterone and have castration-resistant disease. Cohorts 1B will be treated with the combination of DKN-01 at the MTD or highest dose tested given on Days 1 and 15, and docetaxel 75 mg/m^2 (or 60 mg/m^2 depending on clinical discretion) given on Day 1 of every 3 weeks (21-day cycles). Cohort 2B will be treated with DKN-01 monotherapy at the MTD or highest dose tested given on Days 1 and 15 of a 28-day cycle.



Treatment Groups:	**Dose Escalation:** **Cohort 1A** Dose Level 1: DKN-01 300 mg intravenously (IV) on Days 1 and 15, docetaxel 75 mg/m^2 on Day 1 every 3 weeks (21-day cycles). Dose Level 2: DKN-01 600 mg IV on Days 1 and 15, docetaxel 75 mg/m^2 on Day 1 every 3 weeks (21-day cycles). **Cohort 2A** Dose Level 1: DKN-01 300 mg IV on Days 1 and 15 of a 28-day cycle. Dose Level 2: DKN-01 600 mg IV on Days 1 and 15 of a 28-day cycle. **Dose Expansion:** Cohort 1B: DKN-01 at MTD or highest dose tested: Days 1 and 15, docetaxel 75 mg/m^2 Day 1 of every 3 weeks (21-day cycles) Cohort 2B: DKN-01 at MTD or highest dose tested: Days 1 and 15 (28-day cycles)
Number of Patients Planned:	**Dose Escalation:** Cohort 1A: up to 12 patients (up to 6 per Dose Level) Cohort 2A: up to 12 patients (up to 6 per Dose Level) **Dose Expansion:** Cohort 1B: 33 patients Cohort 2B: 27 patients
Diagnosis and Main Criteria for Inclusion:	**Inclusion** Male patients who meet the following inclusion criteria and none of the exclusion criteria will be eligible for enrollment in the study: 1) Age >18 years. 2) Have a histologically or cytologically confirmed cancer of prostate origin (adenocarcinoma, poorly differentiated carcinoma, or neuroendocrine carcinoma are all allowed). I. Patients with pure neuroendocrine carcinoma must have had at least one line of platinum-based chemotherapy unless the patient is intolerant of or is refusing chemotherapy. II. Patients with pure neuroendocrine carcinoma do not need to have been previously treated with androgen receptor (AR) signaling inhibitors (abiraterone or enzalutamide or apalutamide or darolutamide) but must have castrate testosterone and have castration-resistant disease. 3) Surgically or medically castrated, with testosterone levels of < 50 ng/dL (< 2.0 nM). If the patient is being treated with luteinizing hormone-releasing hormone (LHRH) agonists (patient who have not undergone orchiectomy), this therapy must have been initiated at least 4 weeks prior to C1D1 and must be continued throughout the study.

	4) Cohorts 1A, 1B. Patients must have progressed despite 1 or more androgen receptor (AR) signaling inhibitors (abiraterone or enzalutamide or apalutamide or darolutamide) and have not received prior taxane-based chemotherapy for prostate cancer. Prior treatment with an AR signaling inhibitor for castration-sensitive disease will be allowed if the time to progression was within 1 year after starting drug. Prior treatment with a taxane-based chemotherapy for castration-sensitive disease will be exclusionary. (Prior treatment with an AR signaling inhibitor is not required for pure prostate neuroendocrine carcinoma as in inclusion 2.) 5) Cohorts 2A and 2B. Patients must have progressed despite 1 or more AR signaling inhibitor (abiraterone or enzalutamide or apalutamide or darolutamide) and either had disease progression, were intolerant of, or refused 1 or more taxane-based chemotherapies for mCRPC. (Prior treatment with an AR signaling inhibitor is not required for pure prostate neuroendocrine carcinoma as in inclusion 2.) 6) Cohort 1B. Patients must have measurable disease per RECIST v1.1 guidelines AND must have either: a) PSA progression is defined by Prostate Cancer Working Group 3 (PCWG3) criteria as a minimum of two consecutive rising levels, with an interval of ≥1 week between each determination with a minimum PSA of 1 ng/mL, if PSA is the sole evidence of progression, OR b) Radionuclide bone progression as defined by at least two new metastatic lesions (per PCWG3), OR c) Soft tissue progression on transaxial imaging: new or progressive soft tissue masses on computed tomography (CT) or magnetic resonance imaging (MRI) scans as defined by RECIST v1.1. 7) Cohorts 1A, 2A, 2B. Patients must have baseline progression defined as one of the following: a) PSA progression is defined by PCWG3 criteria as a minimum of two consecutive rising levels, with an interval of ≥1 week between each determination with a minimum PSA of 2 ng/mL. b) Radionuclide bone progression as defined by at least two new metastatic lesions (per PCWG3). c) Soft tissue progression on transaxial imaging: new or progressive soft tissue masses on computed tomography (CT) or magnetic resonance imaging (MRI) scans as defined by RECIST v1.1. 8) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. 9) Estimated life expectancy of at least 3 months, in the judgment of the Investigator. 10) Required initial laboratory values within 14 days of C1D1:

a) Total bilirubin within normal limits for the institution. (For Cohorts 2A and 2B, total bilirubin < 3 × ULN is acceptable with known liver metastases).

b) For Cohorts 1A, 1B transaminases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] ≤1.5 × the upper limit of normal (ULN). For Cohorts 2A and 2B, AST and ALT ≤ 5.0 × ULN is acceptable with known liver metastases.

c) Creatinine ≤2.0 or calculated creatinine clearance ≥50 mL/min using the Cockcroft and Gault Method (Cockroft and Gault 1976).

d) Absolute neutrophil count ≥1000 cells/µl.

e) Absolute lymphocyte count ≥500/µl.

f) Hemoglobin ≥8.5 g/dL.

g) Platelet count ≥100,000 cells/µl. (For Cohorts 2A and 2B, Platelet count ≥75,000 cells/µl).

h) International normalized ratio (INR) (prothrombin time [PT])/partial thromboplastin time (PTT) ≤1.5 × ULN unless receiving anticoagulant, in which case INR ≤3.0 and no active bleeding, (ie, no clinically significant bleeding within 14 days prior to first dose of study therapy.

11) Sexually active male patients must agree to use adequate contraception (hormonal or barrier method of birth control) during the study and for 6 months after their last dose of study drug. Should a patient's partner become pregnant or suspect she is pregnant while participating in the study, the Investigator should be immediately informed.

12) Reliable and willing to make themselves available for the duration of the study and are willing to follow study-specific procedures.

13) Provided written informed consent prior to any study-specific procedures.

14) Submission of a next-generation sequencing report from prostate cancer tissue or ctDNA from a CLIA certified lab if available. If no such report is available, a statement attesting to the lack of such a report is sufficient for eligibility.

Exclusion

15) Any anti-cancer therapy (with the exception of luteinizing hormone-releasing hormone [LHRH] analog or antagonist) within 2 weeks prior to initiation of study treatment.

16) Any investigational anti-cancer therapy within 4 weeks of initiation of study treatment.

17) New York Heart Association Class III or IV heart failure, or myocardial infarction within the past 6 months, or unstable arrhythmia within 3 months.

18) Uncontrolled bacterial, viral, or fungal infections, within 7 days of study entry.

19) History of malignancy other than prostate cancer within 2 years prior to screening, except for malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as non-melanoma skin carcinoma or ductal carcinoma in situ

20) Known to be human immunodeficiency virus (HIV) positive, have positive hepatitis B surface antigen (HBSAg), or positive hepatitis C antibody (HCAb) test. (Hepatitis C antibody-positive patients with an undetectable hepatitis C virus (HCV) RNA will be eligible.)

21) History of solid organ transplant (ie, heart, lungs, liver, or kidney).

22) History of autologous/allogenic bone marrow transplant.

23) Serious nonmalignant disease that could compromise protocol objectives in the opinion of the Investigator and/or Sponsor.

24) Major surgical procedures or significant traumatic injury within 4 weeks prior to study entry (minor surgical procedures within 1 week of study entry). Note: Diagnostic cystoscopy is not exclusionary at any time during screening. History of osteonecrosis of the hip. Other hip pathology such as degenerative disease or malignant involvement are not exclusionary. Screening of asymptomatic patients is not required.

25) Active or untreated central nervous system (CNS) malignancy or metastasis. Screening for CNS metastases of asymptomatic patients without a history of CNS metastases is not required. Patients with treated CNS metastases are eligible provided they meet all of the following criteria:

    a) Evaluable disease outside the CNS.

    b) No history of intracranial or intraspinal hemorrhage.

    c) No evidence of significant vasogenic edema.

    d) No ongoing requirement for corticosteroids as therapy for CNS disease. (Anti-convulsants at a stable dose for > one month is allowed.)

    e) No stereotactic radiation, whole brain radiation within 4 weeks of C1D1.

    f) Patients with CNS metastases treated by neurosurgical resection or brain biopsy within 3 month prior to C1D1 will not be allowed.

    g) Radiographic demonstration of interim stability (ie, no progression) between completion of CNS-directed therapy and the screening radiographic study.

    h) Screening CNS radiographic study ≥4 weeks since completion of radiotherapy or surgical resection and ≥2 weeks since discontinuation of corticosteroids.

26) Any other condition, disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.

27) Active substance abuse.

<table>
<tr><td></td><td>28) Receipt of any live vaccine within 30 days before the first dose of study treatment or anticipation that such a live vaccine will be required during study participation.

29) Previously treated with an anti-DKK1 therapy.</td></tr>
<tr><td>Study Treatment:</td><td>Cohorts 1A, 1B: DKN-01 will be administered IV on Days 1 and 15 of each cycle without interruption. The duration of each cycle is 21 days.

Docetaxel will be administered IV on Day 1 of each cycle without interruption. The duration of each cycle is 21 days. Patients will be pre-medicated with a standard institutional regimen as per standard institutional guidelines. Corticosteroids, whether in an IV or oral regimen, are allowed as part of the pre-medication regimen.

Prednisone 5 mg twice daily given for purposes other than pre-medication for infusion will not be allowed until C3D1, after which it will be optional and under the discretion of the Investigator. See Section 5.16 for further details on concomitant medications.

Cohorts 2A, 2B: DKN-01 will be administered IV on Days 1 and 15 of a 28-day cycle.</td></tr>
<tr><td>Dose Escalation Scheme (Part A):</td><td>Dose escalation scheme Cohort 1A:
<table><tr><th>Dose Level</th><th>Dose of DKN-01 on Days 1 and 15 of each 21-day cycle</th><th>Dose of Docetaxel</th></tr><tr><td>Level 1</td><td>300 mg</td><td>75 mg/m^2</td></tr><tr><td>Level 2</td><td>600 mg</td><td>75 mg/m^2</td></tr><tr><td>Level -1*</td><td>150 mg</td><td>75 mg/m^2</td></tr></table>* if required

Dose escalation scheme Cohort 2A:
<table><tr><th>Dose Level</th><th>Dose of DKN-01 on Days 1 and 15 of each 28-day cycle</th></tr><tr><td>Level 1</td><td>300 mg</td></tr><tr><td>Level 2</td><td>600 mg</td></tr><tr><td>Level -1*</td><td>150 mg</td></tr></table>* if required

Data from each cohort in Part A will be evaluated for safety and DLTs prior to dose escalation.

At each dose level (cohort) in Part A, up to 4 patients will be screened simultaneously in order to ensure 3 patients will be treated and evaluable for DLT period. If all 4 patients in Screening are eligible, all will be permitted to enroll. Screening of patients will continue until 3 patients are evaluable for DLTs at each dose level. If none of the treated patients per cohort (up to 4 patients) develop a DLT after a minimum of 21 days (Cohort 1A) or 28 days (Cohort 2A) and 1 cycle of treatment beginning with cycle 1 Day 1, subsequent dose escalation will proceed according to the planned schedule. Prior to the start</td></tr>
</table>

	of the next dosing cohort in Part A, a safety assessment will be performed to assess safety and DLTs. If a DLT is observed in 1 out of 3 patients (or 1 of 4 should 4 patients be enrolled) during C1 of any given dose level, the cohort will be expanded and up to an additional 3 patients (maximum of 6 patients per dose level) will be enrolled and treated at that dose level. If no further DLTs are observed within the expanded cohort, dose escalation will proceed. If 2 or more patients at that dose level have DLTs, the MTD will have been exceeded and dose escalation will cease.
Study Procedures:	Patients will complete up to 5 periods of the study: Screening, Treatment, Follow-up, and Survival/Long-term Follow-up.
Screening Period:	Up to 28 days: Patients will sign consent and be screened for study eligibility.
Treatment Period:	Cohort 1A, 1B (Dose escalation and Dose Expansion): Patients will be treated with the combination of DKN-01 and Docetaxel until PCWG3 progression or unacceptable toxicity. Cohort 2A and 2B: Patients will be treated with DKN-01 until PCWG3 progression or unacceptable toxicity. Following 9 weeks (3 cycles), the decision to continue treatment with additional cycles of study drug(s) will be based on radiological assessments (performed at baseline, end of C3, and every 9 weeks for the first 27 weeks, then every 12 weeks). Tumor progression or response endpoints will be assessed using iRECIST, and PCWG3 guidelines. Treatment beyond progression may be allowed in select patients after discussion and agreement with the Sponsor and Leap Therapeutics. The benefit/risk assessment needs to favors continued administration of study therapy (eg, patients are continuing to experience clinical benefit as assessed by the Investigator and tolerating treatment), and no treatment discontinuation criteria are met: 1. Investigator-assessed clinical benefit, and not having rapid disease progression. 2. Continue to meet all other study protocol eligibility criteria for continued treatment as per Section 5.10 (criteria for continued treatment). 3. Tolerance of study drug; 4. Stable performance status; 5. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases); 6. Patient provides written informed consent prior to receiving any additional DKN-01/docetaxel treatment, using an informed consent form (ICF) describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.
Follow-up Period:	Upon completion of study therapy (or upon completion of DKN-01 if further treatment is warranted), all patients will enter the Clinical/Safety Follow-up

	period once the decision is made to discontinue the patient from treatment (eg, at end of treatment [EOT]). At the time of discontinuation, the most recent on-treatment visit will be the EOT visit. Any assessments required for EOT that were completed within 14 days of the last on-treatment visit do not need to be re-completed. This visit will be considered the start of the Week 1 Clinical/Safety Follow-up visit. Patients who discontinue the treatment phase will enter the Clinical/Safety Follow-up period. Patients must be followed for at least 100 days (representing approximately 5 half-lives for DKN-01) after the last dose of study drug. Follow-up visits should occur at Days 30, 60, and 100 (±10 days) after the last dose of study drug or should coincide with the date of discontinuation (±10 days) if date of discontinuation is greater than 30 days after the last dose of study drug to monitor for adverse events (AEs). All patients will be required to complete 3 Clinical/Safety Follow-up visits regardless of whether they start new anti-cancer therapy, except those patients who withdraw consent for study participation. After completion of the Clinical/Safety Follow-up period, all patients will then enter the Survival/Long-term Follow-up period. During this period, clinic visits or telephone contact every 3 months will be performed to assess survival status. The duration of the Survival/Long-term Follow-up period will be approximately 2 years following the first dose of study drug, and a minimum of 12 months following the last dose of study drug. After completion of the Safety Follow-up period, patients who discontinue study with ongoing stable disease (SD), partial response (PR), or complete response (CR) at the EOT visit will enter the Response Follow-up period. These periods will occur simultaneously with the Survival Follow-up period for mentioned patients. These patients will continue to have tumor radiological and clinical tumor assessments (PSA, CgA, and CEA) every 3 months (every 12 weeks) during the Response Follow-up period or until progressive disease (PD), withdrawal from the study, or initiation of new treatment. Radiological tumor assessments for patients who have ongoing clinical benefit may continue to be collected after completing the survival phase of the study.
Study Evaluations:	Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases the Investigator will take all steps necessary to ensure the safety and well-being of the patient. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely manner. For samples being collected and shipped, detailed collection, processing, storage, shipment instructions and contact information will be provided to the study center prior to initiation of the study.
Safety:	Safety will be evaluated by assessment of AEs, physical examination, ECOG PS, vital signs, electrocardiograms (ECGs), and clinical and laboratory values. Toxicities will be graded and documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v 5 guidelines). DLTs will be evaluated in the dose escalation phase from cycle 1

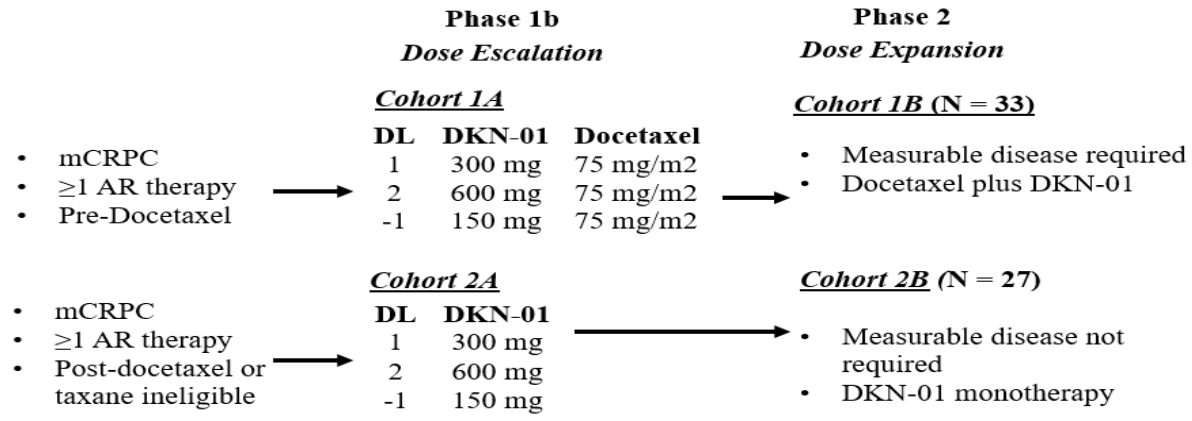
	Day 1 until cycle 2 Day 1 in each Part (DKN-01 in combination with docetaxel and DKN-01 monotherapy) independently and in parallel for Cohort 1A and Cohort 2A. DLT is defined as an AE that is at least possibly related to the study drug and fulfills at least 1 of the following: • Grade 4 neutropenia lasting >5 days or Grade 4 neutropenic fever • Grade 4 thrombocytopenia (or Grade 3 with bleeding) • Grade 4 anemia • Grade 3 or 4 non-hematological toxicity (excluding Grade 3 vomiting and Grade 3 diarrhea lasting > 72 hours including the clinical sequelae (eg, electrolyte abnormalities) despite optimal supportive care and excluding alopecia • Dosing delay greater than 14 days due to treatment-emergent AEs or treatment related severe laboratory abnormalities • Grade 3 hypersensitivity reaction to DKN-01 with premedication (Grade 3 hypersensitivity reaction to DKN-01 without premedication is not considered a DLT) • Grade 4 hypersensitivity reaction to DKN-01 with or without premedication • Any Grade 5 AE • Any treatment-related AE that causes the patient to discontinue treatment during C1 A drug-related fever ≤Grade 3 will not be considered a DLT. The MTD is defined as the highest tested dose level below the dose level at which a DLT is seen in 2 or more patients.
Pharmacokinetic:	Samples for DKN-01 and docetaxel PK studies will be collected pre-dose and post-infusion on Day 1 of each cycle and at EOT.
Efficacy:	Dose escalation in the Phase 1b cohort will be based on DLT assessment and will follow a 3+3 design. For all cohorts, soft tissue (visceral and nodal) radiographic response, PSA, and circulating tumor cells will be evaluated based on PCWG3 guidelines. Bone lesions will be followed and evaluated for evidence of radiologic progression based on PCWG3 criteria. Tumor assessments will be performed during Screening (baseline), at the end of every 9 calendar weeks (±7 days) relative to Study Day 1 (Week 1) up to 27 weeks, then every 12 calendar weeks (±7 days), until confirmed radiologic measurable disease progression by iRECIST or bone progression by PCWG3 criteria, as assessed by the Investigator, loss to follow-up, withdrawal, initiation of new treatment, or study closure. Tumor assessments should be performed at the time of treatment discontinuation if the reason was other than radiologically confirmed disease progression and it has been ≥8 weeks since the last assessment. Tumor assessments should consist of clinical examination, serum PSA, and appropriate imaging techniques (i.e., CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per

	iRECIST); other studies (MRI, X-ray, PET/CT, and ultrasound) may also be performed if required. If a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for iRECIST measurements. Radionuclide bone scanning (whole body) should be performed using 99mTc-methylene. All sites of disease should be followed and the same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment time. Copies of CT scans (and other imaging, as appropriate) If a response is noted, a follow-up radiographic assessment at a minimum of 4 weeks later to confirm response is to be done.
Pharmacodynamics:	Blood sample collection for pharmacodynamic studies will be mandatory and will be collected at the Screening visit and at Days 1 and 15 of each cycle and at the EOT visit. Pre-treatment, on-treatment, and progression tumor samples will also be utilized for pharmacodynamic analysis.
Immunogenicity:	Blood samples will be drawn for assessment of DKN-01 anti-drug antibodies (ADA) as per the Schedule of Events. Immunogenicity blood samples will be assayed for ADA using a validated assay. The testing process will follow a tiered approach of Screening, confirmation, and titer determination. Details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Laboratory Manual to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the Sponsor. On a case by case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.
Tumor Biopsy Samples:	**Tumor biopsy for DKK1 Testing:** Retrospective correlation of anti-tumor activity with tumoral DKK1 expression is a key secondary endpoint of this study. Submission of a tumor sample (archival or fresh) is recommended but not required. Tumor samples will be tested for DKK1 expression but the results of this testing are not required for protocol eligibility. Archival tumor tissue can be from a biopsy/surgery performed within 5 years prior to study enrollment Provision of a formalin-fixed paraffin–embedded (FFPE) tumor tissue block, or of at least 15 unstained slides (if the block cannot be submitted due to documented local/institutional regulations) is requested. Patients in Dose Expansion Cohort 1B can have their fresh biopsy from a locally recurrent or metastatic tumor site amenable to biopsy that is not the only RECIST v1.1 target lesion. Patients in Dose escalation Cohort 1A, 2A and Dose expansion Cohort2B can have their required fresh biopsy from any locally recurrent or metastatic tumor site amenable to biopsy regardless of whether this site is the only RECIST v1.1 target lesion. A core biopsy, using a minimum 18-gauge needle should be performed, in order to maximize the quality and value of obtained tissue. A minimum of 3 separate cores are requested for each biopsy

	procedure. Tumor tissue from soft tissue or effusion cytologic sampling (fine needle aspiration provided as an FFPE cell pellet material) can be submitted, however, we recommend an FFPE tumor tissue block to maximize the chance of identifying DKK1 positive cells. If a block cannot be provided due to documented local/institutional regulations, at least 15 unstained slides are required. Bone biopsy material is acceptable provided that a gentle decalcification protocol was used. Bone core biopsy or bone fine needle aspiration provided as an FFPE cell pellet material (bone FNA is preferred) can be submitted. **Tumor Biopsy for Exploratory Studies:** Archival tumor tissue samples and tissue from biopsies of the primary and/or metastatic lesions will be used to analyze candidate DNA, RNA, or protein markers, or a relevant signature of markers, for their ability to identify those patients who are most likely to benefit from treatment. On-treatment tumor biopsies are encouraged and tumor tissue is requested for those patients who undergo a biopsy or tumor resection as part of routine clinical care at any time during the treatment period. For patients on the combination arm, this biopsy can be obtained from C2D15 through C3D1 or C3D15 through C4D1 at the discretion of the treating investigator and after consideration of the risk of neutropenia related to docetaxel. Patients on monotherapy arms can have their biopsy at any point in C2 or C3 at the discretion of the treating investigator. Every effort should be made to perform a tumor biopsy at the time of iRECIST or PCWG3 confirmed disease progression if a patient discontinues study treatment due to disease progression, except in instances where the procedure poses an unacceptable risk to patients in the clinical research setting. A 14-day window from the EOT visit is permitted. Candidate markers of interest include, but may not be limited to: • Abundance and enrichment of infiltrating CD8+ T cells, CD4+ T cells, granulocytic and monocyte myeloid-derived suppressor cells, natural killer (NK) cells, Regulatory T cells, and Monocyte-derived cells as determined by flow cytometry from peripheral blood and immunohistochemistry (IHC)/immunofixation of FFPE. • Inhibitory ligand and co-receptor expression on tumor and infiltrating immune cells measured by IHC. • Expression of genes associated with active antitumor immunity. • Frequency and diversity of different TCR sequences. • Expression of genes associated with activated Wnt signaling • Expression of genes associated with basal-type prostate cancer • Neutrophil/lymphocyte ratio
Sample Size Determination:	Simon's two-stage design (Simon, 1989) will be used for the power calculation. A 3+3 design will be used for the dose escalation design.
Statistical Methods:	Dose expansion Cohort 1B. Efficacy will be evaluated for the primary endpoint in Dose expansion Cohort 1B only. The null hypothesis that the true response rate is 0.2 will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 4 or fewer responses in these 18 patients,

	the study will be terminated. Otherwise, an additional 15 patients will be accrued for a total of 33. The null hypothesis will be rejected if 11 or more responses are observed in 33 patients. This design yields a Type I error rate of 0.05 and a power of 0.8 when the true response rate is 0.4. Dose escalation and expansion Cohort 2B. Efficacy will be evaluated in all patients receiving the recommended phase 2 dose. Simon's two-stage design (Simon, 1989) will be used to evaluate Dose Expansion Cohorts 2B. The null hypothesis that the true response rate is 0.05 will be tested against a one-sided alternative. In the first stage, 13 patients will be accrued. If there are 0 responses in these 13 patients, the study will be stopped. Otherwise, 14 additional patients will be accrued for a total of 27. The null hypothesis will be rejected if 4 or more responses are observed in 27 patients. This design yields a type I error rate of 0.05 and a power of 0.8 when the true response rate is 0.2. Descriptive statistics will be performed to assess the endpoint of best overall response as a composite endpoint consisting of a decrease in PSA >50%, conversion of CTCs, or iRECIST soft tissue response.

SCHEMATIC OF STUDY DESIGN



LIST OF ABBREVIATIONS

Abbreviation	Definition
^{18}F-DHT PET	^{18}F dihydro-testosterone positron emission tomography
2GHA	2nd-Generation hormonal agents
ADA	Anti-drug antibody
AEs	Adverse events
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AR	Androgen-receptor
AST	Aspartate aminotransferase
BICR	Blinded Independent Central Review
BOR	Best overall response
BUN	Blood urea nitrogen
C	Cycle
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CgA	Chromogranin A
CI	Confidence interval
CK	Creatine kinase
CNS	Central nervous system
CR	Complete response
CT	Computed tomography

Abbreviation	**Definition**
CTC	Circulating Tumor Cell
CTO	Clinical Trials Office
D	Day
DKK1	Dickkopf-1
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DR	Duration of response
DSMC	Data Safety Monitoring Committee
EAS	Evaluable analysis set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOT	End-of-treatment
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin–embedded
GCP	Good Clinical Practice
gem/cis	Gemcitabine/cisplatin
GGT	Gamma-glutamyl transferase
HBSAg	hepatitis B surface antigen
HCAb	Hepatitis C antibody

Abbreviation	Definition
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
iCPD	Confirmed radiographic progression
iCR	Complete response per iRECIST
IDE	Investigational Device Exemption
IHC	Immunohistochemistry
IND	Investigational New Drug Application
INR	International normalized ratio
iPD	Confirmed progressive disease per iRECIST
iPR	Partial response per iRECIST
IRB	Institutional Review Board
iRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
iSD	Stable disease per iRECIST
iUPD	Unconfirmed progressive disease per iRECIST
IV	Intravenous(ly)
LDH	Lactate dehydrogenase
len/dex	Lenalidomide and dexamethasone
LHRH	Luteinizing hormone-releasing hormone
mCRPC	Metastatic castration-resistant prostate cancer

Abbreviation	**Definition**
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
RECIST v1.1	Modified Response Evaluation Criteria in Solid Tumors, version 1.1
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Neuroendocrine
NK	Natural killer
NSCLC	Non-small cell lung cancer
NYU	New York University
OR	Overall response
OS	Overall survival
PCC	Perlmutter Cancer Center
PCWG3	Prostate Cancer Working Group 3
PD	Progressive disease
PFS	Progression-free survival
PI	Principal Investigational
PK	Pharmacokinetic
PP	Per-protocol
PR	Partial response
PS	Performance status
PSA	Prostate-specific antigen

Abbreviation	**Definition**
PT	Prothrombin time
PTT	Partial thromboplastin time
Q2W	Every 2 weeks
RBC	Erythrocyte count
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SUV	Standardized uptake values
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
TTR	Time-to-tumor response
ULN	Upper limit of normal
WBC	Leukocytes

TABLE OF CONTENTS

LIST OF TABLES IN THE TEXT

LIST OF FIGURES IN THE TEXT

1. KEY ROLES

Principle Investigator:

David Wise, MD PhD
Perlmutter Cancer Center at NYU Langone
160 E 34TH Street, 10th Fl, Suite 1009
New York, NY 10016
212-731-6366
David.Wise@nyulangone.org

Biostatistician:

Andrea Troxel
650 First Avenue, 5th Fl, 521
New York, NY 10016
Andrea.Troxel@nyulangone.org

2. INTRODUCTION

2.1. Background and Study Rationale

2.1.1. Prostate Cancer

Metastatic castration-resistant prostate cancer (mCRPC) is an incurable illness that requires innovative clinical studies (Scher et al. 2016). Five life-prolonging drugs, approved in the past decade, were developed in-parallel and exhibit cross-resistance (Lorente et al. 2016). The 2nd-generation hormonal agents (2GHA), enzalutamide and abiraterone, both prolong survival and have an excellent tolerability profile and have become de facto first-line agents for the treatment of mCRPC (Gillessen et al. 2015). The recent LATITUDE (Fizazi et al. 2017) and STAMPEDE (James et al. 2017) results demonstrate the efficacy of abiraterone in the castration-sensitive setting and will likely lead to an increase in the utilization of abiraterone in this setting and increase prevalence of mCRPC that is resistance to an 2GHA. Novel treatments for 2GHA-resistant mCRPC are increasingly needed.

Unfortunately, the available agents for these 2GHA-resistant patients have a relatively poor side effect profile and are limited in their efficacy. Docetaxel and cabazitaxel are the available taxanes that are FDA-approved for the treatment of mCRPC. Recent data failed to demonstrate the superiority of cabazitaxel over docetaxel (Oudard et al. 2017). This suggests that docetaxel will continue to be the first-line taxane used for the majority of patients with mCRPC that has progressed on a 2GHA. The efficacy of docetaxel in the post-2GHA setting has not been published in large patient cohorts. The Tax327 study demonstrated the overall survival (OS) benefit of docetaxel in the pre-2GHA era showed a soft-tissue response rate of 12% and a prostate-specific antigen (PSA) response rate of 45% (Tannock et al. 2004). The FIRSTANA study, which randomized pre-2GHA patients to cabazitaxel or docetaxel, showed that the soft-tissue response rate to docetaxel was 30% and the PSA response rate was 68% (Oudard et al. 2017). In a retrospective study of post-abiraterone patients treated on a phase II study, the soft tissue response rate was 11% and the PSA response rate was 26% (Mezynski et al. 2012). In a larger retrospective study of patients treated on the phase III study of abiraterone naïve to chemotherapy, the subsequent rate of PSA response was 27% (whereas the soft tissue response rate was not reported) (de Bono et al. 2017).

In sum, the available data suggest that the soft tissue response rate of docetaxel in patients previously treated with a 2GHA is likely significantly lower than 30%.

Identification of DKK1 as a biomarker of AR-null/NE-null mCRPC

There is a critical need to identify druggable mechanisms that promote mCRPC resistance to 2GHA therapy. Recent work has demonstrated that prostate cancer can develop resistance to 2GHA through an androgen-receptor (AR)-independent escape mechanism reflected by prostate cancers with low or absent AR expression (Bluemn et al. 2017). These AR-null prostate cancers exist as two subtypes determined by the expression of neuroendocrine (NE) markers – AR-null/NE-high and AR-null/NE-null. Further work has shown that dickkopf-1 (DKK1) is specifically upregulated in AR-null/NE-null prostate cancers (Wise et al. 2020). DKK1 can be

measured in the tumor specimen but it can also be measured in a plasma-based assay (Wise et al. 2020). DKK1-high prostate cancers show loss of CD8+ T cells and reduction in activated natural killer (NK) cells.

Rationale for Targeting DKK1 in mCRPC

Targeted inhibition of DKK1 in an AR-null/NE-null prostate cancer model has been shown to delay the growth of these tumors in a mouse-xenograft model (Hall et al. 2010). Targeted inhibition of DKK1 in patient-derived organoids leads to the upregulation of pro-inflammatory molecules. These studies suggest that targeted inhibition of DKK1 might provide therapeutic benefit for AR-null/NE-null DKK1-high mCRPC patients through upregulating anti-tumor immunity. A further hypothesis is that AR-high/NE-null or AR-null/NE-high patients who have abnormally high plasma DKK1 might also derived benefit from DKK1 blockade.

We have chosen to combine DKK1 blockade with docetaxel in Cohort 1A and 1B because durable treatment responses were seen with DKN-01 in combination with another taxane, paclitaxel, in advanced gastroesophageal cancer. Furthermore, docetaxel likely has broad activity against mCRPC across a broad spectrum of AR activity. The utility of docetaxel in this trial is to synergize with DKN01 in targeting AR-null prostate cancer clones and to target AR-high clones that might be resistant to DKN01.

Patients with mCRPC who have progressed on 2GHA and a taxane-based chemotherapy have limited treatment options that are associated with significant toxicity. The National Comprehensive Cancer Network guidelines offer enrollment on a clinical study as an option for these patients given the significant toxicity associated with treatment with cabazitaxel or radium-223. This population will serve as the patients in Cohort 2A/B/C of this study which will test the hypothesis that DKN-01 monotherapy is active in DKK1-expressing mCRPC through re-activation of anti-tumor immunity.

To summarize, patients with mCRPC that has progressed despite 2GHA therapy represents a population of patients whose main therapeutic options are cytotoxic chemotherapy, which have a poor side effect profile and modest clinical activity. We propose to test DKK1 blockade using DKN-01 either as monotherapy or as a novel combination partner with docetaxel chemotherapy as an immunomodulatory therapeutic strategy for advanced 2GHA-resistant mCRPC.

Correlating DKN01-mediated anti-tumor activity with pathogenic Wnt signaling

Wnt mutations correlate with elevated DKK1

The canonical Wnt signaling pathway refers to a cell signal transduction pathway that leads to stabilization of the transcription factor β-Catenin and ultimately activation of a host of β-Catenin target genes involved in cancer pathogenesis. Recurrent mutations in the genes involved in canonical Wnt signaling are among the most common mutations in human cancer and include mutations and/or genomic alterations in the following genes: APC, CTNNB1, RNF43, ZNRF3, RSPO2, RSPO3 AXIN1, and AXIN2. Mutations in these genes can lead to the constitutive activation of Wnt/b-catenin signaling. DKK1 is a known β-Catenin target gene (Chamorro et al. 2005) and the correlation between Wnt signaling mutations and elevated DKK1 in mCRPC has

been confirmed (Wise et al. 20). Retrospective analysis of patients with a detectable Wnt family gene alteration in tumor or blood will be undertaken to investigate whether these alterations predict response.

Wnt mutations correlate with response to DKN-01

Leap Therapeutics preliminary data indicates that tumors from patients with a Wnt/b-catenin signaling activating mutation are more likely to express elevated levels of DKK1 and therefore may be more likely to respond to a DKK1 neutralizing therapy. As such, endometrial patients with a Wnt/b-catenin signaling activating mutation appear to be more likely to derived clinical benefit from DKN-01 based therapies (Arend et al. 2019).

2.1.2. Dickkopf-1 (DKK1)

DKK1 protein, is over-expressed in a variety of tumor types and this is associated with a poor prognosis such as decreased OS of cancer patients, including NSCLC, esophageal cancer, breast cancer, cholangiocarcinoma, liver cancer, and ovarian cancer as well as multiple myeloma (Shizhuo et al. 2009; Tung et al. 2011; Xu et al. 2012; Sezer 2009; Shi et al. 2013; Hiss 2012). DKK1 has direct tumor effects by increasing tumor growth, metastasis, and angiogenesis and through favoring a stem cell-like phenotype (Smadja et al. 2010; Krause et al. 2014; Malladi et al. 2016; Thudi et al. 2011). Furthermore, DKK1 has been implicated in promoting an immunosuppressive tumor microenvironment by activating myeloid derived suppressor cells and through the downregulation of NK activating ligands on cancer cells (D'Amico et al. 2016; Malladi et al. 2016). Based on these data, neutralizing DKK1 has been hypothesized to not only directly impede tumor growth but also promote an anti-tumor immune response.

Wnt signaling is a multifaceted pathway that regulates stem cell maintenance, cell fate decisions, cell proliferation, survival, migration, and polarity determination during development and adult tissue homeostasis (Logan and Nusse 2004; MacDonald et al. 2009; Clevers and Nusse 2012; Clevers et al. 2014; Sedgwick and D'Souza-Schorey 2016). DKK1 is a secreted modulator of Wnt signaling and is best characterized as an antagonist of the canonical Wnt/β-catenin signaling pathway, however it has also been implicated in the activation of noncanonical Wnt signaling pathways and PI3K/AKT signaling (Niehrs et al. 2006; Wang and Zang 2011; Kimura et al. 2016).

DKK1 is expressed in basal cells of the normal human prostate (Zhang et al. 2016). Overexpression of AR and treatment with DHT in the AR-negative cancer cell line DU145 leads to downregulation of DKK1 (Wise et al. 2020). Serum DKK1 levels inversely correlate and serum PSA positive correlate with ^{18}F dihydro-testosterone positron emission tomography (^{18}F-DHT PET) uptake in patients (Wise DR et al. 2020). These data suggest that activation of AR is one potential upstream repressor of DKK1 expression.

2.1.3. DKN-01

DKN-01 (formerly known as LY2812176) is a potent humanized monoclonal antibody (immunoglobulin G4) with neutralizing activity against DKK1, a modulator of Wnt signaling

pathways that influences a number of important processes such as cell growth and differentiation, bone development, adult bone homeostasis, and anti-tumor immunity (Sato et al. 2010; Gavriatopoulou et al. 2009; Vallet et al. 2010; Pinzone et al. 2009). DKN-01 is in development as an anti-cancer agent and is being investigated in a variety of solid tumors.

As of 21 August 2017, DKN-01 has been evaluated in 30 healthy subjects and 167 patients with cancer in 5 clinical studies. All 30 healthy subjects received a single dose of DKN-01. Among the 167 patients with cancer treated with DKN-01, 55 received DKN-01 monotherapy; 7 received DKN-01 in combination with lenalidomide/dexamethasone (len/dex); 54 received DKN-01 in combination with paclitaxel; and 51 patients received DKN-01 in combination with gemcitabine/cisplatin (gem/cis). In addition, as controls in 2 clinical studies, 18 healthy subjects received a single dose of placebo and 1 patient with MM received len/dex. Safety data for DKN-01 are available from 30 healthy subjects treated with a single dose of DKN-01 monotherapy and 164 patients with cancer treated with DKN-01, of whom 55 received DKN-01 monotherapy, 7 received DKN-01+len/dex, 54 received DKN-01+paclitaxel, and 48 received DKN-01+gem/cis.

Results from completed Phase 1 Study DEK-DKK1-P100, in which DKN-01 was administered as monotherapy to patients with cancer at doses up to 600 mg every other week, demonstrated an acceptable safety profile. Based on these results, clinical evaluation of DKN-01 in combination was initiated, with DKN-01 also shown to be well tolerated when administered in combination with commercially available anti-neoplastic agents. Across all studies, there have been no safety concerns identified that relate to significant injection site reactions or systemic infusion reactions. Furthermore, there have been no known undesirable effects identified with administration of DKN-01. DKN-01 has been observed to be well-tolerated over multiple treatment cycles.

Table 1 describes the cumulative DKN-01 monotherapy cancer treatment experience at doses ranging from 75 mg to 600 mg, and includes all DKN-01-related treatment-emergent adverse events (TEAEs) by SOC and preferred term from DEK-DKK1-P100 (N=32) and the Monotherapy Arm of Study DEK-DKK1-P102 (N=23).

Table 1: All DKN-01-Related Adverse Events by MedDRA SOC and Preferred Term and CIOMS Frequency in DEK-DKK1-P100 and the Monotherapy Arm of Study DEK-DKK1-P102

MedDRA Preferred Term[3]	Monotherapy DKN-01 (n=55)[1,2] n	%	CIOMS Frequency
Fatigue	12	21.8%	Very Common
Nausea	4	7.3%	Common
Decreased appetite	3	5.5%	
Anaemia	3	5.5%	
Vomiting	2	3.6%	
Arthralgia	2	3.6%	
Dysgeusia	2	3.6%	
Asthenia	2	3.6%	
Constipation	1	1.8%	
Stomatitis	1	1.8%	
Oral pain	1	1.8%	
Dehydration	1	1.8%	
Hypocalcaemia	1	1.8%	
Muscle Spasms	1	1.8%	
Musculoskeletal chest pain	1	1.8%	
Myalgia	1	1.8%	
Depression	1	1.8%	
Night sweats	1	1.8%	
Onychoclasis	1	1.8%	
Paraesthesia	1	1.8%	
Periorbital oedema	1	1.8%	
Weight decreased	1	1.8%	

[1] Events reported from Study DEK-DKK1-P100 (n=32) and the monotherapy arm of Study DEK-DKK1-P102 (n=23).
[2] Of these 55 patients, 3 received DKN-01 75 mg, 3 received DKN-01 150 mg, 46 received DKN-01 300 mg, and 3 received DKN-01 600 mg.
[3] MedDRA Version 14.1 used for Study DEK-DKK1-P100 and Version 18.0 used for Study DEK-DKK1-P102.

Evidence of an anti-tumor effect of DKN-01 as a monotherapy has been seen in patients with non-small cell lung cancer (NSCLC). No patient in the study achieved an overall best response of complete response (CR). For patients with NSCLC in Part B, 1 patient (5.3%) had an overall best response of partial response (PR) and 8 (42.1%) achieved stable disease (SD). The overall clinical benefit (PR+SD) was 47.4% (9/19 patients) and overall response (OR) rate was 5.3% (1/19 patients; 95% CI, 0.1, 26.0). For the 19 patients with advanced NSCLC receiving DKN-01

at 300 mg every 2 weeks (Q2W) in Part B, median progression-free survival (PFS) was 2.2 months (95% confidence interval [CI], 1.5, 2.9). Additionally, evidence of an anti-tumor effect has been seen with DKN-01 in combination with paclitaxel in patients with esophagogastric cancer, and in combination with gemcitabine/cisplatin in patients with biliary tract cancer.

Overall, among all 77 esophagogastric cancer patients enrolled, 62 were male and 15 were female, and most (69 patients) were white. The mean age of patients was 62 years (range 34 to 82 years). Patients were required to have esophagogastric cancer to be eligible for the study; 41 patients had a primary diagnosis of esophageal cancer, with 35 patients having a primary diagnosis of gastroesophageal junction cancer; primary cancer type was not reported for 1 patient. The histological type was adenocarcinoma for 64 patients and squamous cell carcinoma for 13 patients. At the time of diagnosis, most (42 patients) had Stage IV disease, with 25 having Stage III disease and 10 having Stage II disease. The median time since diagnosis was 17.2 months (range 2.1 to 70.4 months). All 77 patients had received prior chemotherapy, with 44 having received a prior taxane, 26 in the adjuvant/neo-adjuvant setting and 21 in the metastatic/palliative setting. The median number of prior systemic therapy regimens was 2 (range 1 to 7). Overall, 20 (26.0%) patients had received prior Herceptin (trastuzumab) and 12 (15.6%) patients had received prior ramucirumab. To be evaluable for response according to the modified Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), patients were required to have received at least 1 dose of DKN-01 and have at least 1 evaluable tumor response assessment or have discontinued treatment due to death, toxicity, or clinical progression; as of 21 August 2017, 64 of 77 patients were evaluable for response.

Overall, among all 64 patients evaluable for response, the OR rate was 20.3% (13/64 patients), with all 13 patients experiencing a PR. Twenty-three (30.3%) patients experienced SD; thus, the disease control rate was 56.3% (36/64 patients). With DKN-01 300 mg +paclitaxel, the OR rate was 26.1% (12/46 patients) and the disease control rate was 58.7% (27/46 patients). The OR rate among those treated with DKN-01 300 mg + paclitaxel with prior taxane exposure (N=24) and those without (N=22) was 12.5% (3/24 patients) and 40.9% (9/22 patients) and the disease control rate in each of these groups was 45.8% (11/24 patients) and 72.7% (16/22 patients), respectively.

Full information on DKN-01 is provided in the Investigator's Brochure.

2.2. Rationale for the Dose Selection

2.2.1. Rationale for the DKN-01 Dose Selected

DKN-01 will be administered at a dose of 300 mg or 600 mg intravenously (IV) on Days (D) 1 and 15 every 21 days (Cohorts 1A/1B) and every 28 days (Cohorts 2A/2B).

These DKN-01 doses were selected based on the results of two ongoing Phase 1, multi-part, dose-escalation studies of DKN-01 in combination with other anticancer agents, including paclitaxel (Study DEK-DKK1-P102 [Study P102]) and gem/cis (Study DEK-DKK1-P103 [Study P103]).

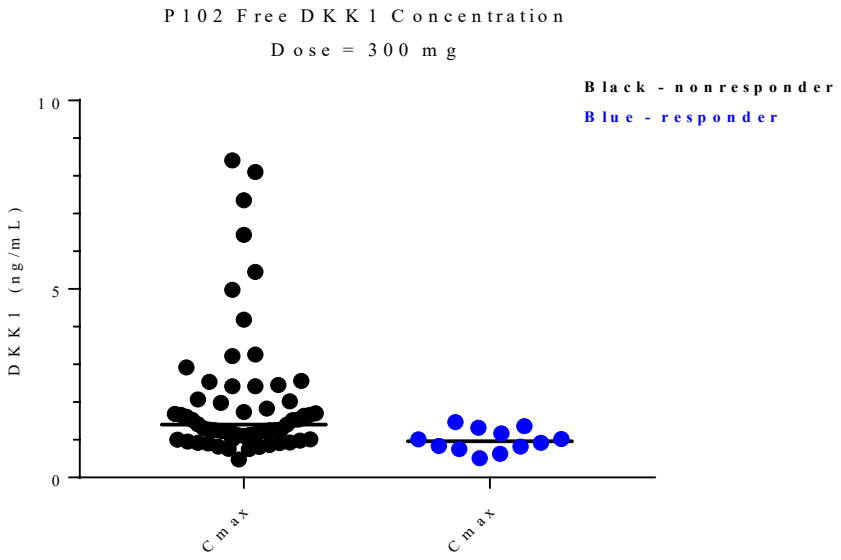
DKN-01 is selective for the DKK1 member of the dickkopf family. It binds human DKK1 with high affinity and, as a consequence, potently neutralizes DKK1. The levels of the protein DKK1 are elevated in a variety of tumor types and have been implicated in tumor growth and disease progression. A preclinical NSCLC A549 xenograft model study demonstrated that suppression of free (unbound) DKK1 concentrations correlated with an inhibition of tumor growth. A pharmacokinetic (PK)/pharmacodynamic model was fit to the data in this study and it was found that a 50% reduction in free DKK1 by DKN-01 binding approximately correlated with 50% maximal tumor growth inhibition (Leap Therapeutics, data on file, 2012).

Several ongoing clinical studies have been conducted to determine the effect of DKN-01 on a variety of cancers. In Study DEK-DKK1-P102 (P102), DKN-01 was dosed in combination with paclitaxel as well as in a separate monotherapy substudy. In this study, patients were administered DKN-01 at doses of 150 or 300 mg Q2W over a 28-day cycle. Patients in Study DEK-DKK1-P103 (P103) were administered DKN-01 at doses of 150 or 300 mg in combination with gemcitabine and cisplatin on Days 1 and 8 of each 21-day cycle.

In both of these studies, PK/Pharmacodynamic modeling showed a dose-dependent decrease in free DKK1 concentrations. In Study P102, the median free DKK1 at the 150 mg dose was 2.27 ng/mL (concentration after the last dose for each patient), whereas the median value was 1.27 ng/mL in the 300 mg group. Preliminary modeling suggested that efficacy was more likely to be observed if the maximal concentration of free DKK1 was below 1 to 1.5 ng/mL (Figure 1[a] and [b]). In the current study, a dose of 600 mg is proposed in order to increase the number of patients that have free DKK1 in the target range (<1 - 1.5 ng/mL). Based on modeling analysis, a 600 mg dose is expected to reduce free DKK1 concentrations to half of that observed at 300 mg dose levels.

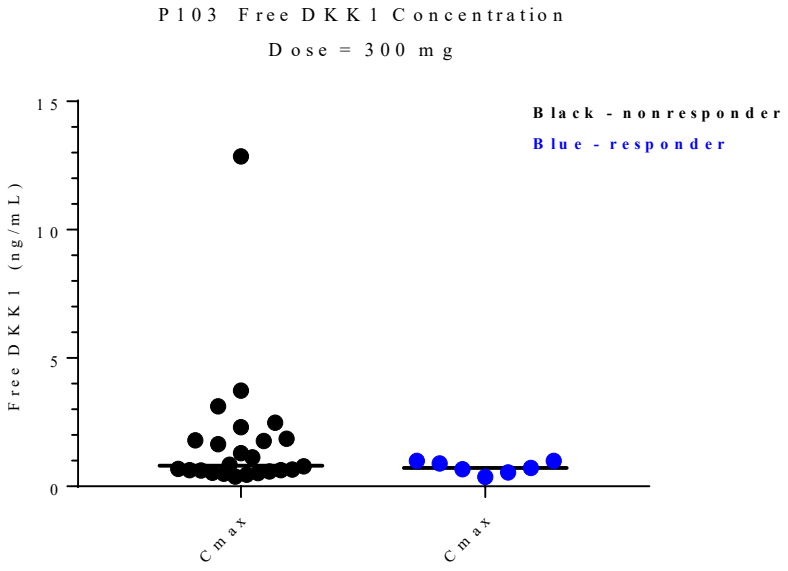
Figure 1: Free DKK1 Concentrations in Studies P102 and P103

(a)



(a) the responder population was observed to have free DKK1 concentrations below ~1.5 ng/mL

(b)



(b) the responder population was observed to have free DKK1 concentrations below ~1 ng/mL.

Preliminary results from ongoing Study P102, conducted in patients with esophagogastric cancer, show DKN-01 to be well tolerated in combination with weekly paclitaxel 80 mg/m^2. The maximum tolerated dose (MTD) of DKN-01 in combination was determined to be 300 mg, the highest dose evaluated. Overall, the most common individual treatment-emergent adverse events (TEAEs) in Study DEK-DKK1-P102 were fatigue (26 patients; 33.8%), anemia (22 patients; 28.6%), alopecia (19 patients; 24.7%), neutropenia (15 patients; 19.5%), vomiting and dyspnea (each 13 patients; 16.9%); and constipation, nausea, and cough (each 12 patients; 15.6%). With DKN-01 monotherapy, the most common TEAEs also was fatigue (7 patients; 30.4%). Other common TEAEs with DKN-01 monotherapy in this patient population were dehydration (6 patients; 26.1%), vomiting and constipation (5 patients; 21.7%), and ascites (4 patients; 17.4%).

Forty (51.9%) patients overall experienced at least 1 TEAE that was considered by the Investigator to be DKN-01-related, with the most common such events including fatigue (13 patients; 16.9%), anemia, decreased appetite, and nausea (each 7 patients; 9.1%), diarrhea (6 patients; 7.8%), and arthralgia, constipation, and vomiting (each 4 patients; 5.2%).

Given the disparity in the numbers of patients treated with 150 mg and 300 mg (3 versus 74, respectively), TEAE incidence rates are not compared by dose.

Thirty-five (45.5%) patients experienced at least 1 Grade 3/4 TEAE. Grade 3 TEAEs reported for >1 patient overall included anemia, hypophosphatemia, and neutropenia (3 patients; 3.9%) and ascites, lung infection, and pneumonia (each 2 patients; 2.6%). All other Grade 3 TEAEs were reported for 1 patient only. Grade 4 TEAEs included neutropenia (2 patients; 2.6%) and gastrointestinal hemorrhage and leukopenia (each 1 patient; 1.3%).

Most Grade 3 TEAEs and all Grade 4 TEAEs were considered to be unrelated to DKN-01. Four (5.2%) patients experienced a Grade 3 TEAE that was considered by the Investigator to be DKN-01-related, including anemia, fatigue, hypophosphatemia, and peripheral neuropathy (each 1 patient; 1.3%).

Similarly, in ongoing Study P103, in which DKN-01 is administered in combination with gemcitabine + cisplatin in patient with advanced carcinoma primary to the intra- or extra-hepatic biliary system or gallbladder, the 300 mg dose of DKN-01 also was determined to be the MTD, the highest dose evaluated, with no dose-limiting toxicities (DLTs) reported. Enrollment in the study is complete, with a total of 51 patients enrolled. Of these 51 patients, 7 patients were enrolled in Part A, of whom 4 received DKN-01 150 mg and 3 received DKN-01 300 mg, and 44 patients were enrolled in Part B, with all 44 patients assigned to receive DKN-01 300 mg. All patients receive DKN-01 in combination with gem/cis. As of 21 August 2017, safety data were available for 48 patients.

As was the case in Study P102, the 300 mg dose of DKN-01 was well tolerated in Study P103. Overall, 46 (95.8%) of 48 patients in the Safety Population patients experienced at least 1 TEAE. Overall, the most common TEAEs in Study DEK-DKK1-P103 were thrombocytopenia (32 patients; 66.7%), neutropenia (28 patients; 58.3%), aspartate aminotransferase (AST) increased (26 patients; 54.2%), fatigue (25 patients; 52.1%), and anemia (23 patients; 47.9%).

Thirty-four (70.8%) patients experienced a Grade 3/4 TEAE. Grade 3 TEAEs reported by >1 patient, regardless of relationship to study drug, included neutropenia (14 patients; 29.2%), leukopenia (10 patients; 20.8%), hypertension and thrombocytopenia (each 8 patients; 16.7%) anemia (6 patients; 12.5%), hyperbilirubinemia (5 patients; 10.4%), AST increased, gamma-glutamyl transferase (GGT) increased, hyponatremia, and hypophosphatemia (each 4 patients; 8.3%), alanine aminotransferase (ALT) increased, blood alkaline phosphatase increased, and leukocytosis (each 3 patients; 6.3%), and abdominal pain, ascites, cholangitis, muscular weakness, upper gastrointestinal hemorrhage, and urinary tract infection (each 2 patients; 4.2%).

Twelve (25.0%) patients experienced at least 1 Grade 4 TEAE, with such events including neutropenia (9 patients; 18.8%), thrombocytopenia (2 patients; 4.2%), and aspiration pneumonia, blood uric acid increased, Escherichia bacteremia, GGT increased, hyperbilirubinemia, hypoglycemia, and respiratory distress (each 1 patient; 2.1%).

Twenty-three (47.9%) patients experienced at least 1 Grade 3/4 TEAE that was considered by the Investigator to be DKN-01-related. DKN-01-related Grade 3 TEAEs reported for >1 patient included neutropenia (13 patients; 27.1%), thrombocytopenia (5 patients; 10.4%), AST increased and leukopenia (each 4 patients; 8.3%), ALT increased and anemia (each 3 patients; 6.3%), and hyperbilirubinemia and hyponatremia (each 2 patients; 4.2%). DKN-01-related Grade 4 TEAEs included neutropenia (5 patients; 10.4%) and thrombocytopenia (1 patient; 2.1%).

The 300 mg dose of DKN-01 also is supported by PK data. DKN-01 exhibits dose proportional PK. Population PK/pharmacodynamic simulation model identified that at a dose of 300 mg, more than 95% of patients are expected to experience a more than 90% reduction in free serum DKK1 levels (Leap Therapeutics, data on file, 2012).

2.2.2. Rationale for the Combination with Docetaxel 75mg/m^2

DKN-01 will be combined with docetaxel in this study based on previously reported synergism between DKN-01 and another taxane, paclitaxel, in gastroesophageal cancer. Docetaxel, rather than paclitaxel was chosen for the current study because it is the standard first-line taxane in mCRPC. Finally, the response rate to docetaxel in the post-2GHA setting is low (10-30%) making this an appropriate context for novel drug combinations.

2.3. Justification of the Study Design

The phase 1b/2 non-randomized design is most appropriate because of the following:

1. MTD determination will be needed because of novel combination with docetaxel.
2. Single-arm design in phase 2 is appropriate because no activity of DKN-01 has yet been demonstrated in prostate cancer.

2.3.1 Rationale for Retrospective Correlation of DKK1 / WNT Status with DKN01 Response

In the prior version of this protocol, patient eligibility was dependent upon the finding of elevated tumoral DKK1 as determined by RNA expression in-situ or a pathogenic genomic alteration in a Wnt family gene. In this amendment, these biomarker results will no longer be required for eligibility, but rather, will be investigated retrospectively to test the hypothesis that DKK1 and or activated Wnt signaling correlate with

response to DKN01. The primary rationale for this change in inclusion is that we have observed clinical activity of DKN01 in combination with Docetaxel even in patients with very low or zero DKK1 expression. For example, we observed a dramatic partial response in a patient whose tumor exhibited a DKK1 H-score of 2 (1+ expression in 2% of cells) and without Wnt gene mutation. We also observed a confirmed partial response in a patient with a circulating Wnt alteration but undetectable DKK1 expression in a tumor biopsy. These data suggest that our biomarkers may be excluding patients who could benefit from the study treatments. We have also observed that the time required for tumor procurement and biomarker testing poses a significant barrier to enrollment in a population of patients who are typically symptomatic. These factors provided the rationale for the proposed protocol amendment to no longer require DKK1/Wnt testing results as a study inclusion criterion. Rather, anti-tumor activity of DKN01 with or without Docetaxel will be retrospectively correlated with these biomarkers to better define a threshold to determine the patient population that will be most likely benefit.

The current amendment also clarifies that patients with treatment-emergent neuroendocrine prostate cancer (te-NEPC) are eligible for study regardless of prior exposure to an androgen receptor (AR) signaling inhibitors (abiraterone or enzalutamide or apalutamide or darolutamide), which is consistent with standard of care guidelines that do not recommend AR signaling inhibitors this histologic variant. Furthermore, we have observed increased DKK1 expression in a subset of these patients (Wise DR et al. JCO Precision Oncology 2020), which provides the biological rationale to include this patient population.

The Sponsor, Monitor, and Investigators will perform this study in compliance with the protocol, GCP, and ICH guidelines, and applicable regulatory requirements.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

- **Part 1: Dose Escalation**: To determine the safety, tolerability, DLTs, and MTD of DKN-01 administered alone and in combination with docetaxel in patients with advanced prostate cancer with elevated DKK1.
- **Part 2, Dose Expansion**: To evaluate the anti-tumor activity of DKN-01 in combination with docetaxel in patients with advanced prostate cancer with elevated DKK1.

3.1.2. Secondary Objectives

1. To determine the anti-tumor activity of DKN-01 as monotherapy using Immune-related Response Evaluation Criteria in Solid Tumors (iRECIST).
2. To characterize the pharmacodynamics effects of DKN-01 administered as monotherapy or in combination with docetaxel.
3. To characterize the PK of DKN-01 administered as monotherapy or in combination with docetaxel.
4. To characterize the immunogenicity if DKN-01 administered as monotherapy or in combination with docetaxel.
5. To determine the concordance between anti-tumor activity and DKK1 expression in the monotherapy and combination cohorts.

3.1.3. Exploratory Objectives

1. To determine the effect of DKN-01 monotherapy on peripheral and intratumoral immune cell abundance and activation.
2. To explore the association between DKN-01 exposure, peripheral and intratumoral immune cell abundance and activation, anti-tumor activity, and key safety measures.
3. To determine the impact of docetaxel on peripheral and intratumoral immune cell abundance and activation.
4. To determine the concordance between plasma and intratumoral DKK1 levels and determine the association between DKK1 level, Wnt pathway, FGF, cell cycle alterations, and anti-tumor activity.
5. To determine the effect of DKN-01 as monotherapy or in combination with docetaxel on ex-vivo intratumoral immune cell abundance and activation in a 3-dimensional organotypic culture model.

6. To explore the association between response to study drug treatment and clinical evidence of "PSA-high" (concordant radiographic and PSA progression) and "PSA-low" (radiographic evidence in the absence of PSA progression) prostate cancer.

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary efficacy endpoints are:

- **Phase 1b, Cohort 1A and Cohort 2A**: DLT observed during the DLT evaluation period (starting from C1D1 until C2D1).
- **Phase 2, Cohort 1B**: Best overall response, based on iRECIST soft tissue response.

3.2.2. Secondary Endpoints

Secondary efficacy endpoints are:

- Radiographic PFS.
- PSA PFS.
- OS.
- Duration of response (DR).
- Time-to-tumor response (TTR).
- ≥50% decline in PSA.
- Percentage change in PSA from baseline to 12 weeks post-treatment.
- Maximal decline in PSA after treatment initiation.
- Circulating tumor cell (CTC) conversion from unfavorable (5 or greater CTC/7.5 mL) to favorable (4 or fewer CTC/7.5 mL) at 13 weeks.
- CTC ≥1 at baseline and 0 at 13 weeks (CTC0).
- BOR stratified by tumoral DKK1 expression, Wnt pathway, FGF pathway, and/or cell cycle gene alteration

3.2.3. Safety Endpoint

The safety endpoint is:

- Adverse events (AEs) as characterized by type, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v 5.0), timing, seriousness, and relationship to study therapy.

3.2.4. Exploratory Endpoints

The exploratory endpoints are:

- Baseline (for tumor tissue and peripheral blood) and on treatment (for tumor and peripheral blood) measurements related to genomic events that might predict outcome,

including Wnt pathway alterations, genome scarring and mutational load, neoantigen analysis, ribonucleic acid (RNA) sequencing, and whole exome sequencing. Genomic studies will be done on tumor tissue and when feasible on cell-free deoxyribonucleic acid (DNA).

- Baseline and on-treatment measurement of the viability of pre-treatment patient-biopsy-derived 3D organotypic cultures as well as the number and phenotype of the immune cells present within these cultures incubated ex-vivo with DKN-01 and docetaxel.
- Baseline (for tumor tissue and peripheral blood) and on treatment (for tumor and peripheral blood) measurements related to target modulation and immune function that may include, but not be limited to, the number and phenotype of immune cells, gene expression profile, abundance and diversity of tumor infiltrating and peripheral blood T cell clones by high throughput T-cell receptor (TCR) sequencing, variation in proteomic signatures within peripheral blood and presence or absence of key driver mutations and quantitation of mutational load within tumor tissue.
- Overall response stratified by “PSA-high” (concordant radiographic and PSA progression) and “PSA-low” (radiographic evidence in the absence of PSA progression) prostate cancer status.
- Overall response stratified by plasma DKK1 “high” and “low” defined as above or below the DKK1 plasma level reference range in a cohort of healthy men.

4. INVESTIGATIONAL PLAN

4.1. Overall Design and Plan of the Study

This is a 2-arm, non-randomized, phase 1b/2a, multicenter, open-label study of DKN-01 as monotherapy or in combination with docetaxel in patients with advanced treatment-refractory prostate cancer with elevated DKK1.

This study will be conducted in two parts: dose escalation and expansion. The dose escalation and expansion parts will each consistent of cohorts in which DKN-01 is combined with docetaxel (Cohorts 1A, 1B) and in which DKN-01 is administered as monotherapy (Cohorts 2A, 2B). Dose escalation (Part 1) will apply exclusively to the dose of DKN-01 in both cohorts.

In dose escalation Cohort 1A, the dose of docetaxel 75 mg/m^2 will remain fixed. The DKN-01 dose level will start with 300 mg and be escalated to 600 mg or de-escalated to 150 mg depending on the absence or presence of identified DLTs. DKN-01 will be administered in combination with docetaxel on Day 1 and as monotherapy on Day 15 of each 21-day cycle. The DLT monitoring period will start with C1D1 and end on C2D1, but may be longer in the setting of a treatment delay. The maximum treatment delay is 28 days prior to necessitating withdrawal from study. The MTD is defined as the highest tested dose level below the dose level at which a DLT is seen in 2 or more patients (see Section 8.1). The MTD or highest dose tested of DKN-01 in combination with docetaxel will be the dose used Dose Expansion Cohort 1B.

In dose escalation Cohort 2A, DKN-01 dose level will start with 300 mg and be escalated to 600 mg or de-escalated to 150 mg, depending on the absence or presence of identified DLTs. DKN-01 will be administered as monotherapy on Days 1 and 15 of the 28-day C1. The DLT monitoring period will start with C1D1 and end on C2D1, but may be longer in the setting of a treatment delay. The maximum treatment delay is 28 days prior to necessitating withdrawal from study. The MTD or highest dose tested of DKN-01 monotherapy will be the dose used Dose Expansion Cohorts 2B.

At each dose level (cohort) in Cohorts 1A and 2A, up to 4 patients will be screened simultaneously in order to ensure 3 patients will be treated. If all 4 patients in Screening are eligible, all will be permitted to enroll. If none of the treated patients per cohort (up to 4 patients) develop a DLT, subsequent dose escalation will proceed according to the planned schedule. Screening of patients will continue until 3 patients are evaluable for DLTs at each dose level. Prior to the start of the next dosing cohort in Part A, a safety assessment will be performed to assess safety and DLTs. Doses of DKN-01 higher than 600 mg will not be tested because of the PK and pharmacodynamic data described Section 2.2.

If a DLT is observed in 1 out of 3 patients (or 1 of 4 should 4 patients be enrolled) during C1 of any given dose level, the cohort will be expanded and up to an additional 3 patients (maximum of 6 patients per dose level) will be enrolled and treated at that dose level. If no further DLTs are observed within the expanded cohort, dose escalation will proceed. If 2 or more patients at that dose level have DLTs, the MTD will have been exceeded and dose escalation will cease. The dose of DKN-01 chosen for dose expansion cohort 1B will be the MTD or highest dose tested in

dose escalation cohort 1A. The dose of DKN-01 chosen for dose expansion cohorts 2B will be the MTD or highest dose tested in dose escalation cohort 2A. Doses of DKN-01 higher than 600 mg will not be tested because of the PK and pharmacodynamic data described Section 2.2.

Dose escalation scheme Cohort 1A:

Dose Level	Dose of DKN-01 on Days 1 and 15 of each 21-day cycle	Dose of Docetaxel
Level 1	300 mg	75 mg/m^2
Level 2	600 mg	75 mg/m^2
Level -1*	150 mg	75 mg/m^2

* if required

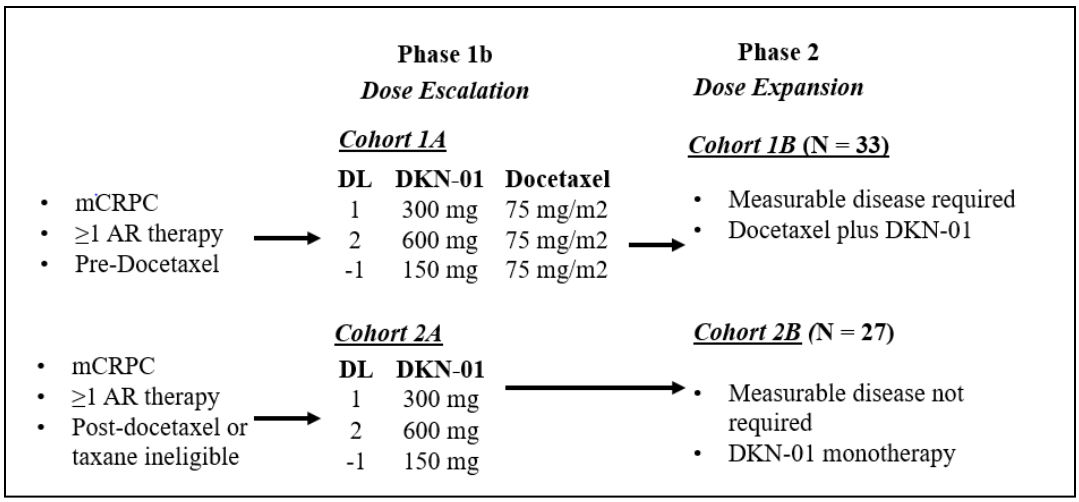
Dose escalation scheme Cohort 2A:

Dose Level	Dose of DKN-01 on Days 1 and 15 of each 28-day cycle
Level 1	300 mg
Level 2	600 mg
Level -1*	150 mg

Data from each cohort in Part A will be evaluated for safety and DLTs prior to dose escalation.

Dose expansion (Part 2) will include two cohorts. Cohort 1B will be restricted to patients who have had 1 or more prior 2nd generation AR targeting therapies (enzalutamide/abiraterone/apalutamide/darolutamide) and no prior docetaxel. Cohort 1B will include patients with RECIST v1.1 measurable disease. The dose of docetaxel in Cohorts 1B will either be 75 mg/m^2 or reduced to 60 mg/m^2 at the discretion of the treating investigator. Cohort 1B will include patients with RECIST v1.1 measurable disease. Cohort 2B will be restricted to patients who have had 1 or more prior 2nd generation AR targeting therapies and have had progression on 1 or more prior taxane chemotherapies or are intolerant of taxane-based chemotherapy or refusing taxane-based chemotherapy. Cohort 1B will be treated with the combination of DKN-01 at the MTD or highest dose tested given on Days 1 and 15, and docetaxel 75 mg/m^2 (or 60 mg/m^2 depending on clinical discretion) given on Day 1 of every 3 weeks (21-day cycles). Cohort 2B will be treated with DKN-01 monotherapy at the MTD or highest dose tested given on Days 1 and 15 of a 28-day cycle. The requirement for prior AR targeting therapies does not apply to patients in any cohort with prostate pure neuroendocrine carcinoma.

A schematic of the study design follows:



4.1.1. Study Periods

Patients will complete up to 5 periods of the study: Screening, Treatment, Follow-up, and Survival/Long-term Follow-up.

4.1.1.1. Pre-Screening Period

This study will not entail any pre-screening period since there is no required testing for Wnt pathway gene alterations or DKK1 expression to confirm eligibility.

4.1.1.2. Screening Period (Up to 28 Days)

Patients will sign consent and be screened for study eligibility.

4.1.1.3. Treatment Period

Cohort 1A, 1B (Dose escalation and Dose Expansion): Patients will be treated with the combination of DKN-01 and Docetaxel until PCWG3 progression or unacceptable toxicity. Treatment with docetaxel beyond 10 cycles can be considered after consultation with the Study Sponsor.

Cohort 2A, 2B (Dose escalation and Dose expansion): Patients will be treated with DKN-01 until PCWG3 progression or unacceptable toxicity.

4.1.1.4. Follow-up Period

Upon completion of study therapy (or upon completion of DKN-01 if further treatment is warranted), all patients will enter the Clinical/Safety Follow-up period once the decision is made to discontinue the patient from treatment (eg, at end-of-treatment [EOT]). At the time of discontinuation, the most recent on-treatment visit will be the EOT visit. Any assessments required for EOT that were completed within 14 days of the last on-treatment visit do not need to be re-completed. This visit will be considered the start of the Week 1 Clinical/Safety Follow-up visit. Patients who discontinue the treatment phase will enter the Clinical/Safety Follow-up period. Patients must be followed for at least 100 days (representing approximately 5 half-lives

for DKN-01) after the last dose of study drug. Follow-up visits should occur at Days 30, 60, and 100 (±10 days) after the last dose of study drug or should coincide with the date of discontinuation (±10 days) if date of discontinuation is greater than 30 days after the last dose of study drug to monitor for AEs. If the patient starts a new treatment than only pre-existing treatment-related AEs that started prior the patient enrolling on the new treatment will need to be followed. All patients will be required to complete 3 Clinical/Safety Follow-up visits regardless of whether they start new anti-cancer therapy, except those patients who withdraw consent for study participation.

4.1.1.5. Survival/Long-term Follow-up Period

After completion of the Clinical/Safety Follow-up period, all patients will then enter the Survival/Long-term Follow-up period. During this period, clinic visits or telephone contact every 3 months will be performed to assess survival status. The duration of the Survival/Long-term Follow-up period will be approximately 2 years following the first dose of study drug, and a minimum of 12 months following the last dose of study drug. After completion of the Safety Follow-up period, patients who discontinue study with ongoing SD, PR, or CR at the EOT visit will enter the Response Follow-up period. These periods will occur simultaneously with the Survival Follow-up period for mentioned patients. These patients will continue to have tumor radiological and clinical tumor assessments (PSA, CgA, and CEA) every 3 months (every 12 weeks) during the Response Follow-up period or until PD, initiation of new therapy, or withdrawal of study. Radiological tumor assessments for patients who have ongoing clinical benefit may continue to be collected after completing the survival phase of the study.

4.2. Study Termination

The study may be prematurely terminated if, in the opinion of the Investigator or Sponsor, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the Investigator or Sponsor by the terminating party.

Circumstances that may warrant termination of the study or discontinuation of a study site include, but are not limited to, the following:

- Determination of unexpected, serious, or unacceptable risk to patients enrolled in the study.
- Failure to enter patients at an acceptable rate.
- Failure to comply with pertinent regulations of appropriate regulatory authorities.
- Submission of knowingly false information from the research facility to the Sponsor.
- Insufficient adherence to protocol requirements.
- Insufficient complete and/or evaluable data.
- Plans to modify suspend or discontinue the development of the study drug.

Should the study be closed prematurely, all study materials must be returned to the Sponsor or its designee.

5. STUDY POPULATION

The study population will consist of men with advanced castration-resistant metastatic or locally-recurrent prostate cancer.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

5.1. Number of Patients

5.1.1. Dose Escalation

Cohort 1A: up to 12 patients.

Cohort 2A: up to 12 patients

5.1.2. Dose expansion

Cohort 1B: 33 patients

Cohort 2B: 27 patients

5.2. Inclusion Criteria

Male patients who meet the following inclusion criteria and none of the exclusion criteria will be eligible for enrollment in the study:

1) Age >18 years.

2) Have a histologically or cytologically confirmed cancer of prostate origin (adenocarcinoma, poorly differentiated carcinoma, or neuroendocrine carcinoma are all allowed).

   I. Patients with pure neuroendocrine carcinoma must have had at least one line of platinum-based chemotherapy unless the patient is intolerant of or is refusing chemotherapy.

   II. Patients with pure neuroendocrine carcinoma do not need to have been previously treated with an androgen receptor (AR) signaling inhibitors (abiraterone or enzalutamide or apalutamide or darolutamide) but must have castrate testosterone and have castration-resistant disease.

3) Surgically or medically castrated, with testosterone levels of < 50 ng/dL (< 2.0 nM). If the patient is being treated with luteinizing hormone-releasing hormone (LHRH) agonists (patient who have not undergone orchiectomy), this therapy must have been initiated at least 4 weeks prior to C1D1 and must be continued throughout the study.

4) Cohorts 1A, 1B. Patients must have progressed despite 1 or more AR signaling inhibitors (abiraterone or enzalutamide or apalutamide or darolutamide) and have not received prior taxane-based chemotherapy for prostate cancer. Prior treatment with an AR signaling inhibitor for castration-sensitive disease will be allowed if the time to progression was within 1 year after starting drug. Prior treatment with a taxane-based chemotherapy for castration-

sensitive disease will be exclusionary. (Prior treatment with an AR signaling inhibitor is not required for pure prostate neuroendocrine carcinoma as in inclusion 2.)

5) Cohorts 2A and 2B. Patients must have progressed despite 1 or more AR signaling inhibitor (abiraterone or enzalutamide or apalutamide or darolutamide) and either had disease progression, were intolerant of, or refused 1 or more taxane-based chemotherapies for mCRPC. (Prior treatment with an AR signaling inhibitor is not required for pure prostate neuroendocrine carcinoma as in inclusion 2.)
6) Cohort 1B. Patients must have measurable disease per RECIST v1.1 guidelines AND must have either:
   I. PSA progression is defined by Prostate Cancer Working Group 3 (PCWG3) criteria as a minimum of two consecutive rising levels, with an interval of ≥1 week between each determination with a minimum PSA of 1 ng/mL, if PSA is the sole evidence of progression, OR
   II. Radionuclide bone progression as defined by at least two new metastatic lesions (per PCWG3), OR
   III. Soft tissue progression on transaxial imaging: new or progressive soft tissue masses on computed tomography (CT) or magnetic resonance imaging (MRI) scans as defined by RECIST v1.1.
7) Cohorts 1A, 2A, 2B. Patients must have baseline progression defined as one of the following:
   I. PSA progression is defined by PCWG3 criteria as a minimum of two consecutive rising levels, with an interval of ≥1 week between each determination with a minimum PSA of 1 ng/mL.
   II. Radionuclide bone progression as defined by at least two new metastatic lesions (per PCWG3)
   III. Soft tissue progression on transaxial imaging: new or progressive soft tissue masses on computed tomography (CT) or magnetic resonance imaging (MRI) scans as defined by RECIST v1.1
8) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
9) Estimated life expectancy of at least 3 months, in the judgment of the Investigator.
10) Required initial laboratory values within 14 days of C1D1:
   I. Total bilirubin within normal limits for the institution (For Cohorts 2A and 2B, total bilirubin < 3 × upper limit of normal (ULN) is acceptable with known liver metastases).
   II. For Cohorts 1A, 1B transaminases [aspartate aminotransferase (AST) and ALT] ≤1.5 × ULN (For Cohorts 2A and 2B, AST and ALT ≤ 5.0 × ULN is acceptable with known liver metastases).

III. Creatinine ≤2.0 or calculated creatinine clearance ≥50 mL/min using the Cockcroft and Gault Method (Cockroft and Gault 1976).

IV. Absolute neutrophil count (ANC) ≥1000 cells/µl.

V. Absolute lymphocyte count ≥500/µl.

VI. Hemoglobin ≥8.5 g/dL.

VII. Platelet count ≥100,000 cells/µl. (For Cohorts 2A and 2B, Platelet count ≥75,000 cells/µl).

VIII. International normalized ratio (INR) (prothrombin time [PT])/partial thromboplastin time (PTT) ≤1.5 × ULN unless receiving anticoagulant, in which case INR ≤3.0 and no active bleeding, (ie, no clinically significant bleeding within 14 days prior to first dose of study therapy

11) Sexually active male patients must agree to use adequate contraception (hormonal or barrier method of birth control) during the study and for 6 months after their last dose of study drug. Should a patient's partner become pregnant or suspect she is pregnant while participating in the study, the Investigator should be immediately informed.

12) Reliable and willing to make themselves available for the duration of the study and are willing to follow study-specific procedures.

13) Provided written informed consent prior to any study-specific procedures.

14) Submission of a next-generation sequencing report from prostate cancer tissue or ctDNA from a CLIA certified lab if available. If no such report is available, a statement attesting to the lack of such a report is sufficient for eligibility.

5.3. Exclusion Criteria

Patients who meet any of the following criteria are not eligible for enrollment in the study:

1) Any anti-cancer therapy (with the exception of LHRH analog) within 2 weeks prior to initiation of study treatment.

2) Any investigational anti-cancer therapy within 4 weeks of initiation of study treatment.

3) New York Heart Association Class III or IV heart failure, or myocardial infarction within the past 6 months, or unstable arrhythmia within 3 months.

4) Uncontrolled bacterial, viral, or fungal infections, within 7 days of study entry.

5) Known to be human immunodeficiency virus (HIV) positive, have positive hepatitis B surface antigen (HBSAg), or positive hepatitis C antibody (HCAb) test. (Hepatitis C antibody-positive patients with an undetectable hepatitis C virus (HCV) RNA will be eligible.)

6) History of malignancy other than prostate cancer within 2 years prior to screening, except for malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as non-melanoma skin carcinoma or ductal carcinoma in situ
7) History of solid organ transplant (ie, heart, lungs, liver, or kidney).
8) History of autologous/allogenic bone marrow transplant.
9) Serious nonmalignant disease that could compromise protocol objectives in the opinion of the Investigator and/or Sponsor.
10) Major surgical procedures or significant traumatic injury within 4 weeks prior to study entry (minor surgical procedures within 1 week of study entry). Note: Diagnostic cystoscopy is not exclusionary at any time during screening.)
11) History of osteonecrosis of the hip. Other hip pathology such as degenerative disease or malignant involvement are not exclusionary. Screening of asymptomatic patients is not required.
12) Active or untreated central nervous system (CNS) malignancy or metastasis. Screening for CNS metastases of asymptomatic patients without a history of CNS metastases is not required. Patients with treated CNS metastases are eligible provided they meet all of the following criteria:
    a. Evaluable disease outside the CNS.
    b. No history of intracranial or intraspinal hemorrhage.
    c. No evidence of significant vasogenic edema.
    d. No ongoing requirement for corticosteroids as therapy for CNS disease. (Anti-convulsants at a stable dose for > one month is allowed.)
    e. No stereotactic radiation, whole brain radiation within 4 weeks of C1D1.
    f. Patients with CNS metastases treated by neurosurgical resection or brain biopsy within 3 month prior to C1D1 will not be allowed.
    g. Radiographic demonstration of interim stability (ie, no progression) between completion of CNS-directed therapy and the screening radiographic study.
    h. Screening CNS radiographic study ≥4 weeks since completion of radiotherapy or surgical resection and ≥2 weeks since discontinuation of corticosteroids.
13) Any other condition, disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.
14) Active substance abuse.

15) Receipt of any live vaccine within 30 days before the first dose of study treatment or anticipation that such a live vaccine will be required during study participation.

16) Previously treated with an anti-DKK1 therapy.

5.4. Clinical Trial Materials

5.4.1. DKN-01

DKN-01 supplied for this study is for investigational use and only to be used within the context of this clinical study. DKN-01 will be supplied to the Investigator by the Sponsor or its designee.

DKN-01 is provided in a glass vial as a lyophilized powder for reconstitution. Each vial is manufactured to deliver 20 mg of DKN-01 and contains the inactive ingredients sucrose, polysorbate 80, sodium chloride, citric acid, and sodium citrate. DKN-01 vials should be stored refrigerated at 2º – 8ºC.

Detailed instructions for the preparation and handling of DKN-01 will be provided by the Sponsor or its designee in the pharmacy manual.

5.4.2. Docetaxel

Docetaxel will be provided as part of a standard of care standard operating procedure.

5.5. Blinding, Packaging and Labeling

5.5.1. Blinding and Breaking the Blind

This is an open-label study; no blinding methods will be employed.

5.5.2. Packaging and Labeling

Vials of DKN-01 vials are manufactured in accordance with Good Manufacturing Practices and packaged and labeled to meet applicable regulatory requirements.

Study drug labels will not bear any statement that is false or misleading in any manner or represent that the study drug is safe or effective for the purposes for which it is being investigated.

5.6. Method of Assigning Patients to Treatment

This study consists of dose escalation and dose expansion cohorts. The dose expansion cohorts consists of non-randomized parallel arms. Assignment to treatment arms will be based on cohort specific eligibility criteria.

5.7. Study Drug Accountability and Disposal

All study drug will be stored, inventoried, reconciled, and destroyed according to applicable regulations.

Accountability for the study drug at the study site is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the date of

delivery of the study drug to the site, inventory at the site, amount dispensed to and returned by each patient, and return to the Sponsor (or disposal of the study drug, if approved by the Sponsor) will be maintained by the clinical site. These records will adequately document that the patients were provided the study drug as specified in the protocol and should reconcile all study drug received from the Sponsor. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. The Sponsor (or designee) will review drug accountability at the site during monitoring visits.

All unused study drug will be retained at the site until inventoried by the monitor. All unused or expired study drug will be returned to the Sponsor or, if authorized, disposed of at the study site and documented.

5.8. Assessment of Treatment Compliance

All study drug will be administered IV at the investigational site, under the direction of the Investigator. As a result, a patient's compliance with study drug administration is ensured. Any deviation(s) from the prescribed dosage regimen or problems with administering the IV infusion should be recorded on the electronic case report form (eCRF).

Patients should attend scheduled clinic visits and must comply with study criteria under their control. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

5.9. Administration of Study Drug(s)

The Investigator or designee is responsible for:

- Explaining the correct use of the investigational agent(s) and planned duration of each individual's treatment to the site personnel,
- Verifying that instructions are followed properly,
- Maintaining accurate records of study drug dispensation, destruction, and collection, and
- Returning or destroying all unused medication to the Sponsor or its designee at the end of the study.

Patients will be instructed to contact the Investigator as soon as possible if they have an issue with the study drug(s) so that the situation can be assessed.

5.9.1. DKN-01 Administration

DKN-01 is a large molecular weight protein that will be given as a flat dose on a Days 1 and 15 of a 21-day cycle in Dose Escalation Cohort 1A and Dose Expansion Cohorts 1B. DKN-01 will be given on Days 1 and 15 on a 28-day cycle in Dose Escalation and Expansion Cohort 2A and 2B. The dose of DKN-01 will be administered as an IV infusion over 60 (±) 15 minutes. If the first infusion is well-tolerated without infusion-associated adverse events, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion well tolerated, all subsequent infusions may be delivered over 30 (±) 10 minutes.

If the patient experiences an infusion reaction following administration of DKN-01 over 60 minutes, the infusion time should be increased to 120 (±30) minutes. If the patient

experiences an infusion reaction following administration of DKN-01 over 30 minutes, the infusion time should be increased to 60 (±15) minutes and all subsequent doses should be administered over this amount of time.

5.9.2. Docetaxel Administration

Docetaxel will be administered as an IV infusion over approximately 60 (±15) minutes on D1 of a 21-day cycle. In Cohort 1A, docetaxel must be dosed at 75 mg/m^2 on cycle 1 day 1. Docetaxel can be dosed at 75 mg/m^2 or 60 mg/m^2 in subsequent cycles depending on clinical discretion and the dose modification guidelines in section 5.12.2. Regardless of dose, docetaxel must be dosed in 21-day cycles. In Cohort 1B, cycle 1 day 1 dosing of docetaxel will either be 75 mg/m^2 or 60 mg/m^2 depending on clinical discretion. Patients will be pre-medicated as per standard institutional guidelines.

On days in which both DKN-01 and docetaxel are given, the order of administration will be:

1. Pre-medication for Docetaxel
2. DKN-01 Infusion
3. Docetaxel Infusion

A minimum of 5 minutes is required between completion of DKN-01 infusion and initiating docetaxel infusion dosing.

5.10. Criteria for Initiation of a New Treatment Cycle

A new cycle may be initiated for patients meeting the following criteria:

- ANC ≥1000/mm^3 (≤Grade 2).
- Platelet count ≥100×10^9/L (≤Grade 1) (≥75×10^9/L in dose escalation and expansion Cohort 2A and 2B).
- Total bilirubin within normal limits for the institution (For Cohorts 2A and 2B, or in Cohort 1A and 1B if the patient is to receive DKN01 monotherapy, total bilirubin < 3 × upper limit of normal (ULN) is acceptable with known liver metastases).
- Transaminases [aspartate aminotransferase (AST) and ALT] ≤1.5 × ULN (For Cohorts 2A and 2B, or in Cohort 1A and 1B if the patient is to receive DKN01 monotherapy, AST and ALT ≤ 5.0 × ULN is acceptable with known liver metastases).

If these conditions are not met on D1 of a new cycle, the administration of both docetaxel and DKN-01 will be held, and the patient will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. The maximum treatment delay is 28 days prior to necessitating withdrawal from study. Treatment windows of +/- 3 days are allowable for day 1 and day 15 starting with cycle 2, however at least 7 days must elapse between Day 15 and the Day 1 treatment of the subsequent cycle.

If, in the opinion of the Investigator, a patient is receiving clinical benefit from continued treatment with DKN-01 alone, patients may discontinue docetaxel and continue with DKN-01 monotherapy until developing documented progressive disease (PD) or otherwise meeting criteria for treatment discontinuation (Section 5.15.1) and patients can be dosed with DKN-01 on D1 and D15 of a 21-day cycle or D1 and D15 of a 28 day cycle.

Patients for whom the Investigator decides it is in their best interest to stop DKN-01 treatment are discontinued and complete the EOT procedures.

5.11. Criteria for Treatment on Day 15 of a Treatment Cycle

Treatment may be administered on D15 for patients meeting the following criteria:

- ANC ≥900 cells/mm^3.
- Platelet count ≥70×10^9/L.
- Total bilirubin within normal limits for the institution (For Cohorts 2A and 2B, or in Cohort 1A and 1B if the patient is to receive DKN01 monotherapy, total bilirubin < 3 × upper limit of normal (ULN) is acceptable with known liver metastases).
- Transaminases [aspartate aminotransferase (AST) and ALT] ≤1.5 × ULN (For Cohorts 2A and 2B, or in Cohort 1A and 1B if the patient is to receive DKN01 monotherapy,tumorAST and ALT ≤ 5.0 × ULN is acceptable with known liver metastases).

If these criteria are not met, the dose will be skipped, and the patient will return for D1 of the next cycle. Treatment windows of +/- 3 days are allowable for day 1 and day 15 starting with cycle 2, however at least 7 days must elapse between Day 15 and the Day 1 treatment of the subsequent cycle.

5.12. Dosing Modifications, Reductions and Re-escalations, and Delays

Management procedures for DKN-01-related toxicities are summarized in Table 2. Docetaxel should be continued in the setting of DKN-01 related toxicities at the Investigator's discretion.

Table 2: Management of DKN-01-related Adverse Reactions

System Monitoring	Severity	Management	Follow-up
Gastrointestinal			
Any changes in normal bowel habits or changes from BL: Diarrhea Abdominal pain	Grade 2	Withhold DKN-01 Administer antidiarrheal treatment while etiology is investigated.	Symptoms Resolve to ≤Grade 1 or baseline: Resume DKN-01 as per Table 3 if symptoms have improved to mild severity or resolution.

System Monitoring	Severity	Management	Follow-up
Blood or mucus in stool with or without fever Peritoneal signs consistent with bowel perforation Ileus	Grade 3 or higher	Permanently discontinue DKN-01 Rule out bowel perforation Consider endoscopic evaluation	
Liver			
Elevations in liver function tests: AST ALT Total bilirubin *Patients in Cohorts 2A or 2B with documented liver metastases and grade 1 or 2 LFT abnormalities (ALT/AST/Total bilirubin) may continue to receive study drug per protocol.	Grade 2	*Withhold DKN-01 Rule out infectious or malignant causes Increase frequency of liver function test monitoring until resolution	Symptoms Resolve to ≤Grade 1 or baseline: Resume DKN-01 as per Table 3 Symptoms Ongoing: If AST or ALT elevation continues to be >5 × ULN OR total bilirubin >3 × ULN, see below.
	Grade 3 or higher	Permanently discontinue DKN-01 Rule out infectious or malignant causes Increase frequency of liver function test monitoring until resolution	
Skin			
Pruritus Rash (acneiform, maculo-papullar, pustular, papulopustular)	Grade 2	Withhold DKN-01 Administer topical corticosteroids if there is no improvement of symptoms within 1 week.	Symptoms Resolve to ≤Grade 1 or baseline: Resume DKN-01 as per Table 3 if dermatitis resolves or improves to mild (localized) symptoms. Symptoms Ongoing: If symptoms worsen, see below.
	Grade 3 or higher	Permanently discontinue DKN-01 Administer systemic corticosteroid therapy	
Neurologic			

System Monitoring	Severity	Management	Follow-up
Monitor for symptoms of motor or sensory neuropathy Unilateral or bilateral weakness Sensory alterations	Grade 2	Withhold DKN-01 Introduce appropriate medical intervention	Symptoms Resolve to ≤Grade 1 or baseline: Resume DKN-01 as per Table 3 when symptoms resolve or return to BL Symptoms Ongoing: If symptoms worsen, see below
	Grade 3 or higher	Permanently discontinue DKN-01 Institute appropriate medical intervention	
Endocrine			
Adrenal insufficiency Abnormal thyroid function tests and/or serum chemistries Hypophysitis Type 1 Diabetes	Grade 2 or higher	Withhold DKN-01 Document signs and/or symptoms of dysfunction Evaluate endocrine function Consider radiographic pituitary gland imaging Continue to assess as indicated Initiate appropriate hormone-replacement therapy	Symptoms Resolve to ≤Grade 1 or baseline: Resume DKN-01 as per Table 3 when: Patient is stable on hormone-replacement therapy (as indicated) Symptoms Ongoing: Permanently discontinue DKN-01

5.12.1. DKN-01 Dosing and Dose Adjustments

DKN-01 will be administered via IV infusion on D1 and 15 in each 21-day treatment cycle (Cohort 1A, 1B) or 28-day cycle (Cohort 2A and 2B).

After the first occurrence of a toxicity necessitating withholding of study treatment, the Investigator may elect to restart DKN-01 treatment for the patient at the previously received dose once the toxicity resolves to ≤Grade 1 or baseline. For subsequent recurrence of the toxicity, DKN-01 treatment, per Investigator discretion, may be resumed at the next lower dose after the toxicity resolves to ≤Grade 1 or baseline (see Table 3).

Table 3 DKN-01 Dose Adjustments

Toxicity Occurrence	DKN-01
First*	Restart at assigned dose level after toxicity resolves to ≤Grade 1 or baseline.
Second	Restart at reduced dose (-1) after toxicity resolves to ≤Grade 1 or baseline. Dose level 1 (300 mg): resume at 150 mg Dose level 2 (600 mg): resume at 300 mg
Third	Restart at reduced dose (-2) after toxicity resolves to ≤Grade 1 or baseline. Dose level 1 (300 mg): resume at 75 mg Dose level 2 (600 mg): resume at 150 mg
Fourth	Discontinue

*If the toxicity is judged to be significant in the opinion of the Investigator or the Investigator does not wish to dose at the same dosing level, he/she may contact the Medical Monitor to consider a one dose reduction level with the first occurrence of toxicity.

Once a patient's DKN-01 dose has been reduced, no re-escalation to a previously received dose is allowed at any time during the study. Intra-patient dose escalation is not permitted at any time during the study. Docetaxel should be continued in the setting of DKN-01 related toxicities at the Investigator's discretion.

DKN-01-related infusion reactions are to be managed as described in Appendix 12.5.

5.12.2. Combination Dosing and Docetaxel Dose Adjustments, if applicable

Toxicities attributable to docetaxel, such as febrile neutropenia, neutrophils <500/mm^3 for >1 week, severe or cumulative cutaneous reactions, platelet nadir <25,000/mm^3 and other Grade 3/4 non-hematologic toxicities, will necessitate holding docetaxel and DKN-01 until the criteria in 5.1 are satisfied followed by a dose reduction to docetaxel 60 mg/m^2. Persistence or recurrence of symptoms will necessitate discontinuation of docetaxel. Once docetaxel is discontinued, the decision to restart DKN-01 as monotherapy will be at the Investigator's discretion and following discussion with the Sponsor.

5.13. Definition of Dose-limiting Toxicity

The DLT period is exclusively in the dose escalation cohort and starts with C1D1 and concludes on C2D1. The dose escalation cohorts will remain independent with respect to DLT assessment and dose modification. A DLT is defined as an AE that is at least possibly related to the study drug (DKN-01) and fulfills at least 1 of the following:

- Grade 4 neutropenia lasting >5 days or Grade 4 neutropenic fever
- Grade 4 thrombocytopenia (or Grade 3 with bleeding)
- Grade 4 anemia
- Grade 3 or 4 non-hematological toxicity (excluding Grade 3 vomiting and Grade 3 diarrhea lasting < 72 hours including the clinical sequelae (eg, electrolyte abnormalities) despite optimal supportive care and excluding alopecia

- Dosing delay greater than 14 days due to treatment-emergent AEs or related severe laboratory abnormalities
- Grade 3 hypersensitivity reaction to DKN-01 with premedication (Grade 3 hypersensitivity reaction to DKN-01 without premedication is not considered a DLT)
- Grade 4 hypersensitivity reaction to DKN-01 with or without premedication
- Any Grade 5 AE
- Any treatment-related AE that causes the patient to discontinue treatment during C1

A drug-related fever ≤Grade 3 will not be considered a DLT.

The MTD is defined as the highest tested dose level below the dose level at which a DLT is seen in 2 or more patients (see Section 8.1).

5.14. Duration of Study Participation and Treatment

Cohort 1A, 1B (Dose escalation and Dose Expansion): Patients will be treated with the combination of DKN-01 and Docetaxel until PCWG3 progression or unacceptable toxicity. Treatment with docetaxel beyond 10 cycles can be considered after consultation with the Study Sponsor.

Cohort 2A, 2B (Dose escalation and Dose expansion): Patients will be treated with DKN-01 until PCWG3 progression or unacceptable toxicity.

Following 9 weeks (3 cycles), the decision to continue treatment with additional cycles of DKN-01 and docetaxel will be based on radiological assessments (performed at baseline, end of C3, and every 9 weeks for the first 27 weeks, then every 12 weeks). Tumor progression or response endpoints will be assessed using iRECIST (measurable disease) and the PCWG3 guidelines (non-target bone progression).

Treatment beyond PD may be allowed in select patients after discussion and agreement with the Sponsor and Leap Therapeutics (Leap). The benefit/risk assessment needs to favors continued administration of study therapy (eg, patients are continuing to experience clinical benefit as assessed by the Investigator and tolerating treatment), and no treatment discontinuation criteria are met:

1) Investigator-assessed clinical benefit, and not having rapid disease progression
2) Continue to meet all other study protocol eligibility criteria;
3) Tolerance of study drug;
4) Stable performance status;
5) Treatment beyond PD will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases);
6) Patient provides written informed consent prior to receiving any additional nivolumab or DKN-01/docetaxel treatment, using an informed consent form (ICF) describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

5.15. Withdrawal and Replacement of Patients

5.15.1. Withdrawal from Treatment or the Study

Patients will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care. The Sponsor and Investigators also have the right to withdraw patients from the study.

All patients who withdraw from the study prematurely will undergo all end of treatment assessments. Regardless of the reason for withdrawal, efforts should be made to follow safety events from the time of withdrawal through resolution or until the event stabilizes.

Study drug should be discontinued for any of the following reasons:

- AEs/unacceptable toxicity justifying treatment or study withdrawal.
- Non-adherence to the study drug regimen or protocol requirements.

- Non-compliance with instructions or failure to return for follow-up.
- Investigator decides that study termination is in the patient's best medical interest.
- Lost to follow-up.
- Enrollment in any other clinical study involving use of an investigational drug or device or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Dosing delay of ≥28 days.
- Development of radiographically-documented PD, as determined by the Investigator using iRECIST (Appendix 12.3).
- An isolated PSA rise in the absence of radiographic progression is not an indication for study drug discontinuation provided that the Investigator deems the patient to be clinically benefitting from the study drug(s).

With the consent of the patient or the legally authorized representative the Investigator may determine that limited data collection may be continued (eg, through medical record review) for the duration of the study after a patient has withdrawn.

5.15.2. Replacement of Study Patients

Patients in the dose escalation phase of the study who discontinue during the DLT period for non-safety related issues will be replaced. Patients in the dose expansion cohorts who discontinue from the study will not be replaced.

5.16. Concomitant Medications, Therapies and Supportive Care

5.16.1. Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Concomitant systemic corticosteroids given with docetaxel prior to C3D1 other than as part of a standard institutional pre-medication regimen or to treat infusion-related allergic reactions or cytokine release syndromes as described below.
- Investigational agents other than DKN-01
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with Sponsor. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.

- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette–Guérin, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, Flu - Mist®) are live attenuated vaccines, and are not allowed.

Patients who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. Patients may receive other medications that the Investigator deems to be medically necessary.

The Exclusion Criteria (Section 5.3) describe other medications that are prohibited in this study.

5.16.2. Rescue Medications, Supportive Care, and Allowed Concomitant Medications

Necessary supportive measures for optimal medical care will be given throughout the study, including IV antibiotics to treat infections, growth factor support, blood components, and standard of care bone-targeted agents, etc. Additional care, including palliative radiotherapy (excluding target lesions and lesions representing progressive disease) (see Section 5.16.1 for exceptions), may be administered as indicated by the treating physician, patient's medical need, and after discussion with the Sponsor.

Concomitant medications refers to any over-the-counter or prescription medications taken by the patient during the period starting 7 days prior to Screening until the EOT visit.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or famotidine or another H2 receptor antagonist, or glucocorticoids as per standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (eg, supplemental oxygen and ß2-adrenergic agonists). Systemic corticosteroids administered prior to C3 may attenuate the beneficial immunological effects of DKN-01 but may administered at the discretion of the treating physician. Tumor necrosis factor-alpha inhibitors may be administered at the discretion of the treating physician in consultation with the Sponsor. Inhaled steroids are allowed for management of asthma and/or chronic obstructive pulmonary disease. Topical steroids also are allowed.

Influenza vaccination should be given during influenza season only (approximately October to March).

5.16.3. Diet/Activity/Other Considerations

5.16.3.1. Diet

Patients should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.16.3.2. Contraception

DKN-01 may have adverse effects on a fetus in utero. Furthermore, it is not known if DKN-01 has transient adverse effects on the composition of sperm. Patients should be informed that taking the study drug may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study patients of childbearing potential must adhere to the contraception requirement (described above) from the day of study drug initiation (or 14 days prior to the initiation of study drug for oral contraception) throughout the study period up to 6 months after the last dose of study therapy. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

6. STUDY ASSESSMENTS

The Schedule of Assessments for the study is provided in Table 5 in Appendix 12.1. Detailed descriptions of the study assessments to be conducted during this study are described in the following sub-sections.

6.1. Clinical Procedures and Safety Assessments

6.1.1. Informed Consent

A complete description of the study is to be presented to each potential study patient. Signed and dated informed consent is to be obtained before any study-specific procedures are performed.

6.1.2. Inclusion / Exclusion Criteria Review

The inclusion and exclusion criteria will be reviewed during the Screening Period as assessments are performed to confirm patient eligibility for the study. The criteria will be reviewed prior to administration of the first dose of study drug in C1D1 to confirm continued study eligibility.

6.1.3. Demographics, Medical and Disease History

Demographic data and medical and disease histories will be obtained for all patients during the Screening Period. Demographic data to be recorded in the source document/eCRF includes gender, race, and date of birth. Information on significant medical and surgical history including dates, outcome, and whether or not ongoing or currently treated will be recorded. The date of original cancer diagnosis will be recorded along with any known cancer genomics profile results and previous treatments, including chemotherapy, radiation therapy, surgery, and use of blood products, including red cell and platelet transfusions and growth factors, within the previous 3 months. In addition, all other medications taken within 28 days of the initial Screening visit will be recorded.

The medical history will be reviewed prior to dosing on C1D1 to assess continued study eligibility and adherence to final inclusion/exclusion criteria. This recent medical history includes a review for changes from Screening as well as a review of the patient's recent medication use to assess whether or not any changes have occurred since the previous study visit.

6.1.4. Physical Examination

A complete physical examination (general appearance, head/ears/eyes/nose/throat, lungs/chest, heart, abdomen, lymph nodes, musculoskeletal, extremities, and neurological examination) will be conducted at the time points designated in Table 5. During Screening, the physical examination is to include measurement of height.

Abbreviated (ie, symptom-directed) physical examinations will be conducted at the time points designated in Table 5 to address any complaints or concerns verbalized by the patient at all other study visits.

6.1.5. Vital Signs and Weight

Vital signs are to be measured at the time points designated in Table 5. Vital signs to be measured include systolic and diastolic blood pressure (mmHg; measured in the same arm), oral temperature (°C), pulse (bpm), and respiration rate (breaths/minute).

Weight will be measured on Day 1 of each treatment cycle and at the EOT visit. Body surface area (BSA) is to be calculated on Day 1 of each treatment cycle using the weight from that cycle and the Screening height measurement.

6.1.6. Electrocardiograms

A 12-lead electrocardiogram (ECG) will be obtained at the time points designated in Table 5. Additional ECGs may be obtained as clinically warranted and judged by the Investigator.

Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

ECGs will be interpreted by a qualified physician (the Investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the Investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether the patient can continue in the study. The Investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes.

6.1.7. Eastern Cooperative Oncology Group Performance Status (ECOG PS)

The ECOG PS (Oken et al. 1982) will be determined at the time points designated in Table 5. Patients must have an ECOG PS of 0-1 to be enrolled into the study. Patients with an ECOG PS of 2 may be entered upon review and approval for study participation by the Medical Monitor.

6.1.8. Clinical Laboratory Evaluations

Routine clinical laboratory evaluations will be performed locally by a certified laboratory selected for the study. Prior to starting the study, the Investigator will provide copies of all laboratory certifications and normal ranges for all laboratory parameters to be assessed by the local laboratory.

Clinical laboratory evaluations are to be performed at the time points designated in Table 5. Final clinical laboratories are to be performed at EOT.

All clinically significant laboratory abnormalities noted on testing will be followed up by repeat testing and further investigated according to the judgment of the Investigator.

The Investigator must review all the patient's laboratory reports in a timely manner. Investigators must document their review of each laboratory report and must assess whether or

not any abnormal test results are clinically significant. The Investigator must complete an appropriate AE form for any abnormal test results that are identified as clinically significant.

Specific tests to be performed are described below:

Hematology

Hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume (MCV), mean cell hemoglobin concentration (MVHC), platelets, leukocytes (WBC) and differential [absolute counts of] neutrophils (segmented and banded), lymphocytes, monocytes, eosinophils, and basophils. Neutrophil/lymphocyte ratio (a calculated ratio) also is to be determined.

Chemistry

Sodium, potassium, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), creatinine, creatine kinase (CK), uric acid, calcium, glucose (random), albumin, cholesterol, serum chloride, phosphorus, carbon dioxide, and total protein.

Coagulation Studies

PT, PTT, and INR.

Tumor Markers

Serum Prostate-Specific Antigen (PSA), Carcinoembryonic antigen (CEA), and Chromogranin A (CgA)

Other Clinical Laboratory Tests

25-hydroxyvitamin D is to be collected at the screening visit.

Circulating Tumor Cell Enumeration:

CTCs will be enumerated using Menarini Silicon Biosystems CellSearch™ platform. CTC samples in all patients will be used to enumerate CTC counts. Refer to the study laboratory manual for specific details on sample collection, handling, storage, and shipping requirements.

6.1.9. Concomitant Medications / Procedures Review

A review of concomitant medications and procedures will be conducted at each study visit. Any medications taken by study participants or concomitant procedures (eg, transfusions, radiation, surgery, or other palliative care) are to be recorded in the eCRF and reviewed for compliance with protocol requirements.

6.1.10. Adverse Event Monitoring

Each participant must be carefully monitored for the development of any AEs, including infusion-related AEs and immune-related AEs (see Section 6.1.11), throughout the study from signing of the informed consent through 100 days after the last dose of DKN-01, when end of treatment procedures are performed. This information should be obtained in the form of non-leading questions (eg, “How are you feeling?”), and from signs and symptoms detected during each examination, from laboratory evaluation, observations of study personnel, participant

diary, and spontaneous reports from participants. If, after study drug discontinuation, patients initiate a new treatment, only study drug-related AEs need to be followed.

During post-treatment follow-up, any serious adverse events (SAEs) which the Investigator considers related to study treatment are to be reported.

All AEs will be graded using the NCI CTCAE, version 5.0, grading system (available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf). The Investigator will assess and grade all AEs. Details of AE monitoring and reporting are provided in Section 7.1 of this protocol.

6.1.11. Medical Events of Interest

The following sections describe the assessment and management of DKN-01 infusion-related AEs. Details for the management and assessment of these events are found in Appendix 11.5 through Appendix 11.6.

6.1.11.1. Infusion-related Reactions

The NCI CTCAE, version 5, definition of infusion-related reactions will be used in this study (see Appendix 12.4), and any reactions will be graded using these same criteria. The Sponsor or designee should be contacted immediately if questions arise concerning the grade of the reaction.

Infusion-related reactions are temporally associated with the infusion of DKN-01 (≤24 hours post-infusion). Symptoms occurring during or following infusion of study drug may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome. In the setting of symptoms occurring during or following infusion of investigational therapy, Investigators are encouraged to use the AE term “Infusion-related reaction” and any additional terms (including those not listed in the NCI CTCAE) that best describe the event.

Guidelines for the management of DKN-01 related reactions are summarized in Appendix 11.5 and Appendix 11.6.

6.2. Efficacy and Response Assessments

6.2.1. Tumor Measurement and Disease Response Assessment by iRECIST

Soft tissue response and evaluation of PD will be determined according to the iRECIST guidelines (Appendix 12.3). Progression in bone will be evaluated according to PCWG3 guidelines. Refer to the Schedule of Assessments (Table 5) for details regarding the timing of specific efficacy measures.

For all cohorts soft tissue (visceral and nodal) disease will be evaluated for evidence of radiographic response based on iRECIST guidelines. Bone lesions will be followed and evaluated for evidence of radiologic progression based on PCWG3 criteria. PSA response will also be evaluated.

Tumor assessments will be performed during Screening (baseline), at the end of every 9 calendar weeks (±7 days) relative to Day 1 (Week 1) up to 27 weeks, then every 12 calendar weeks (±7 days), until confirmed radiologic disease progression by iRECIST (measurable

disease) or PCWG3 criteria (non-target bone lesions), as assessed by the Investigator, loss to follow-up, withdrawal, or study closure.

Tumor assessments should be performed at the time of treatment discontinuation if the reason was other than radiologically confirmed disease progression and it has been ≥8 weeks since the last assessment. Tumor assessments should consist of clinical examination, serum PSA, and appropriate imaging techniques (ie, CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST v1.1); other studies (MRI, X-ray, positron emission tomography[PET]/CT, and ultrasound) may also be performed if required.

If a site can document that the CT performed as part of a PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST measurements. Radionuclide bone scanning (whole body) should be performed using ^{99}mTc-methylene. All sites of disease should be followed and the same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment time. Copies of CT scans (and other imaging, as appropriate) If a response is noted, a follow-up radiographic assessment at a minimum of 4 weeks later to confirm response is to be done.

6.2.2. iRECIST Assessment of Disease

iRECIST is based on RECIST v1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in Appendix 12.3. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease.
- No decline in ECOG PS.
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care.

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective Blinded Independent Central Review (BICR).

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 12.3, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Table 5 and submitted to the central imaging vendor.

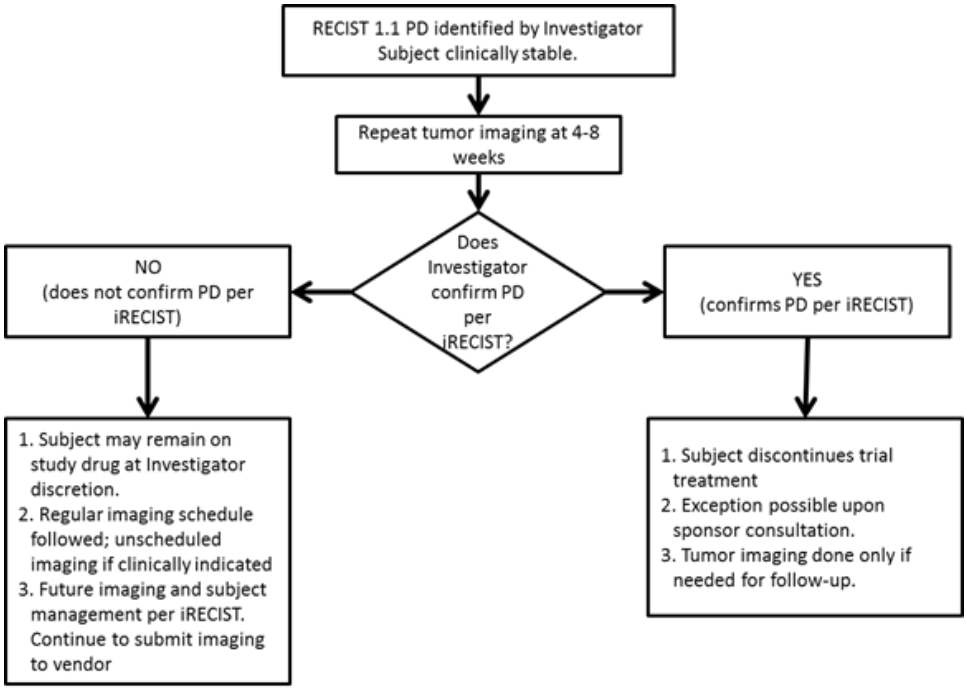
A description of the adaptations and iRECIST process is provided in Appendix 12.3, with additional details in the iRECIST publication (Seymour et al, 2017). A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 4 and illustrated as a flowchart in Figure 2.

Table 4: Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.
Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the central imaging vendor, but no rapid review will occur.

Figure 2: Imaging and Treatment after First Radiologic Evidence of Progressive Disease



6.3. Post-Treatment Follow-up and Mortality Assessments

Upon discontinuation of study drugs, all participants will enter the Clinical/Safety Follow-up period once the decision is made to discontinue the participant from treatment (eg, at EOT). The EOT visit will be the most recent on-treatment visit (with all available safety and response data) and will be considered the start of the Week 1 Clinical/Safety Follow-up visit. Participants who discontinue the treatment phase will enter the Clinical/Safety Follow-up period. Participants must be followed for at least 100 days (representing approximately 5 half-lives for DKN-01) after the last dose of study drug. Follow-up visits should occur at Days 30, 60, and 100 (±10 days) after the last dose of study drug or should coincide with the date of discontinuation (±10 days) if date of discontinuation is greater than 30 days after the last dose of study drug to monitor for AEs. All patients will be required to complete 3 Clinical/Safety Follow-up visits regardless of whether they start new anti-cancer therapy, except those patients who withdraw consent for study participation.

After completion of the Clinical/Safety Follow-up period, all participants will then enter the Survival/Long-term Follow-up period. During this period, clinic visits or telephone contact every 3 months will be performed to assess survival status. The duration of the Survival/Long-term Follow-up period will be approximately 2 years following the first dose of study drug, and a minimum of 12 months following the last dose of study drug. After completion of the Safety Follow-up period, participants who discontinue study with ongoing SD, PR, or CR at the EOT visit will enter the Response Follow-up period. These periods will occur simultaneously with the Survival Follow-up period for mentioned participants. These participants will continue to have tumor radiological and clinical tumor assessments every 3 months (every 12 weeks) during

the Response Follow-up period or until disease progression or withdrawal of study or initiation of a new systemic anti-cancer therapy. Radiological tumor assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the survival phase of the study.

6.4. Pharmacodynamics

Blood sample collection for pharmacodynamic studies will be mandatory and will be collected at the Screening visit and at Days 1 and 15 of each cycle and at the EOT visit. Mandatory pre-treatment, on-treatment, and progression tumor samples will also be utilized for pharmacodynamic analysis.

6.5. Immunogenicity

6.5.1. Immunogenicity in Blood

Blood samples will be drawn for assessment of DKN-01 anti-drug antibodies (ADA) as per the Schedule of Events. Immunogenicity blood samples will be assayed for ADA using a validated assay. The testing process will follow a tiered approach of screening, confirmation, and titer determination. Details regarding the collection, processing, storage, and shipping of the blood samples will be provided in the Laboratory Manual to maintain sample integrity. Any deviations from the processing steps (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the Sponsor. On a case by case basis, the Sponsor may make a determination as to whether sample integrity has been compromised. Any deviation from the specified sample handling procedure resulted in compromised sample integrity, will be considered a protocol deviation.

6.5.2. Tumor Biopsy Samples

6.5.2.1. Tumor biopsy for DKK1 Testing

Retrospective correlation of anti-tumor activity with tumoral DKK1 expression is a key secondary endpoint of this study. Submission of a tumor sample (archival or fresh) is recommended but not required. Tumor samples will be tested for DKK1 expression but neither the sample submission nor the results of said testing are required for protocol eligibility. Archival tumor tissue can be from a biopsy/surgery performed within 5 years prior to study enrollment. Provision of a formalin-fixed paraffin–embedded (FFPE) tumor tissue block, or of at least 15 unstained slides (if the block cannot be submitted due to documented local/institutional regulations) can be submitted.

Patients in Dose Expansion Cohort 1B can have their fresh biopsy from a locally recurrent or metastatic tumor site amenable to biopsy that is not the only RECIST v1.1 target lesion. Patients in Dose escalation Cohort 1A and 2A and Dose expansion Cohort 2B can have their fresh biopsy from any locally recurrent or metastatic tumor site amenable to biopsy regardless of whether this site is the only RECIST v1.1 target lesion. A core biopsy, using a minimum 18-gauge needle should be performed, in order to maximize the quality and value of obtained tissue. A minimum of 3 separate cores are requested for each biopsy procedure. Tumor tissue from soft tissue or effusion cytologic sampling (fine needle aspiration provided as an FFPE cell pellet material) can be submitted, however, we recommend an FFPE tumor tissue block to maximize the chance of identifying DKK1 positive cells. If a block cannot be provided due to

documented local/institutional regulations, at least 15 unstained slides are required. Bone biopsy material is acceptable provided that a gentle decalcification protocol was used. Bone core biopsy or bone fine needle aspiration provided as an FFPE cell pellet material (preferred) can be submitted.

6.5.2.2. Tumor Biopsy for Exploratory Studies

Archival tumor tissue samples and tissue from biopsies of the primary and/or metastatic lesions will be used to analyze candidate DNA, RNA, or protein markers, or a relevant signature of markers, for their ability to identify those patients who are most likely to benefit from treatment. On-treatment tumor biopsies are encouraged and tumor tissue is requested for those patients who undergo a biopsy or tumor resection as part of routine clinical care at any time during the treatment period. For patients on the combination arm, this biopsy can be obtained from C2D15 through C3D1 or C3D15 through C4D1 at the discretion of the treating investigator and after consideration of the risk of neutropenia related to docetaxel. Patients on monotherapy arms can have their biopsy at any point in C2 or C3 at the discretion of the treating investigator. Every effort should be made to perform a tumor biopsy at the time of iRECIST or PCWG3 confirmed disease progression if a patient discontinues study treatment due to disease progression, except in instances where the procedure poses an unacceptable risk to patients in the clinical research setting. A 14-day window from the EOT visit is permitted. Candidate markers of interest include, but may not be limited to:

- Abundance and enrichment of infiltrating CD8+ T cells, CD4+ T cells, granulocytic and monocyte myeloid-derived suppressor cells, NK cells, Regulatory T cells, and Monocyte-derived cells as determined by flow cytometry from peripheral blood and immunohistochemistry (IHC)/immunofixation of FFPE.
- Inhibitory ligand and co-receptor expression on tumor and infiltrating immune cells measured by IHC.
- Expression of genes associated with active antitumor immunity.
- Frequency and diversity of different TCR sequences.
- Expression of genes associated with activated Wnt signaling
- Expression of genes associated with basal-type prostate cancer
- Neutrophil/lymphocyte ratio

7. ADVERSE EVENTS

7.1. Definitions, Documentation, and Reporting

7.1.1. Adverse Event Definition

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (eg, off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

The Investigator is required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safety of the drug under investigation.

In addition to collecting the AE verbatim and the NCI CTCAE severity grade, AE verbatim text will also be mapped by the Sponsor or designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA).

Cases of pregnancy that occur during paternal exposures to study drug should be reported. Data on fetal outcome are collected for regulatory reporting and drug safety evaluation.

7.1.2. Serious Adverse Event Definition

An AE is considered to be serious if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes:

- Death.
- Life-threatening. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- In-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (eg, surgery performed earlier than planned).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. 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 in-patient hospitalization, or the development of drug dependency or drug abuse.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or elective procedures for underlying preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs.

7.1.2.1. Reporting of Pregnancy to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of Investigators or their designees to report any pregnancy (spontaneously reported to them) that occurs during the study.

Pregnancies that occur after the consent form is signed but before treatment allocation must be reported by the Investigator if they cause the patient to be excluded from the study, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies that occur from the time of treatment allocation through 6 months following cessation of study treatment, or 30 days following cessation of treatment if the patient initiates new anticancer therapy, whichever is earlier, must be reported by the Investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor (see Section 7.2).

7.2. Procedures for Recording and Reporting AEs and SAEs

Each patient must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (eg, "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, patient diaries, and spontaneous reports from patients.

All AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate page of the eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the appropriate pages of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Study site personnel must alert the Sponsor or its designee, the PI and Data Safety Monitoring Committee (DSMC) if meeting the requirements for expedited reporting of any SAE within 24 hours of Investigator awareness of the event via a Sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific SAE forms. The AEs which are serious and unexpected, and assessed as at least possibly related to study drug (possibly or related) will be reported to the regulatory authority by the Sponsor, or it's designee in accordance with 21 CFR § 312.32. Patients will be monitored for AEs and concomitant medications starting 14 days prior to C1D1 to 30 days after the last dose of DKN-01. Only SAEs that develop from C1D1 and onwards need to be reported..

All SAEs that occur during the course of the study (starting C1D1) must be reported by the Investigator within 24 hours from the point in time when the Investigator becomes aware of the SAE (Contact information will be provided by the Sponsor or its designee).

Within 24 hours of the event, the Serious Adverse Event Form must be emailed to NYUPCCsafetyreports@nyulangone.org whether full information regarding the event is known or not. Additional follow-up by the Investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

All SAEs must be reported whether or not considered causally related to the study drug. SAE forms will be completed and the information collected will include patient number, a narrative description of the event and an assessment by the Investigator as to the intensity of the event and relatedness to study drug. Follow-up information on the SAE may be requested by the Sponsor or designee.

Certain SAEs require expedited reporting to regulatory authorities and Institutional Review Boards (IRB). If there are serious, unexpected adverse drug experiences associated with the use of the study drug, the Sponsor or designee will notify the appropriate regulatory agency(ies) and all participating Investigators on an expedited basis. It is the responsibility of the Investigator to promptly notify the IRB/IEC of all unexpected serious adverse drug experiences associated with the use of the study drug.

For both serious and non-serious AEs, the Investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Intensity of all AEs, including clinically significant treatment-emergent laboratory abnormalities and potential systemic reactions, will be graded according to the NCI CTCAE, version 5.0 (available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf). For AEs without matching terminology within the NCI CTCAE, version 5, criteria, the Investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event. Note that both CTCAE term (actual or coded) and severity grade must be selected by study site personnel and collected in the eCRF. This collection is in addition to verbatim text used to describe the AE.

The CTCAE grade refers to the severity of the AE and ranges from Grade 1 (mild AE), Grade 2 (moderate AE), Grade 3 (severe AE) and Grade 4 (life-threatening or disabling AE) to Grade 5 (death related to AE).

AEs not listed by the CTCAE will be graded as follows:

- **Mild**: discomfort noticed but no disruption of normal daily activity.
- **Moderate**: discomfort sufficient to reduce or affect daily activity.
- **Severe**: inability to work or perform normal daily activity.
- **Life threatening**: represents an immediate threat to life.
- **Death**

Relationship to study drug administration will be determined by the Investigator according to the following criteria.

- **Not Related**: No relationship can be established between the event and the administration of study drug. The event is related to other etiologies, such as concomitant medications or patient's clinical state.
- **Possible**: A reaction that follows a plausible temporal sequence from administration of the study drug and follows a pattern to the suspected study drug. The event recurs on re-challenge. The event is not commonly associated with drug exposure but is also uncommon in the patient population. The reaction might have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- **Related**: A reaction that is known to be strongly associated with drug exposure. A temporal relationship can be established between the administration of study drug and the event. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.

For the purpose of safety analyses, all AEs that are classified as having a possible or related relationship to study drug will be considered treatment-related events.

SAEs occurring after a patient has received the study drug will be collected for 30 days after the last dose of study drug, regardless of the Investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the Investigator feels the events were related to either the study drug or a protocol procedure.

PD will be documented in the eCRF intended to capture tumor response and PD, and will be analyzed accordingly. Signs and symptoms related to PD should be reported in the appropriate eCRF as either an AE or SAE. Verbatim terms such as "disease progression" or "progressive disease" etc. should not be reported as AEs or SAEs unless the Investigator considers the progression to be atypical, accelerated or caused by the study drug. Similarly, for deaths occurring as a result of PD during the study or until 30 days after the last dose of study drug is administered, the sign or symptom with an outcome of death should be reported on the AE and SAE pages: the verbatim term of "death" should not be used on the AE or SAE forms as the event. Additional information pertaining to the death should be reported on the eCRF intended to capture death information.

7.3. Monitoring of Adverse Events and Period of Observation

AEs and SAEs will be recorded starting at the time of patient consent up to and including 100 days after administration of the last dose of DKN-01. In the event that the patient starts a new treatment after discontinuation of DKN-01 and within the 100-day clinical/safety follow-up period, only treatment-related AEs will need to be followed. All AEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Any SAE that occurs at any time after end of treatment procedures are performed, which the Investigator considers to be related to study drug, must be reported to the Sponsor or designee.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to the Sponsor or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

All AEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Patients will be evaluated for AEs at each visit. Each patient will be instructed to call his or her physician to report any AEs between visits. Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures will be reported to the Sponsor or designee. Any clinically significant findings from ECGs, laboratory, or vital sign measurements that result in a diagnosis should be reported to the Sponsor or its designee. Investigators will be instructed to report to the Sponsor or its designee their assessment of the potential relatedness of each AE to protocol procedure, study drug, and/or drug delivery system via designated data transmission methods.

7.1. Reporting Procedures – Notifying the FDA

The Sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as Investigational New Drug Application (IND)/Investigational Device Exemption (IDE) safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- **Within 7 calendar days** (via telephone or facsimile report)

  Any study event that is:

  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening

- Within 15 calendar days (via written report)

  Any study event that is:

  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening

  or

  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

- Any finding from tests in laboratory animals that:
  - suggest a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity.

7.2. Reporting Procedures – Participating Investigators

For multi-center clinical studies, in addition to reporting certain unanticipated problems and adverse events noted above to the FDA, it is the responsibility of the study Sponsor to report those same adverse events or findings to participating investigators.

The Investigator shall maintain a copy of the Medical Events Form on file at the study site. All report forms must be signed and dated by the PI. If the PI is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the PI, whom sign/date initial report upon return.

Report to:

Email: NYUPCCsafetyreports@nyulangone.org

Telephone: (212) 273-2748

AND

David R. Wise, MD, PhD
160 E. 34th Street, Suite 1009
New York, NY 10016
Phone: 212-731-6366
Email: David.Wise@nyulangone.org

Events of Clinical Interest (any medical event that is deemed significant via PI's expertise, but does not apply to SAE categories) will be reported within 2-5 days, or as per study Sponsor specifications.

7.1. Safety Oversight

It is the responsibility of the PI to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan.

Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the New York University (NYU) Clinical Trials Office (CTO).

All Internal SAEs reported by the CTO, occurring to patients on clinical studies that are not monitored by any other institution or agency, are reported via email to the NYUPCCsafetyreports@nyulangone.org and reviewed within 24 hours by the DSMC. Based on the review, one of three determinations will be made:

- SAE report is considered to be adequate
- Queries for clarification to PI regarding treatment attribution and/or resolution of SAE or completeness of other information. The committee may request a cumulative review of all SAEs on the study to date.
- Request for full DSMC committee review of protocol at the next scheduled meeting.

The DSMC Coordinator will record the committee's decision and incorporate it into the study summary for the next protocol review.

7.2. Data and Safety Monitoring Plan (DSMP)

This Investigator-initiated study will be monitored by the DSMC of the NYU Perlmutter Cancer Center (PCC). The DSMC operates based on the NCI approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical studies) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for clinical studies conducted in the NYULH Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULH PCC.

Per the NYU PCC Institutional Data Safety and Monitoring Plan, this phase Ib/ II study will be monitored by DSMC at least quarterly, (from the date the first patient is enrolled), subsequent cohort activation, and at the completion of the study prior to study closure. This review includes accrual data, patient demographics, and AEs. Accrual to the next dose level cohort or expansion cohort will be held until real-time review of the toxicity from the prior cohort has occurred to assure no defined DLTs have occurred prior to proceeding to the next level or expanding the current cohort. PIs are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, Investigator-identified issues, external information, etc. The DSMC will review safety data every 3 months.

NYU CTO oversight responsibilities:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Provide study accrual progress, safety information and data summary reports to the Sponsor-Investigator (David Wise, MD PhD) and NYU PCC DSMC.

Documentation of DSMC reviews will be provided to the Sponsor-Investigator. Issues of immediate concern by the DSMC will be brought to the attention of the Sponsor-Investigator and other regulatory bodies as appropriate. The Sponsor-Investigator will address the DSMC's concerns.

Other external sites will be monitored and informed of other AEs by the DSMC within 7 days of toxicities and within 3 business days of SAE. Scheduled conference calls will be conducted after 3 patients are enrolled. Additional conference calls will be scheduled as indicated based on the recommendations from the DSMC and the PI of the study.

7.3. Study Monitoring Plan

This study will be monitored according to the monitoring plan detailed below. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit. At each visit, the monitor will review various aspects of the study including, but not limited to: compliance with the protocol and study manual and with the principles of GCP; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the Investigator and the investigational site staff must be available in order to discuss the progress of the study, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other study-related inquiries of the monitor. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other study-related inquiries will occur throughout the course of the study through regular communication with the NYU CTO monitoring study team and review/entry of data into the electronic study database.

7.3.1. Subsite Monitoring

Monitoring visits are done remotely unless otherwise specified, via remote electronic medical record access. If not possible, secure email exchange will be utilized. The quality assurance specialist will confirm an upcoming monitoring visit with a Subsite Investigator and staff. If remote EMR access is not available, then the Subsite Coordinator will ensure that all source documents for patients are de-identified and labeled only with the patient ID number(s), and emails all requested documents to the quality assurance specialist by the specified visit date. All documents are reviewed and a monitoring report is submitted within 5 business days from the date of the visit. Any outstanding documents will be listed in the report as a high-priority

request for the next monitoring visit. It is expected that response to data clarification requests and other study-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database. Continued non-compliance and failure to submit documentation will result in the suspension of patient enrollment at the site, until the documents have been received.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The Investigator must promptly inform NYU CTO of any audit requests by health authorities, and NYU CTO will provide Sponsor-Investigator and Leap Therapeutics with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

At the NYULH Perlmutter Cancer Center, all Investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and study conduct for this study occurs at several levels:

1. PI: AEs are evaluated monthly by the PI in conjunction with the research nurses, data manager, and research team.
2. DSMC, quarterly.
3. IRB: An annual report to the IRB is submitted by the study PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of patients as well as available research data.
4. In addition, the quality assurance unit will monitor this study every 4-6 weeks, this includes real-time review of all eCRFs to ensure completeness and to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH GCP guidelines. Additionally, a first patient audit is to be conducted within four weeks of enrollment.

7.4. Data Quality Oversight Activities

Remote validation of electronic data capture (EDC) system data will be completed on a continual basis throughout the life cycle of the study. Automated edit check listings will be used to generate queries in the EDC system and transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

The study site may also be subject to quality assurance audit by Leap Therapeutics or its designee as well as inspection by appropriate regulatory agencies.

7.5. Onsite Monitoring

There will be at least one routine visit per site per year for sites that have accrued. Additional for cause visits may occur as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the Investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The Investigator and institution guarantee access to source documents by NYU CTO or its designee.

7.6. Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act and the Food and Drug Administration Amendments Act, the Sponsor-Investigator of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. The Sponsor-Investigator has delegated responsibility to NYU CTO for registering the study and posting the results on clinicaltrials.gov. Information posted will allow patients to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

8. STATISTICAL CONSIDERATIONS

8.1. Sample Size Determination

A standard 3 + 3 design will be used for the dose escalation cohorts with up to 6 patients tested per dose level for a total of up to 12 patients per cohort.

Simon's two-stage design (Simon, 1989) will be used to evaluate Dose Expansion Cohorts 1B. The null hypothesis that the true response rate is 0.2 will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 4 or fewer responses in these 18 patients, the study will be terminated. Otherwise, an additional 15 patients will be accrued for a total of 33. The null hypothesis will be rejected if 11 or more responses are observed in 33 patients. This design yields a Type I error rate of 0.05 and a power of 0.8 when the true response rate is 0.4.

Simon's two-stage design (Simon, 1989) will be used to evaluate Dose Expansion Cohorts 2B. The null hypothesis that the true response rate is 0.05 will be tested against a one-sided alternative. In the first stage, 13 patients will be accrued. If there are 0 responses in these 13 patients, the study will be stopped. Otherwise, 14 additional patients will be accrued for a total of 27. The null hypothesis will be rejected if 4 or more responses are observed in 27 patients. This design yields a type I error rate of 0.05 and a power of 0.8 when the true response rate is 0.2.

8.2. Randomization

No randomization will take place as part of this study.

8.3. Populations for Analysis

The following populations will be used for analysis:

- Evaluable analysis set (EAS): All evaluable patients, i.e., patients who received any amount of DKN-01 and have at least one evaluable post-baseline tumor response assessment or who discontinued treatment due to death, toxicity, or clinical progression. All primary analyses of ORR, PFS, OS, DoR, PSA response rate, and time to response, OS will use the EAS. This set will also support analysis of tumor-related endpoints, and exploratory endpoints.
- Safety population: All enrolled patients who receive any amount of study treatment (DKN-01 or docetaxel). All safety analyses will be based on this population.
- A per-protocol (PP) subset may also be used for secondary analysis of select efficacy endpoints and will be based on study drug exposure (compliance and/or time on study drug) and major protocol deviations. The criteria for inclusion in the PP subset will be finalized and documented. The PP set will be defined and finalized separately for each group.
- PK analysis set: The PK analysis set includes all patients in the safety analysis set who have at least one PK assessment.

- Pharmacodynamic/Biomarker analysis set: The biomarker analysis set includes all patients in the safety analysis set who have at least one screening biomarker assessment. Analysis sets will be defined separately for blood-based and tumor tissue-based biomarkers.

8.4. Procedures for Handling Missing, Unused and Spurious Data

The procedures for handling missing, unused, or spurious data, along with the detailed method for analysis of each variable, transformations, and exploratory analyses will be presented in the statistical Analysis Plan (SAP).

8.5. Interim Analyses

Independent interim efficacy analysis will be carried out for Cohorts 1B in the dose expansion phase. If there are 4 or fewer responses in the first 18 patients accrued, the study will be terminated. Enrollment to the study to Cohorts 1B will be on hold during the interim efficacy analysis. Enrollment to the study on Cohort 2A and 2B will continue during the interim analysis.

An interim analysis will be carried out after 13 patients are be accrued in Cohort 2B. If there are 0 responses in these 13 patients, the study will be stopped. Enrollment to Cohort 2B will be on hold during the interim efficacy analysis. Enrollment to Cohort 1B will continue during this interim analysis.

8.6. Statistical Methods

A 3 + 3 strategy will be employed for the dose escalation phase. A Simon's 2-stage design will be used for dose expansion Cohorts 1B and 2B.

8.6.1. General Methods

Descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables. Frequency distributions (counts and associated percentages) will be presented for categorical variables. Median, 25^{th} and 75^{th} percentiles and standard error will be presented for time-to-event data.

This study is descriptive in nature; no formal comparisons between groups will be performed. All CIs will be 95%, unless stated otherwise.

Individual patient data listings will be provided to support summary tables.

The effects of noncompliance, treatment discontinuations, premature study withdrawals, subsequent therapies, and covariates will be assessed to determine the impact on the general applicability of results from this study.

8.6.2. Disposition of Patients

All patient discontinuations will be documented, and the extent of each patient's participation in the study will be reported. If known, a reason for their discontinuation will be given. The following information will be summarized:

- Number enrolled
- Number receiving treatment

- Number and percentage who completed the protocol
- Number and percentage of patients who discontinued treatment
- Reason for discontinuation

8.6.3. Baseline Characteristics

Patient characteristics will include a summary/listing of the following:

- Patient demographics
- Baseline disease characteristics
- Prior disease-related therapies
- Concomitant medications

Other patient characteristics will be summarized as deemed appropriate.

8.6.4. Efficacy Analysis

8.6.4.1. Primary Efficacy Endpoint and Analysis

The primary endpoint for Dose Expansion Cohort 1B is OR rate. OR is defined as the proportion of patients with a best overall soft tissue response of CR or PR per iRECIST from the first dose of study treatment until disease progression or death due to any cause. Soft tissue responses will be confirmed by a follow-up radiographic assessment at least 4 weeks later with a repeated CT or MRI with no evidence of confirmed bone disease progression per PCWG3 criteria by Investigator. The radiographic assessment of soft tissue disease will use iRECIST, and bone disease will be evaluated per PCWG3.

A secondary endpoint for Dose Expansion Cohort 2B is composite OR rate defined as the number of patients with a reduction of PSA by ≥50% relative to baseline or conversion of CTC from unfavorable ≥5 to 4 or fewer CTC per 7.5 mL or iRECIST soft tissue response.

8.6.4.2. Secondary Efficacy Endpoints and Analysis

Secondary efficacy variables in the study include:

- TTR is defined as the time from the first dose of study treatment to the first objective evidence of soft tissue response with no evidence of confirmed bone disease progression on bone scan per PCWG3. Soft tissue response is defined as a BOR of CR or PR as assessed by Investigator using iRECIST. The response must be confirmed at least 4 weeks later with a repeated CT/MRI.
- DR is defined for patients with confirmed objective response (CR or PR) as the time from the first objective evidence of soft tissue response (subsequently confirmed) as assessed by Investigator iRECIST and no evidence of confirmed bone disease progression by PCWG3 to the first time of objective evidence of radiographic progression or death due to any cause, whichever occurs first. Radiographic progression is defined as soft tissue progression as assessed by Investigator using iRECIST or bone disease progression as assessed by Investigator using PCWG3.

- PFS is defined as the time from the first dose of study treatment to documentation of radiographic progression in soft tissue as assessed by Investigator using iRECIST (see Appendix 12.3), in bone as assessed by Investigator using PCWG3 (see Appendix 12.7), or death, whichever occurs first.
- PSA response is defined as the proportion of patients with confirmed PSA decline ≥50% compared to baseline. PSA response will be calculated as a decline from baseline PSA (ng/mL) to the maximal PSA response with a threshold of 50%. A PSA response must be confirmed by a second consecutive value at least 3 weeks later. The proportion of patients with confirmed PSA decline ≥50% compared with baseline will be calculated along with the 90% and 95% CIs. Percentage change in PSA from baseline to 12 weeks post-treatment and maximal decline in PSA after treatment initiation will also be calculated and displayed as a waterfall plot as per PCWG3 guidelines.
- Time to PSA progression for patients with metastatic CRPC is defined as the time from the first dose to the date that a ≥25% increase in PSA with an absolute increase of ≥2 µg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline) is documented, confirmed by a second consecutive PSA value obtained ≥3 weeks (21 days) later. Details associated with censoring will be presented in the SAP.
- OS is defined as the time from the first dose of study treatment to the date of death. Patients without an event (death) will be censored at the date of last contact.
- TTR will be summarized using simple descriptive statistics (eg, median and range). DR, PFS, time to PSA progression and OS will be analyzed using Kaplan Meier methods and descriptive statistics. Point estimates will be presented with their 90% and 95% CIs.
- CTC conversion from unfavorable (5 or greater CTC/7.5 mL) to favorable (4 or fewer CTC/7.5 mL).
- CTC ≥1 per 7.5 mL at baseline and 0 CTC per 7.5 mL at 13 weeks (CTC0) will be calculated.

8.6.5. Safety Analysis

All analysis of safety and toxicity will be conducted in the safety population.

AE terms and severity grades will be assigned by the Investigator using the NCI CTCAE, version 5.0. Safety parameters will be listed and summarized using standard descriptive statistics.

Analyses will be conducted to characterize the safety and tolerability of DKN-01.

Safety analyses will include presentations of the following:

- DLTs
- TEAEs, including severity and possible relationship to study drug
- Dose adjustments
- Laboratory values
- Vital signs
- ECOG performance status

- Physical examinations
- ECG readings
- Infusion-related reactions
- Concomitant medication

8.6.5.1. Study Drug Exposure

Descriptive statistics of the amount of each drug, the number of infusions administered, and compliance will be tabulated, along with information on missed doses, dosing delays, and dose reductions.

8.6.5.2. Adverse Events

AEs will be coded using the current MedDRA dictionary.

Analyses of AEs will be performed for those events that are considered treatment-emergent, where a TEAE is defined as any AE with onset or (worsening of a pre-existing condition) after the first dose of study drug through 100 days following the last dose of study drug. AEs with partial dates will be assessed using the available date information to determine if treatment-emergent; AEs with completely missing dates will be assumed to be treatment-emergent.

TEAEs, TEAEs leading to study drug discontinuation, TEAEs leading to dose reduction/interruption, TEAEs related to study drug, SAEs, TEAEs leading to study drug discontinuation, and TEAEs with an outcome of death will be summarized by system organ class, and preferred term. A summary of TEAEs of CTCAE Grade 3 or higher, will also be provided. The number and percent of patients with infusion-related reactions and immune-reactions will be summarized, overall and by visit.

No formal hypothesis-testing analysis of TEAE incidence rates will be performed. All TEAEs occurring on-study will be listed in patient data listings. By-patient listings also will be provided for the following: patient deaths, SAEs, TEAEs leading to study drug discontinuation, and TEAEs with intensity ≥Grade 3.

8.6.5.3. Clinical Laboratory Data

Clinical laboratory values will be summarized in SI units (Système Internationale d'Unités; International System of Units).

The actual value and change from baseline to each on-study evaluation will be summarized for each clinical laboratory parameter, including hematology and clinical chemistry. Summaries will be presented. In the event of multiple evaluations for the same parameter at the same visit, the last non-missing value per study day/time will be used.

Shift tables that present changes from baseline to worst on-study values relative to NCI CTCAE classification ranges and incidence of treatment-emergent Grade 3 / 4 clinical laboratory abnormalities will be presented.

All laboratory data will be provided in data listings. A subset listing will be presented for all clinically significant abnormal laboratory values.

8.6.5.4. Other Safety Parameters

Safety will be evaluated by assessment of adverse events, physical examination, ECOG PS, vital signs, ECG, clinical and laboratory values.

8.6.6. Analysis of Exploratory Endpoints

- Flow cytometry-based intratumoral and peripheral immunoprofiling will be carried out in the immune monitoring core facility at Perlmutter cancer center at NYU Langone and will be used to compare the effect of the DKN-01 as monotherapy and in combination with docetaxel on the abundance and activation of the immune cell repertoire enriched in the tumor.
- PK levels of DKN-01 as monotherapy and in combination with docetaxel.
- Concordance analysis of plasma DKK1 and tumoral DKK1
- Pre-treatment, on-treatment, and time-of-progression assessment of peripheral and intratumoral immune cell abundance and activation
- Viability of pre-treatment patient-derived 3D organotypic cultures incubated with DKN-01 and docetaxel
- Immune cell abundance and activation of pre-treatment patient-derived 3D organotypic cultures incubated with DKN-01 and docetaxel.
- Overall response stratified by “PSA-high” (concordant radiographic and PSA progression) and “PSA-low” (radiographic evidence in the absence of PSA progression) prostate cancer status.

8.6.7. Procedures for Reporting Deviations to the Original Statistical Analysis Plan

All deviations from the original SAP will be provided in the final clinical study report.

9. ADMINISTRATIVE REQUIREMENTS

9.1. Good Clinical Practice

The study will be conducted in accordance with ICH GCP and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

9.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see Appendix 12.6). The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

9.3. Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

9.3.1. Consent Procedures and Documentation

The consenting process and documentation will follow Standard Operating Procedures (Obtaining Informed Consent for Clinical Trials) of the NYULH PCC CTO.

9.3.1.1. Informed Consent

A participating Investigator who has completed requisite training for human patient research and has been instructed by the PI about the potential participant; also must address any questions/concerns prior to obtaining written informed consent for participation and HIPAA authorization can also obtain consent.

Patients will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, or qualified research study team member all of whom have completed requisite training for human patient research. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

The Investigator will explain to each potential participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved,

potential compensation and or costs incurred by the patient and any discomfort this study may entail. This informed consent should be given by means of standard written statement, written in non-technical language. All patients will be required to sign a written informed consent prior to being registered on this study. No patient can enter the study before his/her informed consent has been obtained. Every effort will be made to answer questions raised by patients and their families or advocates regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

The informed consent form is considered to be part of the protocol, and must be submitted by the Investigator with it for IRB approval.

For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYU Langone Health PCC CTO guidelines and policies.

For patients who cannot read. A witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The Investigator will ask the patient questions to ensure s/he understands the study. If the Investigator determines the patient understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

9.3.1.2. Documentation of Consent

The PI or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the patient's medical chart.

9.3.2. Registration Procedures

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULH PCC Clinical Trials Office. The following materials must be submitted to the CTO for patient registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated eligibility checklist
3. All supporting documentation verifying each eligibility criterion has been met

Registration will occur within 48 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be disbursed to the study team upon registration.

Once eligibility is verified, a unique patient study number will be issued within 24 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered accrued on study.

9.3.3. Multi-Site Surveillance

As the lead investigator in a multi-site study, the PI is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall study's quarterly Data and Safety Monitoring report to the DSMC to include minutes from monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC's quarterly reviews to their IRB of record at the time of continuing review. Additionally, the NYU Langone Health PPC CTO, Quality Assurance Unit will provide a remote interim monitoring visit, beginning within the first 6-8 weeks of the first patient enrollment and every 6-8 weeks thereafter to ensure completeness, accuracy and consistency of the data.

9.3.4. Patient Registrations at Additional Sites

Enrollment at addition sites can begin once each site's IRB has approved this protocol, a copy of each site's IRB approval, collaborative institutional training initiative (CITI) training certificates, Medical Licenses and signed curricula vitae are provided to NYU Langone Health PCC CTO. Once, all required documents are provided to NYU Clinical Trials Office an activation notification will be sent to the PI and research coordinator of that site. Central registration for this study will take place at NYU Langone Health PCC Quality Assurance Unit (PCC-QAU@nyulangone.org).

Each patient must sign and date an informed consent form before undergoing any study specific procedures unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYU Langone Health PCC Quality Assurance Unit and forward a copy of the signed consent to NYU Langone Health PCC CTO within 24 hours.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU Langone Health PCC CTO. The following materials must be submitted to the Quality Assurance Unit at NYU Langone Health via email (PCC-QAU@nyulangone.org):

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met.

Registration will occur once the Senior Research Nurse for Quality Assurance conducts a central review of the submitted materials. Once eligibility is verified, a unique patient study number will be issued within 48 hours of receiving all required registration material. This number is unique to the participant and must be written on all data and correspondence for the participant. The NYU Langone Health PCC CTO will return a signed eligibility confirmation worksheet email with the patient's unique study number.

The patient will not be identified by name. This is the point, at which, the patient is considered accrued on study. Protocol treatment should begin within designated timeframe; issues that

would cause treatment delays should be discussed with the overall PI, Dr. Wise. All screen failures/ineligible patients, as well as patient's who withdraw consent prior to initiation of protocol therapy must be submitted to the CTO in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

Patients must not start any protocol procedures prior to registration; each participating institution will order the study agent directly from the supplier.

Each site is responsible for reporting all unexpected problems involving risks to participants or others to NYU Langone PCC Clinical Trials Office and to their IRB as per site institutional policy. Please email all SAEs to NYUPCCsafetyreports@nyulangone.org, Dr. Wise, and the NYU Langone Health CTO regulatory specialist.

9.4. Patient Confidentiality

In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9.5. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor, and given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The Sponsor will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the Sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the eCRF and source documentation.

9.6. Direct Access to Source Data

The NYU CTO will serve as the Clinical Research Organization for this study. TrialMaster, an electronic database capture system will be created to record the data for this study. Research coordinators will input clinical study data into the database. This database is password protected and only the PI, assigned study team members, and CTO personnel will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data requested in the system must be reported. All missing data

must be explained. The quality assurance specialists will monitor this study every 4-6 weeks for data entry accuracy. All data will be collected and entered into the EDC system by study site personnel from participating institutions.

Monitoring and auditing procedures developed by the Sponsor or designee will be followed, in order to comply with GCP guidelines.

The study will be monitored by the Sponsor or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) and will include on-site review of the eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, and fax).

All unused study drug and other study materials are to be returned to the Sponsor after the clinical phase of the study has been completed or, if authorized, disposed of at the study site and documented (see Section 5.7).

Regulatory authorities, the IEC/IRB, and/or the clinical quality assurance group of the Sponsor or designee may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

9.7. Case Report Form Completion

The Sponsor or its designee will provide the study sites with an eCRF that will be completed for each study patient.

It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's eCRF. Source documentation supporting the eCRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, adverse events, and patient status.

The Investigator, or designated representative, should complete the eCRF pages as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the eCRF to endorse the recorded data.

9.8. Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

9.9. Liability and Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

9.10. Publication of Study Findings and Use of Information

All information regarding DKN-01 supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. The Investigator is obligated to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of DKN-01 and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee, comprised of investigators participating in the study and representatives from the Sponsor, as appropriate, will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual investigators may publish results from the study in compliance with their agreement with the Sponsor. A pre-publication manuscript is to be provided to the Sponsor at least 30 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company-prepared manuscript to the investigators for review at least 30 days prior to submission to a publisher.

9.11. Research Use of Stored Human Samples, Specimens, or Data

- Intended Use: Samples and data collected under this protocol will be stored indefinitely for future cancer research. No germline genetic testing will be performed.
- Storage: Access to stored samples will be limited using password-protected computers. Only investigators will have access to the samples and data.
  - Disposition at the completion of the study: All stored samples will be archived through the NYU Center for Biospecimen Research and Development for indefinite storage. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

9.12. Future Use of Stored Specimens

Data collected for this study will be analyzed and stored at the NYU CTO Coordinating Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Perlmutter Cancer Center under the supervision of David Wise for use by other researchers including those outside of the study. Permission to transmit data to the Perlmutter Cancer Center will be included in the informed consent.

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored indefinitely at the NYU Center for Biospecimen Research and Development

(CBRD) with the same goal as the sharing of data. The storage of these samples for future research will be optional for participants. For participants who consent to the storage of their samples for future research, these samples could be used for research into the causes of cancer, its complications and other conditions for which individuals with cancer are at increased risk, and to improve treatment. The data repository will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to bio-sample storage will not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the Perlmutter Cancer Center.

9.13. Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study. The study leadership in conjunction with the relevant NIH Institute or Center has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit with a Committee-sanctioned conflict management plan that has been reviewed and approved by the Sponsor prior to participation in this study. All NYULH investigators will follow the applicable conflict of interest policies.

11. REFERENCES

Arend, R.C.*, et al.* Safety and efficacy of a DKK1 inhibitor (DKN-01) as monotherapy or in combination with paclitaxel in patients with Wnt activated recurrent gynecologic malignancies. *Gynecologic Oncology* **154**, 34 (2019).

Bluemn EG, Coleman IM, Lucas JM, et al. Androgen Receptor Pathway-Independent Prostate Cancer Is Sustained through FGF Signaling. Cancer Cell 2017;32:474-489.e476.

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0, DCTD, NCI, NIH, DHHS. 2009. Publish date: 28 May 2009.

Chamorro, M.N., et al. FGF-20 and DKK1 are transcriptional targets of β-catenin and FGF-20 is implicated in cancer and development. The EMBO Journal 24, 73-84 (2005).

Clevers H, Loh KM, Nusse R. Stem cell signaling. An integral program for tissue renewal and regeneration: Wnt signaling and stem cell control. Science. 2014;346(6205):1248012.

Clevers H, Nusse R. Wnt/β-catenin signaling and disease. Cell. 2012 Jun 8;149(6):1192-205.

Cockcroft DW, Gault MD. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.

D'Amico L, Mahajan S, Capietto AH, Yang Z, Zamani A, Ricci B, et al. Dickkopf-related protein 1 (Dkk1) regulates the accumulation and function of myeloid derived suppressor cells in cancer. J Exp Med. 2016;213(5):827-40.

de Bono JS, Smith MR2, Saad F, et al. Subsequent Chemotherapy and Treatment Patterns After Abiraterone Acetate in Patients with Metastatic Castration-resistant Prostate Cancer: Post Hoc Analysis of COU-AA-302. Eur Urol 2017;71:656-664.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-247.

Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2017;377(4):352-360.

Gavriatopoulou M, Dimopoulos M-A, Christoulas D, et al. Dickkopf-1: a suitable target for the management of myeloma bone disease. Expert Opin Ther Targets. 2009;13(7):839-848.

Gillessen S, Omlin A, Attard G, et al. Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015. Ann Oncol. 2016 May 2.

Hales RK, Banchereau J, Ribas A, Tarhini AA, Weber JS, Fox BA, Drake CG. Assessing oncologic benefit in clinical trials of immunotherapy agents. Ann Oncol. 2010 Oct;21(10):1944-51.

Hall CL, Zhang H, Baile S, et al. p21(CIP-1/WAF-1) Induction Is Required to Inhibit Prostate Cancer Growth Elicited by Deficient Expression of the Wnt Inhibitor Dickkopf-1 (DKK-1). Cancer Res 2010;70:9916-9926.

Heider U, Kaiser M, Mieth M, et al. Serum concentrations of DKK-1 decrease in patients with multiple myeloma responding to anti-myeloma treatment. Eur J Haematol. 2009;82(1):31-8.

Hiss D. Optimizing molecular-targeted therapies in ovarian cancer: the renewed surge of interest in ovarian cancer biomarkers and cell signaling pathways. J Oncol 2012;2012:737981.

James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. New Engl J Med 2017;377:338-351.

Kimura H, Fumoto K, Shojima K, Nojima S, Osugi Y, Tomihara H, et al. CKAP4 is a Dickkopf1 receptor and is involved in tumor progression. J Clin Invest. 2016;126(7):2689-705.

Krause U, Ryan DM, Clough BH, Gregory CA. An unexpected role for a Wnt-inhibitor: Dickkopf-1 triggers a novel cancer survival mechanism through modulation of aldehyde-dehydrogenase-1 activity. Cell Death Dis. 2014;5:e1093.

Leap Therapeutics, Inc. DKN-Dkk1-P300 study report: A methods study to determine DKK1 levels from healthy subject and cancer patient serum samples [data on file], 2012.

Logan CY, Nusse R. The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol. 2004;20:781-810.

Lorente D, Fizazi K, Sweeney C, de Bono JS. Optimal Treatment Sequence for Metastatic Castration-resistant Prostate Cancer. Eur Urol Focus. 2016;2(5):488-498.

MacDonald BT, Tamai K, He X. Wnt/beta-catenin signaling: components, mechanisms, and diseases. Dev Cell. 2009 Jul;17(1):9-26.

Malladi S, Macalinao DG, Jin X, He L, Basnet H, Zou Y. Metastatic Latency and Immune Evasion through Autocrine Inhibition of WNT. Cell. 2016;165(1):45-60.

Mezynski J, Pezaro C, Bianchini D, et al. Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? Ann Oncol 2012;23:2943-2947.

Niehrs C. Function and biological roles of the Dickkopf family of Wnt modulators. Oncogene. 2006;25(57):7469-81.

Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol. 1982;5:649-655.

Oudard S, Fizazi K, Sengeløv L, et al. Cabazitaxel Versus Docetaxel As First-Line Therapy for Patients With Metastatic Castration-Resistant Prostate Cancer: A Randomized Phase III Trial-FIRSTANA. J Clin Oncol. 2017;35(28):3189-3197.

Pinzone JJ, Hall BM, Thudi NK, et al. The role of Dickkopf-1 in bone development, homeostasis, and disease. Blood. 2009;113:517-525.

Sato N, Yamabuki T, Takano A, et al. Wnt inhibitor Dickkopf-1 as a target for passive cancer immunotherapy. Cancer Res. 2010;70(13):5326-5336.

Scher HI, Morris MJ, Stadler WM, et al. Trial Design and Objectives for Castration-Resistant Prostate Cancer: Updated Recommendations From the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-18.

Sedgwick AE, D'Souza-Schorey C. Wnt Signaling in Cell Motility and Invasion: Drawing Parallels between Development and Cancer. Cancers (Basel). 2016;8(9).

Seymour L, Bogaerts J, Perrone A, et al. iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18(3):e143-e152.

Shi RY, Yang XR, Shen QJ, Yang LX, Xu Y, Qiu SJ, Sun YF, Zhang X, Wang Z, Zhu K, et al. High expression of dickkopf-related protein 1 is related to lymphatic metastasis and indicates poor prognosis in intrahepatic cholangiocarcinoma patients after surgery. Cancer 2013;119:993-1003.

Shizhuo W, Tao J, Shulan Z, Bing Z. The expression and significance of Dickkopf-1 in epithelial ovarian carcinoma. Int J Biol Markers. 2009;24(3):165-70.

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10(1):1-10.

Smadja DM, d'Audigier C, Weiswald LB, Badoual C, Dangles-Marie V, Mauge L, et al. The Wnt antagonist Dickkopf-1 increases endothelial progenitor cell angiogenic potential. Arterioscler Thromb Vasc Biol. 2010;30(12):2544-52.

Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. New Engl J Med 2004;351:1502-1512.

Thudi NK, Martin CK, Murahari S, Shu ST, Lanigan LG, Werbeck JL. Dickkopf-1 (DKK-1) stimulated prostate cancer growth and metastasis and inhibited bone formation in osteoblastic bone metastases. Prostate. 2011;71(6):615-25.

Tung EK, Mak CK, Fatima S, et al. Clinicopathological and prognostic significance of serum and tissue Dickkopf-1 levels in human hepatocellular carcinoma. Liver Int. 2011;31(10):1494-504.

Vallet S, Smith MR, Raje N. Novel bone-targeted strategies in oncology. Clin Cancer Res. 2010;16:4084-4093.

Wang S, Zhang S. Dickkopf-1 is frequently overexpressed in ovarian serous carcinoma and involved in tumor invasion. Clin Exp Metastasis. 2011;28(6):581-91.

Wise, DR., et al. Dickkopf-1 Can Lead to Immune Evasion in Metastatic Castration-Resistant Prostate Cancer. Journal of Clinical Oncology Precision Oncology. 2020 :4, 1167-1179.

Xu WH, Liu ZB, Yang C, Qin W, Shao ZM. Expression of dickkopf-1 and beta-catenin related to the prognosis of breast cancer patients with triple negative phenotype. PLoS One. 2012;7(5):e37624.

Zhang D, Park D, Zhong Y, Lu Y, Rycaj K, Gong S, et at Stem cell and neurogenic gene-expression profiles link prostate basal cells to aggressive prostate cancer. Nature Communications 2016;7:10798.

12. APPENDICES

12.1. Schedule of Assessments

The schedule of study assessments is presented in Table 5.

Table 5 Schedule of Assessments

Activity	Screening		All Cycles		EOT (± 14 days)	Clinical/ Safety Follow-up	Long-term Follow-up
	-28 days of C1D1	-14 days of C1D1	Day 1 (+/- 3 days for Cycle ≥2)	Day 15 (+/-3 days)			
Study team procedures							
[1]**Informed Consent**	X						
[2]**Diagnosis and Staging**	X						
[3]**Medical History and Height**	X						
[4]**Physical Examination**	X		X	X	X	X	
[5]**Vitals signs and ECOG PS**	X		X	X	X	X	

1 Consent. Must be obtained prior to undergoing any study-specific procedure and maybe obtained >28 days prior to enrollment. .

2 Diagnosis and staging to include pathology report and TNM staging.

3 Medical history. Includes oncology history, information on prior regimens (duration of administration, best overall response [BOR] observed, and recurrence date), surgery, and radiation therapy. Includes history of medically significant diseases or injuries (active or resolved) and concomitant illnesses that are not considered to be the disease under study.

4 A complete physical examination will be required during Screening. Abbreviated physical exams are allowed starting C1D1 and at the subsequent designated time points.

5 Vital signs. Record blood pressure, pulse, heart rate, and temperature; weight will be measured Day1 of each cycle. On days when both docetaxel and DKN-01 are infused, one set of vital signs is to be recorded pre-dose. Repeat vital signs, between completion of DKN-01 and administration of docetaxel, are not required.

Activity	Screening		All Cycles		EOT (± 14 days)	Clinical/ Safety Follow-up	Long-term Follow-up
	-28 days of C1D1	-14 days of C1D1	Day 1 (+/- 3 days for Cycle ≥2)	Day 15 (+/-3 days)			
AE and concomitant medications		X	X		X	X[6]	
Review of inclusion/exclusion criteria	X	X					
Laboratory and Safety Assessments							
Electrocardiogram	X						
[7]Chemistries		X	X	X	X	X	
[8]Hematology		X	X	X	X	X	
[9]Serum PSA, CgA, CEA		X	X		X	X	X
Coagulation Studies (PT, PTT, and INR)	X						
Serum 25-hydroxyvitamin D	X						
Serum Testosterone		X					

6 Follow-up visits should occur at Days 30, 60, and 100 (±10 days) after the last dose of study drug or should coincide with the date of discontinuation (±10 days) if date of discontinuation is greater than 30 days after the last dose of study drug to monitor for AEs. If the patient starts a new treatment than only pre-existing treatment-related AEs that started prior the subject enrolling on the new treatment will need to be followed.

7 Chemistries includes a basic metabolic panel (sodium, potassium, chloride, bicarbonate, calcium, creatinine, blood urea nitrogen, and glucose [random]), liver function tests (AST, ALT, total bilirubin, alkaline phosphatase, total protein, and albumin), direct bilirubin, lactate dehydrogenase (LDH), creatine kinase (CK), uric acid, cholesterol, phosphorus, and carbon dioxide.

8 Hematology includes hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume (MCV), mean cell hemoglobin concentration (MVHC), platelets, leukocytes (WBC) and differential [absolute counts of] neutrophils (segmented and banded), lymphocytes, monocytes, eosinophils, and basophils, Neutrophil/lymphocyte ratio (a calculated ratio).

9 (PSA, CgA, and CEA) testing will continue every 3 months (every 12 weeks) until progressive disease (PD), withdrawal from the study, or initiation of new treatment.

Activity	Screening		All Cycles		EOT (± 14 days)	Clinical/ Safety Follow-up	Long-term Follow-up
	-28 days of C1D1	**-14 days of C1D1**	**Day 1 (+/- 3 days for Cycle ≥2)**	**Day 15 (+/-3 days)**			
[10]**Hepatitis B and C Virus Tests**	X						
[11]**Serious adverse event and adverse event review**		X	X	X	X	X	
Disease Assessments							
[12]**Bone Scan and CT Chest, Abdomen, Pelvis**	X				X		X[13]
Specimen Collection							
[14]**Pre-Treatment Tumor Specimen**	X						
[15]**On-Treatment Tumor Biopsy**			X				

10 Includes HBV surface antigen and anti-HCV antibody tests. If anti-HCV antibody test is positive, HCV RNA test must be performed.

11 Patients continuing to experience toxicity following discontinuation of investigational products will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. Only SAEs that begin at C1D1 need to be reported.

12 Every 9 weeks (±7 days) after C1D1 for the first 27 weeks. Every 12 weeks thereafter until progression of disease. Tumor assessment should be performed at the time of treatment discontinuation if the reason was other than radiologically confirmed disease progression and it has been ≥8 weeks since the last assessment (see Section 6.2).

13 Participants who discontinue study with ongoing SD, PR, or CR at the EOT visit will enter the Response Follow-up period. These participants will continue to have tumor radiological and clinical tumor assessments every 12 weeks during the Response Follow-up period or until disease progression, withdrawal of study, or initiation of new treatment. Radiological tumor assessments for participants who have ongoing clinical benefit may continue to be collected after participants complete the survival phase of the study (see Section 6.3 for further detail).

14 In all instances, if a block cannot be provided due to documented local/institutional regulations, at least 15 unstained slides are acceptable.

15 An on-treatment tumor biopsy is encouraged. For patients on the combination arm, this biopsy can be obtained from C2D15 through C3D1 or C3D15 through C4D1 at the discretion of the treating investigator and after consideration of the risk of neutropenia related to docetaxel. Patients on monotherapy arms can have their biopsy at any point in C2 or C3 at the discretion of the treating investigator. Tumor tissue is requested for those patients who undergo a biopsy or tumor resection as part of routine clinical care at any time during the treatment period. In all instances, if a block cannot be provided due to documented local/institutional regulations, at least 15 unstained slides are required.

Activity	Screening		All Cycles		EOT (± 14 days)	Clinical/ Safety Follow-up	Long-term Follow-up
	-28 days of C1D1	-14 days of C1D1	Day 1 (+/- 3 days for Cycle ≥2)	Day 15 (+/-3 days)			
Tumor Biopsy at Progression					X		
[16]Blood for DKN-01 PK/ADA			X				
[17]Whole blood for Immune Biomarkers and ctDNA		X	X	X	X		
[18]Whole blood for DKK1 testing	X		X		X		
[19]Whole Blood for CTC enumeration			X				
Treatment Exposure							
[20]Docetaxel administration			X				
[21]DKN-01 administration			X	X			

16 Collect blood (serum) pre-dose on Day 1, and then within 1 hour post-infusion at the end of infusion on Day 1. For each pre-dose sample collect enough for ADA analysis as well; ADA should only be collected pre-dose.

17 Required pre-dose whole blood will be collected for immunoprofiling and ctDNA analysis at the prescribed time points (required). Serial blood samples will be collected to support biomarker research (required). Serum and plasma will be collected from a whole blood sample and peripheral blood mononuclear cells will be isolated.

18 Required pre-dose whole blood for DKK1 testing will be obtained in the Screening period, however DKK1 level will not affect eligibility.

19 Blood for CTC enumeration should be collected at Cycle 1 Day 1 and at Week 13 (C5D1 for Cohorts 1A/1B and C4D1 for Cohorts 2A/2B). Blood should be collected at the indicated time points in CellSave tubes (10ml) for analysis with the CellSearch assay.

20 In Dose Escalation Cohort 1A and expansion Cohort 1B (combination docetaxel + DKN-01 cohorts), cycle length = 21 days. Treatment windows of +/- 3 days are allowable for day 1 and day 15 starting with cycle 2, however at least 7 days must elapse between Day 15 and the Day 1 treatment of the subsequent cycle.

21 In dose escalation Cohort 2A and expansion Cohort 2B (DKN-01 monotherapy cohorts), the cycle length = 28 days. Treatment windows of +/- 3 days are allowable for day 1 and day 15 starting with cycle 2, however at least 7 days must elapse between Day 15 and the Day 1 treatment of the subsequent cycle.

12.2. Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference Guide

Response and progression will be evaluated in this study using the international criteria proposed in: Eisenhauer EA, Therasse P, Bogaerts J, et al. 2009. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247.

Eligibility

Only patients with measurable disease at baseline should be included in protocols where ORR is the primary endpoint. Measurable disease is defined as the presence of at least one measurable lesion.

Methods of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

- CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (eg, for body scans but not for lung).
- Lesions on a chest X-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Ultrasound should not be used to measure tumor lesions.
- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response.
- Cytology and histology can be used in rare cases (eg, for evaluation of residual masses to differentiate between Partial Response [PR] and Complete Response [CR] or evaluation of new or enlarging effusions to differentiate between Progressive Disease [PD] and Response/Stable Disease [SD]).

Use of endoscopy and laparoscopy is not advised. However, they can be used to confirm complete pathological response.

Baseline Disease Assessment

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Measurable Lesions - Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non- measurable).
- 20 mm by chest X-ray
- Malignant lymph nodes
  - To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
  - Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.
  - 'Cystic lesions' thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Non-Measurable Lesions - Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Blastic bone lesions are non-measurable.

Lesions with prior local treatment, such as those situated in a previously irradiated area or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements.
- All measurements should be recorded in metric notation using calipers if clinically assessed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters, which will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

Non-Target Lesions

All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Special Notes on the Assessment of Target Lesions

- Lymph nodes identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met since a normal lymph node is defined as having a short axis of <10 mm.
- Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure', in which case a default value of 5 mm should be assigned.
- Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions

Complete Response (CR)	• Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (< 10 mm short axis)
Non-CR/Non-PD	• Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	• Unequivocal progression of existing non-target lesions. • When patient has measurable disease. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status • When patient has only non-measurable disease. There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread progression status.

New Lesions

The appearance of new malignant lesions denotes disease progression:

- The finding of a new lesion should be unequivocal (ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, especially when the patient's baseline lesions show partial or complete response).
- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

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

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Time Point Response

A summary of the overall response status calculation at each time point for patients who have measurable disease at baseline is presented in Table 1 below.

Table 1 Time Point Response: Patients with Target (+/–non-target) Disease

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-PD/or not all evaluated	No	SD
SD	Non-PD/or not all evaluated	Yes or No	PD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PR – partial response; SD – stable disease; PD = progressive disease; NE – inevaluable

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 2 Time Point Response: Patients with Non-target Disease

Non-Target lesions	New Lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[1]
Not all evaluated	No	NE
PD	Yes or No	PD
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PR – partial response; SD – stable disease; PD = progressive disease; NE – inevaluable.

[1] Non-CR / non-PD is preferred over 'Stable Disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials. To assign this category when no lesions can be measured is not advised.

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials.

However, in all other circumstances, (ie, in randomized Phase 2 or 3 trials or studies where stable disease or progression are the primary endpoints), confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies, which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.

If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would most likely happen in the case of PD.

Criteria for Continuing Treatment after Evidence of Progressive Disease by RECIST 1.1

Radiologic tumor flare, which is not defined in RECIST 1.1, has been observed in patients undergoing treatment (Hales et al., 2010). Thus, patients who have evidence of clinical benefit but with PD as defined by RECIST 1.1 may be considered for continued study treatment at the Investigator's discretion (after discussion with the Medical Monitor) if they meet the following criteria:

- Tumor shrinkage (at least 30% decrease in diameter from baseline) of one or more evaluable lesions

Improvement in one or more symptoms or signs attributable to the underlying cancer as assessed by the Investigator.

12.3. Description of iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator; the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 4 and Figure 2). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR as necessary.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed PD). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 2 and submitted to the central imaging vendor.

Detection of Progression at Visits after Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time

- Additional new lesions appear
- Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
- Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication (Seymour et al, 2017).

12.4. NCI-CTCAE v 5 Infusion-related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDS, narcotics, I.V. fluids); prophylactic medications indicated for ≤ 24 hrs	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae. Intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% Oxygen	Hypotension managed with one pressor; hypoxia requiring >40% O2	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.					

12.5. Management of DKN-01 Infusion-related Reactions

Grade	Management
Grade 1	• Slow the infusion rate by 50%. • Monitor the patient for worsening of condition. • For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the Investigator's discretion.
Grade 2	• Stop the infusion. • Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally for fever, and oxygen. • Resume the infusion at 50% of the prior rate once the infusion reaction has resolved or decreased to Grade 1. • Monitor for worsening of condition. • For subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent); additional premedication may be administered at the Investigator's discretion. • For a **second** Grade 1 or 2 infusion reaction, administer dexamethasone 10 mg IV (or equivalent); then, for subsequent infusions, premedicate with diphenhydramine hydrochloride 50 mg IV (or equivalent), acetaminophen 650 mg orally, and dexamethasone 10 mg IV (or equivalent).
Grade 3	• Stop the infusion and disconnect the infusion tubing from the patient. • Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 10 mg IV (or equivalent), bronchodilators for bronchospasm, and other medications/treatment as medically indicated. • Patients who have a Grade 3 infusion reaction with premedication will not receive further DKN-01 treatment, but will continue to be followed on the protocol.
Grade 4	• Stop the infusion and disconnect the infusion tubing from the patient. • Administer diphenhydramine hydrochloride 50 mg IV (or equivalent), dexamethasone 10 mg IV (or equivalent), and other medications/treatment as medically indicated. • Give epinephrine or bronchodilators as indicated. • Hospital admission for observation may be indicated. • Patients who have a Grade 4 infusion reaction with or without premedication will not receive further DKN-01 treatment, but will continue to be followed on the protocol.

12.6. Declaration of Helsinki

World Medical Association Declaration of Helsinki:

Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects

Adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, and the 41st WMA General Assembly, Hong Kong, September 1989, the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added); 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added); and 59th WMA General Assembly, Seoul, October 2008.

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable

and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, Sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the Sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects

must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would

pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations, the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

12.7. PCWG3 Criteria for Disease Assessment

PCWG3 endorses RECIST v1.1 for soft tissue response assessment (see RECIST v1.1 appendix).

PCWG3 criteria will be used to document evidence of disease progression in bone lesions as described by Scher, et al. 2016.

Imaging of Baseline Bone Disease:

The use of bone scan as the standard for bone imaging is retained in PCWG3, with the presence or absence of metastasis recorded first. A quantitative measure of disease burden, such as lesion number, the bone scan index, or lesion area, is also suggested, recognizing that these measures require further analytical and prospective clinical validation. Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial. Different modalities for imaging bone metastases can provide different information for the same patient. However, because of the lack of standards for reporting disease presence or changes after treatment, positron emission tomography imaging with sodium fluoride, fluorodeoxyglucose, choline, or prostate-specific membrane antigen, bone marrow MRI (body MRI), and other modalities that are in use to image bone, should be approached as new biomarkers subject to independent validation.

Criteria for progression in bone at study entry

- Two new lesions observed on 99mTc-methylene diphosphonate radionuclide bone scintigraphy
- Confirm ambiguous results by other imaging modalities (eg, CT or MRI) however only positivity on the bone scan defines metastatic disease to bone

Documentation of baseline bone disease

- Presence or absence of metastasis recorded first
- A quantitative measure of disease burden, such as lesional number, the bone scan index, or lesion area, is required
- Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a trial.

Following for bone progression during the study

- Exclude pseudoprogression in the absence of symptoms or other signs of progression

At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule)

- If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan when the first two new lesions were documented
- For scans after the first post-treatment scan, at least two new lesions relative to the first posttreatment scan confirmed on a subsequent scan
- Date of progression is the date of the scan that first documents the second lesion
- Changes in intensity of uptake alone do not constitute either progression or regression