Protocol DEK-DKK1-P204

A Phase 2 Study Evaluating the Efficacy and Safety of DKN-01 as a Monotherapy or in Combination with Paclitaxel in Patients with Recurrent Epithelial Endometrial Cancer, Epithelial Ovarian Cancer, or Carcinosarcoma

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Amendment 1	31 July 2017 (Version 2.0)
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Amendment 3	18 May 2018 (Version 4.0)
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CLINICAL STUDY PROTOCOL

Protocol DEK-DKK1-P204

A Phase 2 Study Evaluating the Efficacy and Safety of DKN-01 as a Monotherapy or in Combination with Paclitaxel in Patients With Recurrent Epithelial Endometrial Cancer, Epithelial Ovarian Cancer, or Carcinosarcoma

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:

Leap Therapeutics, Inc.
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Amendment 5	01 July 2020 (Version 6.0)

SIGNATURE PAGE

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Protocol Number:	DEK-DKK1-P204
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REVIEWED/APPROVED BY:

Cynthia Sirard, MD	Cynthia Sirard	*Electronically signed by: Cynthia Sirard Reason: person(s) who reviewed and are responsible to approve document Date: Jul 1, 2020 14:53 EDT*	07/01/2020
Chief Medical Officer Leap Therapeutics, Inc.	Signature		Date

INVESTIGATOR STATEMENT

I understand that all documentation provided to me by Leap Therapeutics, Inc. 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 Leap Therapeutics, Inc. 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)

CLINICAL STUDY SYNOPSIS

Name of Sponsor:	Leap Therapeutics, Inc.
Name of Investigational Product:	DKN-01
Protocol Title:	A Phase 2 Study Evaluating the Efficacy and Safety of DKN-01 as a Monotherapy or in Combination with Paclitaxel in Patients With Recurrent Epithelial Endometrial Cancer, Epithelial Ovarian Cancer, or Carcinosarcoma
Protocol Number:	DEK-DKK1-P204
Study Phase:	2
Study Centers:	Approximately 20 study centers
Objectives:	This study employs a "basket" design to concurrently investigate DKN-01 as monotherapy and in combination with paclitaxel in patients with recurrent epithelial endometrial cancer (EEC), epithelial ovarian cancer (EOC), or carcinosarcoma (malignant mixed Mullerian tumor [MMMT]) (see **Study Design** for details). Thus, 6 distinct patient groups are being independently investigated: 1. DKN-01 monotherapy in recurrent EEC (Group 1) 2. DKN-01+paclitaxel in recurrent EEC (Group 2) 3. DKN-01 monotherapy in recurrent EOC (Group 3) 4. DKN-01+paclitaxel in recurrent EOC (Group 4) 5. DKN-01 monotherapy in recurrent carcinosarcoma (MMMT) (Group 5) 6. DKN-01+paclitaxel in recurrent carcinosarcoma (MMMT) (Group 6) The primary objective in each independent study group (Groups 1-4) is: • To determine the objective response rate (ORR). Secondary objectives in each independent study group (Groups 1-4) are: • To determine the objective disease control rate (ODCR). • To determine overall survival (OS). • To determine progression-free survival (PFS).

	• To evaluate additional measures of efficacy, including time to progression (TTP), duration of response (DoR), duration of complete response (DoCR), duration of clinical benefit (DoCB), and time to treatment failure (TTTF). • To evaluate the safety of the study treatment regimen. • To characterize the pharmacokinetics (PK) of DKN-01 as monotherapy and in combination with paclitaxel in patients with recurrent EEC or EOC. • To detect anti-DKN-01 antibodies in human serum. The primary objectives in each independent study group (Groups 5-6) are: • To characterize the safety of DKN-01 600 mg ± paclitaxel in patients with recurrent carcinosarcoma (MMMT). • To identify the recommended Phase 2 dose (RP2D) of DKN-01 ± paclitaxel in patients with recurrent carcinosarcoma (MMMT) based on safety, PK, and pharmacodynamics (PcD). Secondary objectives in each independent study group (Groups 5-6) are: • To determine the ORR. • To determine the ODCR. • To determine overall OS. • To determine PFS. • To evaluate additional measures of efficacy, including TTP, DoR, DoCR, DoCB, and TTTF. • To characterize the PK of DKN-01 as monotherapy and in combination with paclitaxel in patients with recurrent carcinosarcoma (MMMT). • To detect anti-DKN-01 antibodies in human serum. The exploratory objectives in each independent study group (Groups 1-6) are: • To evaluate response to therapy in patients with and without activating β-catenin mutations and/or Wnt signaling genetic alterations. • To evaluate Dickkopf-1 (DKK1) concentration in serum and plasma relative to safety and efficacy outcomes.

	• To evaluate tumor genetics, gene expression levels (e.g., RNA-Seq), DKK1 expression (e.g., RNAscope in situ hybridization), immunohistology, infiltrating immune cells and additional immunohistochemistry (IHC) staining (DKK1 and associated downstream elements [e.g., β-catenin]) on tumor tissue relative to safety and efficacy outcomes.
Endpoints: **Efficacy:**	The primary efficacy endpoint in each independent study group (Groups 1-4) is: • ORR (i.e., best overall response [BOR] of complete response [CR] + partial response [PR]), as assessed by the Investigator using the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009). Secondary efficacy endpoints in each independent study group (Groups 1-4) are: • ODCR (i.e., CR+PR+ stable disease [SD] > 6 weeks), as assessed by the Investigator using RECIST 1.1. • OS, defined as the time from first study drug dose (i.e., Cycle 1, Day 1 [C1D1]) to death from any cause. • PFS, defined as the time from first study drug dose (C1D1) to first radiographically-documented progressive disease (PD), as determined using RECIST 1.1, or death due to any cause. • TTP, defined as the time from first study drug dose (C1D1) until the date of first radiographically-documented PD, as determined using RECIST 1.1. • DoR, defined as the time from initial response (≥PR) until radiographically-documented PD or death; PD is defined using RECIST 1.1. • DoCR, defined as the time from initial CR until radiographically-documented PD or death; PD is defined using RECIST 1.1. • DoCB, defined as the time from the first tumor assessment of CR, PR or SD to the time of PD, as determined using RECIST 1.1, or death due to any cause. • TTTF, defined as the time from first study drug dose (C1D1) until the date of treatment discontinuation of DKN-01 for any reason, including PD, toxicity, and death.

	In support of objectives relating to an investigation of the safety and clinical effectiveness of a DKN-01 dose exceeding 300 mg, the secondary endpoints for Group 5 and Group 6 are equivalent to those specified as efficacy endpoints for Groups 1-4.
Safety:	Safety endpoints in each independent study group are: • Incidence of treatment-emergent adverse events (TEAEs), Grade 3 /4 / 5 TEAEs, serious adverse events (SAEs), and TEAEs leading to study drug discontinuation. • Incidence of treatment-emergent Grade 3 / 4 clinical laboratory abnormalities. • Incidence of infusion reactions. • Changes from baseline in clinical laboratory parameters (serum chemistry, hematology, coagulation, and urinalysis). • Changes from baseline in vital signs and electrocardiogram (ECG) parameters. • Shift from baseline in Eastern Cooperative Oncology Group (ECOG) performance status. In support of objectives relating to an investigation of the safety and clinical effectiveness of a DKN-01 dose exceeding 300 mg, the primary endpoints for Group 5 and Group 6 include those specified as safety endpoints. In addition, the evaluation of the higher DKN-01 dose will also be based on a review of pharmacokinetic and pharmacodynamic data. Additionally, for Groups 5 and 6: • Incidence of DLTs.
Pharmacokinetic:	• Peak drug concentration (C_{max}), time to peak concentration (T_{max}), and areas under the concentration-time curve (AUCs).
Immunogenicity (ADA):	• Anti-DKN-01 antibodies.

Exploratory:	The exploratory endpoints in each independent study group are: • DKK1 concentration in serum and plasma relative to safety and efficacy outcomes. • Tumor genetics, gene expression levels (e.g., RNA-Seq), DKK1 expression (e.g., RNAscope in situ hybridization), immunohistology, infiltrating immune cells and additional IHC staining (e.g., DKK1 and associated downstream elements, [e.g., β-catenin]) on tumor tissue relative to safety and efficacy outcomes
Study Design:	Study DEK-DKK1-P204 is a Phase 2 basket study designed to evaluate DKN-01 activity either in combination with paclitaxel or as a monotherapy in patients with recurrent EEC or recurrent platinum-resistant/refractory EOC, or recurrent carcinosarcoma (MMMT) who have received at least one prior systemic therapy for advanced disease. Note that this basket study is enriching for activating β-catenin mutations and/or Wnt signaling alterations (see **Screening**). A maximum of 124 evaluable patients aged 18 years or older with histologically-confirmed recurrent EEC or recurrent platinum-resistant/refractory EOC, or recurrent carcinosarcoma (MMMT) requiring therapy will be enrolled in the study. Patients who are not eligible to receive paclitaxel, as determined by the Investigator, will be enrolled in the monotherapy group by primary tumor. Four distinct patient groups are being enrolled with up to 21 evaluable patients in Groups 1, 3, and 4, up to 31 evaluable patients in Group 2, up to 10 evaluable patients in Group 5, and up to 20 evaluable patients in Group 6. Group 1: DKN-01 monotherapy in recurrent EEC Group 2: DKN-01+paclitaxel in recurrent EEC Group 3: DKN-01 monotherapy in recurrent EOC Group 4: DKN-01+paclitaxel in recurrent EOC Group 5: DKN-01 monotherapy in recurrent carcinosarcoma (MMMT) Group 6: DKN-01+paclitaxel in recurrent carcinosarcoma (MMMT) Groups 1-4 employ a 2-stage design conducted separately for each group. For each monotherapy group (Groups 1 and 3), after 12 evaluable patients are enrolled (Stage 1), an additional 9 evaluable patients will be enrolled in that group (Stage 2) if 1 or more patients respond (i.e., experience CR or PR). If there are no responses in Stage

	1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group. For the EEC combination therapy group (Group 2), after 20 evaluable patients are enrolled (Stage 1), if 3 or more patients respond (i.e., experience CR or PR), an additional 11 evaluable patients will be enrolled in that group (Stage 2). If there are fewer than 3 responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group. For the EOC combination therapy group (Group 4), after 16 evaluable patients are enrolled (Stage 1), if 2 or more patients respond (i.e., experience CR or PR), an additional 5 evaluable patients will be enrolled in that group (Stage 2). If there are fewer than 2 responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group. Groups 5 and 6 are exploratory in nature. Group 5 will enroll approximately 10 evaluable patients and Group 6 will enroll approximately 20 evaluable patients. For Groups 5 and 6, 3 patients in each group will initially be enrolled in a safety run-in phase. If the first 2 of 3 patients in a group have a dose-limiting toxicity (DLT), the maximum tolerated dose (MTD) will have been exceeded and a cohort will be enrolled to evaluate DKN-01 at a dose of 300 mg (±paclitaxel, depending on group assignment) (see Synopsis **Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition**). If none of the 3 treated patients in a group develop a DLT after a minimum of one cycle of treatment, enrollment into the group will proceed according to the planned schedule. If a DLT is observed in 1 of the 3 patients in a group, up to an additional 3 patients will be enrolled and treated. If no further DLTs are observed within the expanded group of 6, enrollment into the group will proceed. If ≥2 of 6 patients within a group experience a DLT, the MTD will have been exceeded and a cohort will be enrolled to evaluate DKN-01 at a dose of 300 mg (±paclitaxel, depending on group assignment). For the Rollover Treatment Phase, patients remain on the same dose and schedule as they received in the previous study part.
	The study has 6 distinct periods, as follows: **Screening** Potentially eligible patients will sign informed consent prior to undergoing any study-related procedures. Patients will undergo Screening assessments for protocol eligibility within 28 days of study entry, as outlined in Table 6.

	Fresh tumor tissue samples are required to be collected from all patients during Screening for genomic cancer profiling (i.e., CTNNB1 mutation and Wnt-signaling mutation), gene expression levels (e.g., RNA-Seq), DKK1 expression (e.g., RNAscope in situ hybridization), immunohistology, infiltrating immune cells and additional IHC staining (DKK1 and associated downstream elements, [e.g., β-catenin]). Although fresh biopsy is preferred, an archived specimen collected within 3 months of C1D1 may be acceptable, with the prior approval of the Medical Monitor. This basket study is enriching for activating β-catenin mutations and/or Wnt signaling alterations, whereby approximately 50% of all evaluable patients enrolled in each group, in Stage 1 and in Stage 1 and 2 combined (Groups 1-4) and in Groups 5 and 6, are required to have an activating β-catenin mutation (CTNNB1 mutation) or other Wnt signaling alteration (e.g., LRP5/6, APC, AXIN1/2, GSK3B, RNF43, ZNRF3, RSPO2/3, FBXW7, ARID1A, or CBP/CREBBP; see full list in Appendix 12.6), based on testing of the Screening tumor tissue sample or previously documented alteration by a Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory. To allow-for real-time testing of Screening tumor tissue samples, the Screening period may be extended to 42 days, with results obtained and confirmed to be positive before the performance of additional Screening procedures. Note that all other Screening assessments must be performed within 28 days before C1D1. Patients with prior documentation of a known activating β-catenin mutation (CTNNB1 mutation) or other Wnt signaling alteration by a CLIA-accredited laboratory will be permitted to enroll based on this documentation. In such patients, a Screening tumor sample will be collected and analyzed centrally; however, confirmatory results are not required for study enrollment. Groups 1-4 employ a 2-stage design conducted separately for each group. For each monotherapy group (Groups 1 and 3), once 6 evaluable patients are enrolled who do not have activating β-catenin mutation and/or Wnt signaling alterations, Stage 1 enrollment for that group will continue only with patients with activating β-catenin mutation and/or Wnt signaling alterations. For combination therapy Group 2, once 10 evaluable patients are enrolled who do not have activating β-catenin mutation and/or Wnt signaling alterations, Stage 1 enrollment for that group will continue only with patients with activating β-catenin mutation and/or Wnt signaling alterations. For combination therapy Group 4, once 8 evaluable patients are enrolled who do not have activating β-catenin mutation and/or Wnt signaling

	alterations, Stage 1 enrollment for that group will continue only with patients with activating β-catenin mutation and/or Wnt signaling alterations. At any time for Groups 1, 3, or 4, once 10 evaluable patients who do not have a documented activating β-catenin mutation and/or other Wnt signaling alteration have been enrolled in a group, enrollment in that group will continue only with patients with activating β-catenin mutation (CTNNB1 mutation) or other identified Wnt signaling alteration. At any time for Group 2, once 15 evaluable patients who do not have a documented activating β-catenin mutation and/or other Wnt signaling alteration have been enrolled, enrollment in that group will continue only with patients with activating β-catenin mutation (CTNNB1 mutation) or other identified Wnt signaling alteration.
	Study Treatment Period The Study Treatment Phase includes either DKN-01 monotherapy or DKN-01 in combination with paclitaxel; patients will be assigned to receive monotherapy or combination therapy at the Investigator's discretion. Patients who initially start combination therapy but subsequently discontinue paclitaxel may continue to receive DKN-01 as monotherapy during the Treatment Period. Patients are to begin study treatment as soon as possible (and preferably within 24 hours) after completion of all screening procedures and confirmation of study eligibility. Study visits will be performed as outlined in Table 6. During the Treatment Period, tumor measurements are to be performed using the same radiographic methods used during Screening. Tumor response, including PD, is to be assessed by the Investigator within ±7 days of the first study drug dose in every other cycle, starting in C3, and at the End of Treatment (EOT) Visit using RECIST 1.1. The severity of TEAEs will be graded according to the United States National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0. **Rollover Treatment Phase** The Rollover Treatment Phase will permit patients who are still experiencing clinical benefit continued access to study drug(s) until they meet discontinuation criteria as per Section 6.4.1. Study visits will be performed as outlined in Table 7. **Study Treatment Discontinuation**

	All patients will continue study treatment in the Treatment Phase until development of radiographically-documented PD or unacceptable toxicity or another discontinuation criterion is met, as determined by the Investigator. All patients will return for an EOT Visit approximately 30 days (+7 days) after the last treatment administration in the Treatment Period. The reason for discontinuation from study treatment will be documented in the electronic case report form (eCRF). **Progressive Disease Follow-up Phase** To ensure accuracy and completeness for the disease response-related endpoints, patients who permanently discontinued study treatment prior to PD will continue to be followed up in the PD follow-up phase until radiographically documented PD. During this PD follow-up period, efficacy assessments for disease response and PD per RECIST 1.1 will be performed every 8 weeks [see Table 6 and (Table 7 for the Rollover Treatment Phase only)]. Patients are expected not to start any other anti-cancer therapy during the PD follow-up phase prior to radiographically documented PD; however, if alternate therapy is started, patients will continue to be followed for radiologic progression even after starting subsequent therapy. After radiographically-documented PD, all patients will be followed for survival in the Survival Follow-up Phase. **Survival Follow-up Phase** After discontinuation of treatment and radiographic documentation of PD, all patients will be followed in the survival follow-up phase for survival until death, withdrawal of consent, loss to follow-up, implementation of the rollover treatment phase, or closure of the study by the Sponsor. Survival follow-up will occur 4 times per year (every 12 weeks [±14 days]) after the EOT visit or end of PD Follow-up Phase, as applicable, and may be conducted via telephone or office visit. During survival follow-up, the following information will be collected: survival and subsequent anti-cancer therapies.

Dose-Limiting Toxicity Determination and Maximum Tolerated Dose/Recommended Phase 2 Dose Definitions:	A DLT is defined as an AE during C1 that is possibly related to the study drug(s) and fulfills any one of the following criterion using the NCI CTCAE version 5.0. • Grade 4 neutropenia lasting ≥ 5 days or Grade 3 or 4 neutropenia with fever and/or infection • 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 including the clinical sequelae [e.g., 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. Patients in Group 6 must have completed 100% of the DKN-01 doses and 75% of the paclitaxel doses in C1 to be evaluable for DLT. Furthermore, in any study part, if a patient experiences a TEAE meeting the definition of DLT in the first cycle of treatment, he/she will be discontinued from study treatment. 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. The RP2D is defined as the MTD or up to the highest planned dose level evaluated in Groups 5-6 without identification of the MTD.
Number of Patients Planned:	A maximum of 124 evaluable patients are planned to be enrolled, with up to 21 evaluable patients in Groups 1, 3, and 4; up to 31 evaluable patients in Group 2, up to 10 evaluable patients in Group 5, and up to 20 evaluable patients in Group 6.

Diagnosis and Main Criteria for Inclusion:	Patients meeting all of the following criteria will be considered eligible for study entry: ***Epithelial Endometrial Cancer*** 1. Must have a histologically confirmed diagnosis (by either primary surgical specimen or biopsy for recurrence) of recurrent previously treated EEC. ***Epithelial Ovarian Cancer*** 2. Must have a histologically confirmed diagnosis (by either primary surgical specimen or biopsy for recurrence) of recurrent platinum-resistant/refractory EOC, primary peritoneal, or fallopian tube cancer (i.e., disease recurrence within 6 months of completion of or progression during platinum-based chemotherapy). ***Carcinosarcoma/Malignant Mixed Mullerian Tumors (Groups 5-6)*** 3. Must have a histologically confirmed diagnosis (by either primary surgical specimen or biopsy for recurrence) of recurrent uterine or ovarian carcinosarcoma (MMMT). 4. Patient must have had only 1 prior chemotherapeutic regimen for management of recurrent or advanced carcinosarcoma that may have included chemotherapy (including in adjuvant setting with refractory or disease recurring within 6 months), chemotherapy and radiotherapy, and/or consolidation/maintenance therapy. ***General*** 5. Must be refractory or intolerant to at least one prior standard therapy(ies) for metastatic or locally advanced disease (see Inclusion Criterion #4 for Groups 5-6). a. If prior therapy consisted of palliative chemoradiation therapy, it will be considered one line of therapy. b. Prior treatment with paclitaxel as part of a definitive therapy regimen is acceptable, provided the patient is not intolerant of paclitaxel. c. Patients who are not eligible to receive paclitaxel will be allowed to receive single agent DKN-01. 6. Tumor tissue for mandatory pre-treatment and on–treatment evaluation (fresh biopsy during Screening preferred; archived

	specimen (≤3 months) may be acceptable with prior approval from the Medical Monitor). 7. One or more tumors measurable on radiographic imaging as defined by RECIST 1.1. 8. Ambulatory and ≥18 years of age. 9. ECOG performance status (PS) of 0 or 1. a. PS of 2 on the ECOG scale may be eligible upon the review and approval of the Medical Monitor. 10. Estimated life expectancy of at least 3 months, in the judgment of the Investigator. 11. Disease-free of active second/secondary or prior malignancies for ≥2 years with the exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma *in-situ* of the cervix or breast. 12. Acceptable liver function: a. Total bilirubin ≤2.0 × upper limit of normal (ULN). b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN. If liver metastases are present, then ≤5 × ULN is allowed. 13. Acceptable renal function: a. Creatinine normal for age: if serum creatinine is abnormal for age the patient must have a calculated creatinine clearance ≥30 mL/min using the Cockcroft and Gault Method (Cockroft and Gault 1976). 14. Acceptable hematologic status: a. Granulocyte ≥1500 cells/mm^3. b. Hemoglobin ≥9 g/dL (transfusion permitted within 30 days of study entry). c. Platelet count ≥75,000 cells/mm^3. 15. Acceptable coagulation status: a. Prothrombin time (PT)/partial thromboplastin time (PTT) ≤1.2 × ULN (unless receiving anticoagulation therapy, in which case, eligibility will be based upon International Normalized Ratio [INR], see below).

	b. If receiving anticoagulant: INR ≤3.0 and no active bleeding, (i.e., no clinically significant bleeding within 14 days prior to first dose of study therapy). 16. Females of child-bearing potential and male partners of female 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 become pregnant or suspect she is pregnant while participating in the study, the Investigator should be immediately informed. 17. Reliable and willing to make themselves available for the duration of the study and are willing to follow study-specific procedures. 18. Provided written informed consent prior to any study-specific procedures. **Rollover Treatment Phase:** 19. Received DKN-01 either as a monotherapy or in combination with paclitaxel in this study and is tolerating study drug(s) and currently displaying clinical benefit, in the Investigator's opinion.
Exclusion Criteria:	Patients meeting any of the following criteria are not eligible for study entry: 1. Any of the following pure histologies of endometrial or ovarian cancer: germ cell, sex cord stroma, or sarcoma. 2. New York Heart Association Class III or IV cardiac disease, myocardial infarction within the past 6 months, or unstable arrhythmia. 3. Have Fridericia-corrected QT interval (QTcF) >470 msec, or history of congenital long QT syndrome. Any ECG abnormality that in the opinion of the Investigator would preclude safe participation in the study; patients with pacemakers where QTc is not a reliable measure will require an evaluation by a cardiologist to exclude co-existing cardiac conditions which would prohibit safe participation in the study. 4. Active, uncontrolled bacterial, viral, or fungal infections, within 7 days of study entry requiring systemic therapy.

	5. Known to be human immunodeficiency virus (HIV) positive, have hepatitis B surface antigen (HBSAg), or hepatitis C antibodies (HCAb), unless hepatitis C virus ribonucleic acid (HCV RNA) undetected/negative. 6. History of major organ transplant (i.e., heart, lungs, liver, or kidney). 7. History of autologous/allogenic bone marrow transplant. 8. Serious nonmalignant disease that could compromise protocol objectives in the opinion of the Investigator and/or Sponsor. 9. Pregnant or nursing. 10. History of osteonecrosis of the hip or evidence of structural bone abnormalities in the proximal femur on MRI scan that are symptomatic and clinically significant. Degenerative changes of the hip joint are not exclusionary. Screening of asymptomatic patients is not required. 11. Symptomatic central nervous system (CNS) malignancy or metastasis. Patients with treated CNS metastases are eligible provided their disease is radiographically stable, asymptomatic, and they are not currently receiving corticosteroids and/or anticonvulsants. Screening of asymptomatic patients without a history of CNS metastases is not required. 12. Known osteoblastic bony metastasis. Screening of asymptomatic patients without a history of metastatic bony lesions is not required. ***Medication-Related*** 13. Treatment with surgery or chemotherapy within 21 days prior to study entry (42 days for nitrosoureas or mitomycin C). 14. Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to study entry. 15. Clinically significant peripheral neuropathy at the time of study entry. Patients with pre-existing peripheral neuropathy will be allowed to receive single agent DKN-01. 16. History of hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil). Patients who exhibit these hypersensitivities will be eligible to receive single agent DKN-01.

	17. Prior radiation therapy within 14 days prior to study entry. 18. Currently receiving any other investigational agent or received an investigational agent within last 30 days of study entry. 19. Previously treated with an anti-DKK1 therapy. 20. Significant allergy to a pharmaceutical therapy that, in the opinion of the Investigator, poses an increased risk to the patient. ***Lifestyle-Related*** 21. Active substance abuse.
Test Products, Doses, and Mode of Administration:	The study treatment regimens for Groups 1-4 are: • DKN-01 monotherapy: DKN-01 300 mg on D1 and 15 every 28 days. • DKN-01+paclitaxel: DKN-01 300 mg on D1 and 15 + paclitaxel 80 mg/m^2 on D1, 8, and 15 every 28 days. The study treatment regimens for Groups 5-6 are: • DKN-01 monotherapy: DKN-01 600 mg on D1 and 15 every 28 days. • DKN 01+paclitaxel: DKN-01 600 mg on D1 and 15 + paclitaxel 80 mg/m^2 on D1, 8, and 15 every 28 days. DKN-01 will be administered intravenously (IV) over a minimum of 30 minutes and up to a maximum of 2 hours given on D1 and 15 of each cycle without interruption. For patients receiving DKN-01 in combination, paclitaxel will be administered IV over 1 hour on days 1, 8, and 15 of each 28-day cycle according to standard clinical practice. The dose for paclitaxel is 80 mg/m^2. For patients receiving the combination, DKN-01 will be administered first followed by paclitaxel as separate infusions on D1 and 15 of each cycle. Additionally, for Groups 5 and 6, 3 patients in each group will initially be enrolled in a safety run-in phase. If the first 2 of 3 patients in a group have a DLT, the MTD will have been exceeded and a cohort will be enrolled to evaluate DKN-01 at a dose of 300 mg (±paclitaxel, depending on group assignment) (see Synopsis **Dose-Limiting Toxicity Determination and Maximum Tolerated Dose Definition**). If none of the 3 treated patients in a group develop a DLT after a minimum of one cycle of treatment, enrollment into the group will proceed according to the planned schedule. If a DLT is observed in

	1 of the 3 patients in a group, up to an additional 3 patients will be enrolled and treated. If no further DLTs are observed within the expanded group of 6, enrollment into the group will proceed. If ≥2 of 6 patients within a group experience a DLT, the MTD will have been exceeded and a cohort will be enrolled to evaluate DKN-01 at a dose of 300 mg (±paclitaxel, depending on group assignment). Premedication for paclitaxel will be given according to local standard of care prior to each infusion. Suggested premedications include dexamethasone 20 mg orally [PO] 12 to 6 hours prior; diphenhydramine 50 mg IV 30 to 60 minutes prior; and cimetidine or ranitidine 50 mg IV 30 to 60 minutes prior) or equivalents. For the Rollover Treatment Phase, patients remain on the same dose and schedule as they received in the previous study part.
Duration of Treatment:	No maximum duration of treatment has been set; patients may continue treatment until the development of PD or unacceptable toxicity or another discontinuation criterion has been met.
Duration of Study:	It is estimated that the total study duration will be approximately 36 months, assuming a 24-month accrual period and 12 months of follow-up for the last patient enrolled. Patients who are still experiencing clinical benefit will continue to have access to study drug(s) in the Rollover Treatment Phase, until they meet discontinuation criteria as per Section 6.4.1.
Sample Size Calculation:	This is a proof-of-concept basket study designed primarily to seek information on the safety and efficacy of DKN-01 in combination with paclitaxel and as DKN-01 monotherapy in patients with recurrent EEC or EOC with and without activating β-catenin mutation and/or Wnt signaling alterations, or carcinosarcoma (MMMT). A maximum of 124 evaluable patients (monotherapy groups and combination groups) will be enrolled in the study. This is an exploratory open-label study with 6 groups. Groups 1-4 employ a 2-stage study design conducted separately for each group. Up to 21 evaluable patients are enrolled in each of Groups 1, 3, and 4, and up to 31 evaluable patients in Group 2. Groups 5 and 6 are exploratory in nature and will have up to 10 and 20 evaluable patients enrolled and dosed at the RP2D, respectively. The sample sizes of 10 and 20 patients for Groups 5 and 6, respectively, are based on practical considerations and clinical judgement to obtain sufficient information on the safety, initial clinical effectiveness, and PK data in the carcinosarcoma groups at the 600-mg dose. The sample size of Groups 1 through 4 employ a 2-stage study design and were calculated as follows: For each monotherapy group (Groups

	1 and 3), after 12 evaluable patients are enrolled (Stage 1), an additional 9 evaluable patients will be enrolled in that group (Stage 2) if 1 or more patients respond (i.e., experience CR or PR). If there are no responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group. If the group continues to Stage 2, a total of 21 evaluable patients will be studied for that group. The group will be considered successful if ≥3 treated patients respond. This design is applied to each monotherapy group separately and is based on a 2-stage Simon Minimax design (Simon 1989) for a total of 21 evaluable patients (null hypothesis that ORR ≤5% versus the alternative hypothesis that ORR ≥20% with alpha=0.080 and power=0.803). For combination therapy Group 2, after 20 evaluable patients are enrolled (Stage 1), an additional 11 evaluable patients will be enrolled in that group (Stage 2) if 3 or more patients respond (i.e., experience CR or PR). If there are fewer than 3 responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group. If the group continues to Stage 2, a total of 31 evaluable patients will be studied for that group. The group will be considered successful if ≥6 treated patients respond. This design is applied to combination therapy Group 2 separately and is based on a 2-stage Simon Minimax design for a total of 31 evaluable patients (null hypothesis that ORR ≤12% versus the alternative hypothesis that ORR ≥25% with alpha=0.150 and power=0.802). For combination therapy Group 4, after 16 evaluable patients are enrolled (Stage 1), an additional 5 evaluable patients will be enrolled in that group (Stage 2) if 2 or more patients respond (i.e., experience CR or PR). If there are fewer than 2 responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group. If the group continues to Stage 2, a total of 21 evaluable patients will be studied for that group. The group will be considered successful if ≥4 treated patients respond. This design is applied to combination therapy Group 4 separately and is based on a 2-stage Simon Minimax design for a total of 21 evaluable patients (null hypothesis that ORR ≤10% versus the alternative hypothesis that ORR ≥25% with alpha=0.149 and power=0.803). There are no formal comparisons planned between groups. Any statistical results will be interpreted in the perspective of the exploratory nature of the study.

Analysis Populations:	**Study Population Definitions** Several study populations will be used for analysis, as follows: • Evaluable Analysis Set (EAS): All patients who received any amount of DKN-01 and have at least one evaluable post-baseline RECIST tumor response assessment or were discontinued due to toxicity. The EAS will be the primary population for analyses of ORR, ODCR, PFS, DoR, DoCR, DoCB, and TTP. • Full analysis set (FAS): All enrolled patients who receive any amount of DKN-01. The FAS will be used for analyses of OS, TTTF, sensitivity analysis of select tumor-related endpoints, and exploratory endpoints. • Safety population, defined as all enrolled patients who receive any amount of study treatment (either DKN-01 or paclitaxel). All safety analyses will be based on this population. The safety population and FAS are identical, unless a patient received paclitaxel but did not receive DKN-01. • A Per-Protocol (PP) subset may also be used to analyze 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: All enrolled patients who receive at least a single dose of DKN-01 and have sufficient data to determine PK parameters.

Statistical Methodology:	**General Considerations** Summaries will be tabulated for each group and within each group, where applicable, by presence of Wnt signaling alterations and/or CTNNB1 activating mutations. Select parameters may also be summarized by dose and will be detailed in the Statistical Analysis Plan (SAP). 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, 25th and 75th 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 confidence intervals (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.
	Efficacy Analysis Efficacy data will be summarized for each group. Selected summaries may also be done within each group, as applicable, by presence of Wnt signaling alterations and/or CTNNB1 activating mutations, and by subgroups as described in the SAP. The EAS will be the primary population for analysis of ORR, ODCR, PFS, DoR, DoCR, DoCB, and TTP. Secondary and exploratory analyses of efficacy endpoints (including OS and TTTF) will be performed using the FAS. The proportion of patients with ORR and ODCR, along with a 95% CI based on the Clopper-Pearson interval, will be reported. The Kaplan-Meier method will be used to summarize OS, PFS, TTP, TTTF, DoR, DoCR, and DoCB. The Investigator disease response assessments according to RECIST 1.1 will be used as the primary measures for analysis.

	Safety Analyses All safety analyses will be conducted in the safety population and presented by group. Adverse events (AEs) will be coded according to the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to the United States NCI CTCAE, version 5.0. Treatment-emergent adverse events (TEAEs) are defined as any AE with onset or (worsening of a pre-existing condition) after the first dose of study drug through 30 days following the last dose of study drug. Events including TEAEs, AEs leading to dose reduction/interruption, AEs related to study drug, SAEs, AEs leading to study drug discontinuation, and AEs with an outcome of death will be summarized by system organ class and preferred term for each treatment group. A summary of AEs of NCI CTCAE Grade 3 or higher, as well as the most frequent AEs (preferred terms), and AEs by relationship to study treatment, will be provided. For Groups 5 and 6, incidence of DLTs will be summarized. Number and percent of patients with infusion-related reactions will be summarized by group, overall and by visit. Values and changes from baseline in clinical laboratory results will be summarized by visit. Clinical laboratory values will be graded according to the NCI CTCAE, for applicable tests. Shifts in toxicity grades from baseline grade will be summarized. Shifts from baseline in ECOG performance status also will be summarized. Vital sign, ECG, and concomitant medication data will be summarized. **PK Analyses** Peak drug concentration (C_{max}), time to peak concentration (T_{max}), and areas under the concentration-time curve (AUCs) will be reported, as feasible. Data may be pooled with data from other studies to conduct population PK modeling. **Immunogenicity Analyses** Details regarding immunogenicity analyses will be provided in the SAP. **Exploratory Analyses** Exploratory analysis will be evaluated for exploratory endpoints. Details for these exploratory analyses will be provided in the SAP.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-DKN-01 antibodies
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the serum concentration-time curve
BOR	Best overall response
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
C1D1	Cycle 1, Day 1 (pattern set for cycle and days [e.g., C1D8, C2D1, etc.])
CI	Confidence interval
CK	Creatine kinase
C_{max}	Peak drug concentration in serum / plasma
CEA	Carcinoembryonic antigen
CLIA	Clinical Laboratory Improvement Amendments
CL/F (or CL)	Apparent systemic clearance
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DKK1	Dickkopf-1
DLT	Dose-limiting toxicity
DoCB	Duration of clinical benefit
DoCR	Duration of complete response
DoR	Duration of response
EAS	Evaluable analysis set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture

Abbreviation	Definition
EEC	Epithelial endometrial carcinoma
ELISA	Enzyme-linked immunosorbent assay
EOC	Epithelial ovarian carcinoma
EOT	End of Treatment
FDG-PET	Fludeoxyglucose-positron emission tomography
GCP	Good Clinical Practice
HEENT	Head, eyes, ears, nose, and throat
HBSAg	Hepatitis B surface antigen
HCAb	Hepatitis C antibodies
HCV RNA	Hepatitis C virus ribonucleic acid
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonization
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
IRB / IEC	Institutional review board / Independent ethics committee
INR	International normalized ratio
IV	Intravenous(ly)
Leap	Leap Therapeutics, Inc.
LD	Longest diameter
LDH	Lactate dehydrogenase
Mab	Monoclonal antibody
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MM	Multiple myeloma
MMMT	Malignant mixed Mullerian tumor
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
NLR	Neutrophil-to-lymphocyte ratio
NSCLC	Non-small cell lung cancer

Abbreviation	Definition
ODCR	Objective disease control rate
ORR	Objective response rate
OS	Overall survival
PcD	Pharmacodynamic(s)
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PP	Per population
PR	Partial response
PS	Performance status
PT/PTT	Prothrombin time / Partial thromboplastin time
QW	Once weekly
Q2W	Once every 2 weeks
QTcF	Fridericia-corrected QT interval
RBC	Red blood cells
RDW	Red blood cell distribution width
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SI	Système internationale d'unités (International System of Units)
TEAE	Treatment-emergent adverse event
TTP	Time to progression
TTTF	Time to treatment failure
ULN	Upper limit of normal
WBC	White blood cells
WMA	World Medical Association

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1. INTRODUCTION

1.1. Background

1.1.1. DKN-01

DKN-01 (formerly known as LY2812176) is a potent humanized monoclonal antibody (Mab) (immunoglobulin G4 [IgG4]) with neutralizing activity against dickkopf-1 (DKK1), a modulator of Wnt signaling pathways that influences a number of important processes such as cell growth and differentiation, bone development, and adult bone homeostasis (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.

To date, DKN-01 has been evaluated in a 30-subject healthy volunteer study and in approximately 167 patients with cancer in 5 clinical studies. 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.

Evidence of an anti-tumor effect of DKN-01 as a monotherapy has been seen in patients with non-small cell lung cancer (NSCLC). Additionally, evidence of an anti-tumor effect has been seen with DKN-01 in combination in patients with esophageal cancer, particularly those with adenocarcinoma of the esophagus or gastro-esophageal junction who had received fewer lines of therapy, and in patients with biliary tract cancer.

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

1.1.2. Dickkopf-1 (DKK1)

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 protein, is over-expressed in a variety of tumor types and this is associated with a poor prognosis such as decreased overall survival (OS) of cancer patients, including NSCLC, esophageal cancer, breast cancer, cholangiocarcinoma, liver cancer, and ovarian cancer (Shizhuo et al. 2009; Tung et al. 2011; Xu et al. 2012; 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.

1.1.3. Wnt/β-Catenin Signaling Pathway and Gynecological Cancers

Elevated levels of DKK1 have been observed in patients with gynecological cancer (Jiang et al. 2009; Chamorro et al. 2005; Shizhuo et al. 2009; Wang and Zang 2011). Assessment of DKK1 levels in the sera of 104 patients with gynecological cancer, including ovarian (N=36), cervical (N=40), and endometrial (N=28) cancers, revealed significantly higher DKK1 levels in patients with either cervical cancer (314.13 pg/mL, $p < 0.001$) or with endometrial cancer (46.95 pg/mL, $p < 0.001$) relative to healthy individuals (29.45 [11.86] pg/mL). Furthermore, the serum levels of DKK1 were associated with clinical stage in all patients in this study (Jiang et al. 2009).

Mutations of CTNNB1, the gene that encodes β-catenin, have been identified in a high percentage of patients with endometrioid endometrial carcinoma and low-grade endometrioid ovarian carcinoma (Liu et al. 2014; McConechy et al. 2014). CTNNB1 mutations that are associated with active canonical Wnt/β-catenin signaling have been identified in an aggressive subset of endometrioid endometrial carcinoma occurring in younger women (Lui et al. 2014). Activation of canonical Wnt/β-catenin signaling that can occur through CTNNB1 mutations leads to increased expression of DKK1 and this may further promote tumor growth (Chamorro et al. 2005; Niida et al. 2004; Chen et al. 2016; Bu et al. 2008). Furthermore, patients with tumors that co-stain for β-catenin, a marker of active canonical Wnt/β-catenin signaling, and DKK1 frequently have a worse prognosis (Yu et al. 2009; Xu et al. 2012; Chen et al. 2014). Taken together these results suggest that patients with activated Wnt/β-catenin signaling may benefit from a DKK1 neutralizing therapy.

1.2. Rationale and Justification for the Study

Molecular subtyping of cancers may inform diagnosis, prognosis, and selection of appropriate targeted therapies. The development of molecular-targeted therapies has been a growing area of interest for the treatment of both endometrioid ovarian carcinoma (Matsuzaki et al. 2015; Banerjee and Kay 2013; Bast 2011; Hiss 2012; Twu and Han 2012; Sudo 2012; Weberpals et al. 2011) and endometrioid endometrial carcinoma (Uppendahl et al. 2017; Bookman et al. 2014; Bansal et al. 2009), with a number of potential targets identified. Molecularly-targeted agents hold the promise of greater selectivity with lower toxicity than conventional chemotherapy (Banerjee 2013).

As stated previously, CTNNB1 mutations have been seen both in patients with endometrioid endometrial carcinoma and endometrioid ovarian carcinoma (Liu et al. 2014; McConechy et al. 2014; Markowska et al. 2014). Furthermore, high expression levels of DKK1 have been observed in patients with gynecological cancers, including ovarian and endometrial (Jiang et al. 2009). Activation of canonical Wnt/β-catenin signaling that can occur through CTNNB1 mutations is associated with increased expression of DKK1 (Chamorro et al. 2005; Niida et al. 2004; Chen et al. 2016; Bu et al. 2008). Furthermore, patients with tumors that co-stain for β-

catenin, a marker of active canonical Wnt/β-catenin signaling, and DKK1 frequently have a worse prognosis (Yu et al. 2009; Xu et al. 2012; Chen et al. 2014).

This study will enroll patients with either epithelial endometrial cancer (EEC) or epithelial ovarian cancer (EOC) (Groups 1-4), or carcinosarcoma (malignant mixed Mullerian tumor [MMMT]) (Groups 5-6) and for all groups will enrich for activating β-catenin mutations (CTNNB1 mutation) or other Wnt signaling alterations (e.g., LRP5/6, APC, AXIN1/2, GSK3B, RNF43, ZNRF3, RSPO2/3, FBXW7, ARID1A, or CBP/CREBBP; see full list in Appendix 12.6), whereby approximately 50% of all patients enrolled are required to have such mutations or alterations.

DKN-01 will be administered as monotherapy or, at the Investigator's discretion, in combination with paclitaxel in the current study. Paclitaxel is indicated as first-line and subsequent treatment in advanced ovarian cancer and has been studied extensively in patients with endometrial cancer and is recommended as a chemotherapeutic option in this disease setting (NCCN Guidelines Version 1.2017; Bestvina and Flemming 2016).

1.3. Rationale for the Dose Selected

DKN-01 will be administered at a dose of 300 mg (Groups 1-4) or 600 mg (Groups 5 and 6) intravenously (IV) on Days (D) 1 and 15 every 28 days either as monotherapy or, at the Investigator's discretion, in combination with paclitaxel.

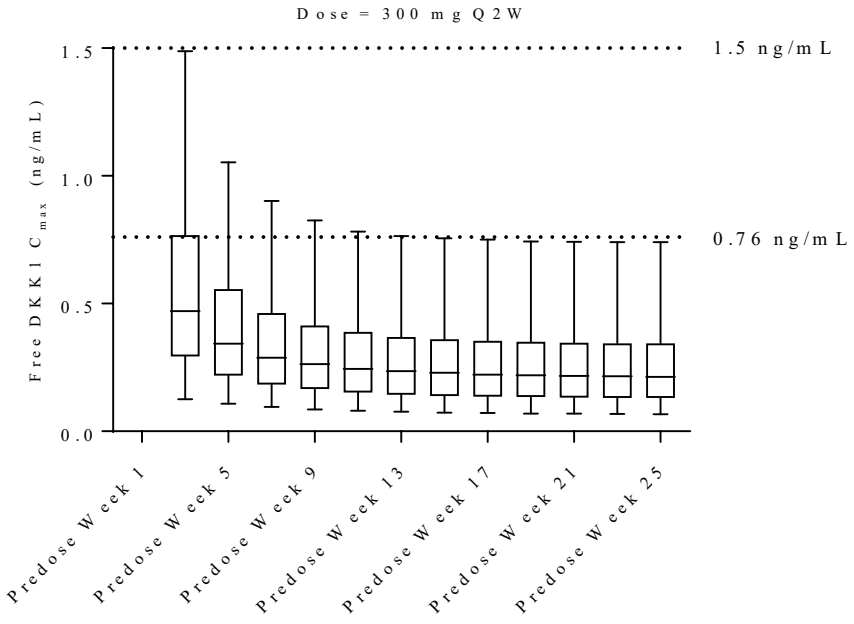
DKN-01 is selective for the DKK1 member of the dickkopf family. It binds human DKK1 with high affinity and, as a consequence, potently neutralizes DKK1. The levels of the protein DKK1 are elevated in a variety of tumor types and have been implicated in tumor growth and disease progression. A preclinical NSCLC A549 xenograft model study demonstrated that suppression of free (unbound) DKK1 concentrations correlated with an inhibition of tumor growth.

A target-mediated disposition model was utilized to fit the clinical DKN-01/DKK1 concentration data. The model incorporated two DKN-01 clearance pathways, one non-specific (linear) clearance pathway, and one target-mediated (nonlinear) clearance that included saturable binding to DKK1. The resulting one-target model assumed quasi-equilibrium (QE) and was utilized to simultaneously fit both total DKN-01 and total DKK1 serum concentrations. This approach was used to assess the degree of target engagement (formation of the DKN01/ DKK1 complex) by DKN-01 and the resulting suppression of free DKK1 concentrations in serum.

Based on modeling in combination with xenograft results, DKK1 neutralization (lower free DKK1) was associated with maximal tumor growth inhibition in an A549 xenograft study (see Investigators Brochure, Section 5.1.6). In order to relate these preclinical results to clinical data, model simulations were generated to predict human clinical DKN-01 and the resulting free DKK1 serum concentrations after IV drug administration once every 2 weeks (Q2W). These simulations focused on the maximal concentration for free DKK1 (DKK1 peak drug concentration [C_{max}]) over the Q2W dosing interval. The initial baseline value of free DKK1 was approximately 5.4 ng/mL (data not shown). The graphs below demonstrate that DKK1 C_{max} is substantially reduced (relative to baseline) by the administration DKN-01.

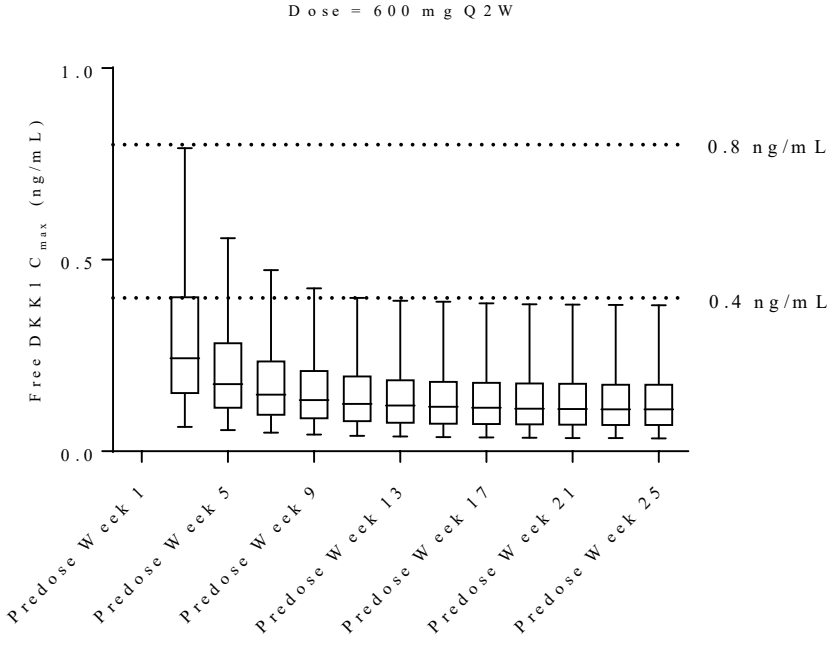
These plots illustrate that in the majority of patients (> 95%), DKK1 C_{max} concentrations could be suppressed to 1.5 ng/mL or less after one dose of 300 mg DKN-01 (Figure 1). In addition, after repeat 300 mg Q2W dosing, the highest free DKK1 C_{max} levels declined to approximately 0.76 ng/mL or less for 95% of patients (Figure 1). Simulations showed that when the DKN-01 dose was increased to 600 mg, the highest free DKK1 C_{max} was decreased to approximately 0.8 ng/mL after the first dose, and then to 0.4 ng/mL after repeat Q2W dosing to steady-state (Figure 2).

Figure 1 Predicted Maximal Free Serum DKK1 (C_{max}) Concentrations after 300 mg DKN-01 IV Dosing Administered Once Every Two Weeks (Q2W)



Note: Plot whiskers represent an interval containing 80% of patients.

Figure 2 Predicted Maximal Free Serum DKK1 (C_{max}) Concentrations after 600 mg DKN-01 IV Dosing Administered Once Every Two Weeks (Q2W)



*Plot whiskers represent an interval containing 90% of patients.

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; NCT02013154), 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; NCT02375880) 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. The dosing cycles for P102 and P103 are not comparable and the simulations above only apply to a Q2W dosing schedule, such as that used in P102.

In both of these clinical studies, pharmacokinetic (PK)/pharmacodynamic (PcD) modeling showed a dose-dependent decrease in free DKK1 C_{max} concentrations. For example, in Study P102, the median free DKK1 C_{max} after a 150 mg DKN-01 dose was 0.95 ng/mL (after the last dose for each patient), whereas the median value was 0.55 ng/mL in the 300 mg dose group. Although this last value is higher than the steady-state values in the 300 mg Q2W simulation above, it should be noted that many patients were not dosed to steady-state in the P102 clinical study.

In P102 and P103, preliminary modeling showed that for patients with a partial response (PR), the median free DKK1 C_{max} was 0.39 ng/mL and 0.50 ng/mL (respectively), and the highest individual free DKK1 C_{max} was 0.86 and 0.77 ng/mL, respectively. In non-responders, the median C_{max} was 0.65 and 0.61 ng/mL (respectively) and the highest individual free C_{max} observed was 5.7 and 10.8 ng/mL, respectively. Thus, for patients showing a PR, maximal free DKK1 C_{max} levels did not exceed 0.86 ng/mL and the median free C_{max} values were lower than those for the non-responders. Currently, it is not understood if the 0.86 ng/mL threshold is a

meaningful target for efficacy, or if median free DKK1 C_{max} values (≤ 0.39-0.50 ng/mL) are important. However, it can be stated that there is an overall trend for lower free DKK1 levels in partial responders versus non-responders. By extension, higher doses of DKN-01 (i.e., 600 mg) should lower free DKK1 levels sufficiently to see additional efficacy in patients.

Safety data for DKN-01 are available from 30 healthy subjects treated with a single dose of DKN-01 monotherapy and 229 patients with cancer treated with DKN-01, of whom 65 received DKN-01 monotherapy; 7 received DKN-01 in combination with lenalidomide/dexamethasone; 69 received DKN-01 in combination with paclitaxel; 51 patients received DKN-01 in combination with gemcitabine/cisplatin; and 37 received DKN-01 in combination with pembrolizumab.

Study DEK-DKK1-P100 was a 2-part (Parts A and B), Phase 1, multicenter, nonrandomized, open-label, multiple-dose, dose-escalation study of DKN-01 administered IV to patients 30 years of age or older. Study Part A (dose escalation) consisted of a standard 3 + 3 dose escalation designed to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of DKN-01 in patients with multiple myeloma (MM) or advanced solid tumors. Study Part B (dose confirmation) was designed to administer DKN-01 at the MTD (or highest dose tested if the MTD is not reached) to further characterize safety and tolerability and to evaluate progression-free survival in patients with relapsed/refractory NSCLC.

A total of 32 patients were enrolled in the study and received study treatment. Thirteen patients were enrolled and treated in Part A and 19 patients in Part B. In Part A, DKN-01 doses of 75, 150, and 300 mg were administered IV (once weekly) QW and 600 mg was administered IV Q2W to different cohorts of patients. There were no DLTs observed in Part A; therefore, study Part B proceeded with enrolling a total of 19 patients who received 300 mg DKN-01 Q2W. DKN-01 given IV at escalating doses from 75 mg QW to 600 mg Q2W in Part A and as a single IV agent at a dose of 300 mg Q2W in Part B was safe and well tolerated. All treatment-related adverse events (TEAEs) were Grade 1 or 2 in severity. There were no related serious adverse events (SAEs) and no discontinuations due to a TEAE.

Study DEK-DKK1-P102 is an ongoing Phase 1 non-randomized, dose-escalating, open-label, multicenter study conducted in multiple parts (Parts A through F). In addition, a separate monotherapy substudy is being conducted concurrently with Parts B through F. A maximum of approximately 224 patients aged 18 years or older with histologically confirmed recurrent or refractory esophageal, gastro-esophageal junction or gastric cancer with progressive disease requiring therapy will be enrolled in the study.

As of 20 August 2018, 124 patients have been enrolled, including 9 patients in Part A; 20 in Part B; 25 in Part C, 3 in Part D; 2 in Part E; 37 in Part F; and 28 in the monotherapy substudy. Overall, 3 patients have received DKN-01 150 mg+paclitaxel; 56 have received DKN-01 300 mg+paclitaxel; 2 have received DKN-01 150 mg+pembrolizumab; 35 have received DKN-01 300 mg+pembrolizumab; and 28 patients have received DKN-01 300 mg as monotherapy in this study.

Among patients treated with DKN-01 as monotherapy (N=28) in the monotherapy substudy, the most common type of TEAEs were gastrointestinal disorders (18 patients; 64%) and the most

common individual TEAEs were fatigue (13 patients; 46%), vomiting (8 patients; 29%), dehydration (7 patients; 25%), and nausea, constipation, and anemia (each 6 patients; 21%).

At least 1 TEAE was considered by the Investigator to be DKN-01-related for 16 (57%) patients, with the most common such events being fatigue (7 patients; 25%), anemia and vomiting (each 4 patients; 14%), and nausea and decreased appetite (each 3 patients; 11%). All other DKN-01-related TEAEs were reported for ≤2 patients.

One (4%) patient treated with DKN-01 monotherapy experienced DKN-01-related Grade 3 TEAEs, hyponatremia and lymphopenia. All other DKN-01-related TEAEs were Grade 1 or 2 in intensity.

Among patients treated with DKN-01 300 mg+paclitaxel (N=56), the most common type of TEAEs were gastrointestinal disorders (41 patients; 73%) and the most common individual TEAEs were fatigue (29 patients; 52%), anemia (27 patients; 48%), alopecia and peripheral sensory neuropathy (each 19 patients; 34%), neutropenia (17 patients; 30%), cough (16 patients; 29%), and dyspnea (14 patients; 25%).

Among the 3 patients treated with the lower DKN-01 dose of 150 mg+paclitaxel, the TEAE profile was similar to that seen with the 300 mg dose, with the most common TEAEs being diarrhea and fatigue (each 3 patients; 100%) and arthralgia, headache, and toothache (each 2 patients; 67%). All other TEAEs were reported for 1 patient only at this dose level.

Thirty-two (57%) of 56 patients treated with DKN-01 300 mg +paclitaxel experienced a DKN-01-related TEAE, most commonly fatigue (13 patients; 23%), diarrhea (7 patients; 13%), nausea (6 patients; 11%), anemia and decreased appetite (each 5 patients; 9%), and constipation and neutropenia (each 4 patients; 7%).

Six (11%) patients experienced a DKN-01-related Grade 3 TEAE, including hypophosphatemia (2 patients; 4%), anemia, monocytosis, neutropenia, and peripheral neuropathy (1 patient; 2%).

DKN-01-related TEAEs reported with DKN-01 150 mg + paclitaxel included single incidences of dysgeusia, fatigue, headache, peripheral sensory neuropathy, and stomatitis, with fatigue and peripheral sensory neuropathy being Grade 3 in intensity.

Among the 56 patients who received DKN-01 300 mg + paclitaxel, 22 (39%) experienced at least 1 SAE, with infections and infestations being the most common type (9 patients; 16%). Individual SAEs reported for >1 patient included pneumonia (4 patients; 7%), and aspiration, lung infection, and pulmonary embolism (each 2 patients; 4%). All SAEs were considered by the Investigator to be unrelated to DKN-01.

Three patients experienced a Grade 5 TEAE, including aspiration (2 patients) and pulmonary embolism and respiratory failure in 1 patient each. For all 3 patients, the TEAE resulting in death was considered by the Investigator to be unrelated to DKN-01.

For summaries of the clinical safety of DKN-01 300 mg administered in conjunction with pembrolizumab (Study DEK-DKK1-P102) or in conjunction with gemcitabine and cisplatin (Study DEK-DKK1-P103), please refer to the Investigator's Brochure.

In the current study, as of 20 August 2018, the most common TEAEs among patients receiving DKN-01 as monotherapy (N=5) and in combination with paclitaxel (N=10) in Study

DEK-DKK1-P204 are summarized. Overall, 11 (73%) of 15 patients experienced at least 1 TEAE. TEAEs reported for >1 patient included arthralgia, constipation, hypokalemia, and lymphopenia.

Eight (53%) patients experienced at least 1 TEAE that was considered by the Investigator to be DKN-01-related. Such events reported for >1 patient included hypokalemia and lymphopenia (each 2 patients), with 1 case of lymphopenia assessed as Grade 3 in intensity. All other DKN-01-related TEAEs were Grade 1 or 2 in intensity.

The dose of paclitaxel selected for use in the current study, 80 mg/m^2, is the same as that employed in combination with DKN-01 in Study P102. For detailed information related to clinical safety, please refer to the Investigator's Brochure.

1.4. Justification of the Study Design

This study employs a "basket" design, a relatively new form of oncologic clinical study design predicated on the hypothesis that the presence of a molecular marker predicts response to a targeted therapy independent of tumor histology (Redig and Jänne 2015; Mandrekar et al. 2015; Menis et al. 2014). Several recent studies have employed this type of design, including the large (estimated 1000 patients) "NCI-MATCH" study (i.e., National Cancer Institute Molecular Analysis for Therapy Choice) (ClinicalTrials.gov identifier NCT02465060) and "CUSTOM" study (i.e., Molecular Profiling and Targeted Therapies in Advanced Thoracic Malignancies) (ClinicalTrials.gov identifier NCT01306045).

Per the basket design, patients will be assigned to 1 of 4 specific treatment groups in a non-randomized fashion, with each group essentially representing an independent Phase 2 study conducted in parallel, with each group employing a 2-stage design. According to this design, a particular group may be stopped if a preliminary lack of antitumor activity is seen in that group in Stage 1 without impacting the other study groups. Conversely, patients will be enrolled in Stage 2 for a particular group if Stage 1 did not reveal a preliminary lack of antitumor activity.

The Sponsor, Monitor, and Investigators will perform this study in compliance with the protocol, Good Clinical Practice (GCP) and International Council for Harmonisation (ICH) guidelines, and applicable regulatory requirements.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective in each independent study group (Groups 1-4) of this study is:

- To determine the objective response rate (ORR).

The primary objectives in each independent study group (Groups 5-6) are:

- To characterize the safety of DKN-01 600 mg ± paclitaxel in patients with recurrent carcinosarcoma (MMMT).
- To identify the recommended Phase 2 dose (RP2D) of DKN 01 ± paclitaxel in patients with recurrent carcinosarcoma (MMMT) based on safety, PK, and PcD.

2.1.2. Secondary Objectives

The secondary objectives in each independent study group (Groups 1-4) of this study are:

- To determine the objective disease control rate (ODCR).
- To determine OS.
- To determine progression-free survival (PFS).
- To evaluate additional measures of efficacy, including time to progression (TTP), duration of response (DoR), duration of complete response (DoCR), duration of clinical benefit (DoCB), and time to treatment failure (TTTF).
- To evaluate the safety of the study treatment regimen.
- To characterize the PK of DKN-01 as monotherapy and in combination with paclitaxel in patients with recurrent EEC or EOC.
- To detect anti-DKN-01 antibodies in human serum.

The secondary objectives in each independent study group (Groups 5-6) of this study are:

- To determine the ORR.
- To determine the ODCR.
- To determine OS.
- To determine PFS.
- To evaluate additional measures of efficacy, including TTP, DoR, DoCR, DoCB, and TTTF.
- To characterize the PK of DKN-01 as monotherapy and in combination with paclitaxel in patients with recurrent carcinosarcoma (MMMT).
- To detect anti-DKN-01 antibodies in human serum.

2.1.3. Exploratory Objectives

The exploratory objectives of this study in each independent study group (Groups 1-6) are:

- To evaluate response to therapy in patients with and without activating β-catenin mutations and/or Wnt signaling genetic alterations.
- To evaluate DKK1 concentration in serum and plasma relative to safety and efficacy outcomes.
- To evaluate tumor genetics, gene expression levels (e.g., RNA-Seq), DKK1 expression (e.g., RNAscope in situ hybridization), immunohistology, infiltrating immune cells and additional immunohistochemistry (IHC) staining (DKK1 and associated downstream elements [e.g., β-catenin]) on tumor tissue relative to safety and efficacy outcomes.
- To evaluate the frequency of myeloid derived suppressor cells (MDSCs) and T effector memory cells in peripheral blood mononuclear cells relative to safety and efficacy outcomes.

2.2. Study Endpoints

In support of objectives relating to an investigation of the safety and clinical effectiveness of a DKN-01 dose exceeding 300 mg, the secondary efficacy endpoints for Group 5 and Group 6 are those specified as primary and secondary endpoints for Groups 1-4. Safety endpoints for Group 5 and Group 6 include those specified as safety endpoints for Groups 1-4, with the addition of a summary of the incidence of DLTs for Groups 5 and 6. In addition, the evaluation of the higher DKN-01 dose will also be based on a review of pharmacokinetic and PcD data.

2.2.1. Efficacy Endpoints

The primary efficacy endpoint in each independent study group (Groups 1-4) is:

- ORR (i.e., best overall response [BOR] of complete response [CR] + partial response [PR]), as assessed by the Investigator using the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) (Eisenhauer et al. 2009).

Secondary efficacy endpoints in each independent study group (Groups 1-4) are:

- ODCR (i.e., CR+PR+ stable disease [SD] > 6 weeks), as assessed by the Investigator using RECIST 1.1.
- OS, defined as the time from first study drug dose (i.e., Cycle 1, Day 1 [C1D1]) to death from any cause.
- PFS, defined as the time from first study drug dose (C1D1) to first radiographically-documented PD, as determined using RECIST 1.1, or death due to any cause.
- TTP, defined as the time from first study drug dose (C1D1) until the date of first radiographically-documented PD, as determined using RECIST 1.1.
- DoR, defined as the time from initial response (≥PR) until radiographically-documented PD or death; PD is defined using RECIST 1.1.
- DoCR, defined as the time from initial CR until radiographically-documented PD or death; PD is defined using RECIST 1.1.

- DoCB, defined as the time from the first tumor assessment of CR, PR or SD to the time of PD, as determined using RECIST 1.1, or death due to any cause
- TTTF, defined as the time from first study drug dose (C1D1) until the date of discontinuation of DKN-01 for any reason, including PD, toxicity, and death.

Secondary efficacy endpoints in each independent study group (Groups 5-6) are:

- ORR (i.e., BOR of CR + PR), as assessed by the Investigator using RECIST 1.1.
- ODCR (i.e., CR+PR+SD > 6 weeks), as assessed by the Investigator using RECIST 1.1.
- OS, defined as the time from first study drug dose (i.e., C1D1) to death from any cause.
- PFS, defined as the time from first study drug dose (C1D1) to first radiographically-documented PD, as determined using RECIST 1.1, or death due to any cause.
- TTP, defined as the time from first study drug dose (C1D1) until the date of first radiographically-documented PD, as determined using RECIST 1.1.
- DoR, defined as the time from initial response (≥PR) until radiographically-documented PD or death; PD is defined using RECIST 1.1.
- DoCR, defined as the time from initial CR until radiographically-documented PD or death; PD is defined using RECIST 1.1.
- DoCB, defined as the time from the first tumor assessment of CR, PR or SD to the time of PD or death due to any cause; PD is defined using RECIST 1.1.
- TTTF, defined as the time from first study drug dose (C1D1) until the date of treatment discontinuation of DKN-01 for any reason, including PD, toxicity, and death.

2.2.2. Safety Endpoints

The safety endpoints in each independent study group (Groups 1-6) are:

- Incidence of TEAEs, Grade 3 /4 / 5 TEAEs, serious adverse events (SAEs), and TEAEs leading to study drug discontinuation.
- Incidence of treatment-emergent Grade 3 / 4 clinical laboratory abnormalities.
- Incidence of infusion reactions.
- Changes from baseline in clinical laboratory parameters (serum chemistry, hematology, coagulation, and urinalysis).
- Changes from baseline in vital signs and electrocardiogram (ECG) parameters.
- Shift from baseline in Eastern Cooperative Oncology Group (ECOG) performance status.

Additionally, for Groups 5 and 6:

- Incidence of DLTs.

2.2.3. Pharmacokinetic Endpoint

The PK endpoint is:

- C_{max}, time to peak concentration (T_{max}), and areas under the concentration-time curve (AUCs).

2.2.4. Immunogenicity Endpoint

The immunogenicity endpoint is:

- Anti-DKN-01 antibodies.

2.2.5. Exploratory Endpoints

The exploratory endpoints in each independent study group are:

- DKK1 concentration in serum and plasma relative to safety and efficacy outcomes.
- Tumor genetics, gene expression levels (e.g., RNA-Seq), DKK1 expression (e.g. RNAscope in situ hybridization), immunohistology, infiltrating immune cells and additional IHC staining (e.g., DKK1 and associated downstream elements, [e.g., β-catenin]) on tumor tissue relative to safety and efficacy outcomes.

3. INVESTIGATIONAL PLAN

3.1. Overall Design and Plan of the Study

Study DEK-DKK1-P204 is a Phase 2 basket study designed to evaluate DKN-01 activity either as monotherapy or, at the Investigator's discretion, in combination with paclitaxel in patients with recurrent EEC, recurrent platinum-resistant/refractory EOC (Groups 1-4), or recurrent carcinosarcoma (MMMT) (Groups 5-6) who have received at least one prior systemic therapy for advanced disease. For Groups 1-4, this basket study will enrich for activating β-catenin mutation and/or Wnt signaling alterations (see **Screening,** Section 3.2.1). A maximum of 124 evaluable patients aged 18 years or older with histologically confirmed recurrent EEC, recurrent platinum-resistant/refractory EOC, or recurrent carcinosarcoma (MMMT) with PD requiring therapy will be enrolled in the study. Patients who are not eligible to receive paclitaxel will be enrolled in the monotherapy group by primary tumor. Six (6) distinct patient groups are being enrolled with up to 21 evaluable patients in Groups 1, 3 and 4, up to 31 evaluable patients in Group 2, up to 10 evaluable patients in Group 5, and up to 20 evaluable patients in Group 6, as follows:

- Group 1: DKN-01 monotherapy in recurrent EEC
- Group 2: DKN-01+paclitaxel in recurrent EEC
- Group 3: DKN-01 monotherapy in recurrent EOC
- Group 4: DKN-01+paclitaxel in recurrent EOC
- Group 5: DKN-01 monotherapy in recurrent carcinosarcoma (MMMT)
- Group 6: DKN-01+paclitaxel in recurrent carcinosarcoma (MMMT)

Groups 1-4 employ a 2-stage design conducted separately for each group. For each monotherapy group (Groups 1 and 3), after 12 evaluable patients are enrolled (Stage 1), an additional 9 evaluable patients will be enrolled in that group (Stage 2) if 1 or more patients respond (i.e., experience CR or PR). If there are no responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group. For the EEC combination therapy group (Group 2), after 20 evaluable patients are enrolled (Stage 1), if 3 or more patients respond (i.e., experience CR or PR), an additional 11 evaluable patients will be enrolled in that group (Stage 2). If there are fewer than 3 responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group. For the EOC combination therapy group (Group 4), after 16 evaluable patients are enrolled (Stage 1), if 2 or more patients respond (i.e., experience CR or PR), an additional 5 evaluable patients will be enrolled in that group (Stage 2). If there are fewer than 2 responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group.

Groups 5 and 6 are exploratory in nature. Group 5 will enroll approximately 10 evaluable patients and Group 6 will enroll approximately 20 evaluable patients.

For Groups 5 and 6, 3 patients in each group will initially be enrolled in a safety run-in phase. If the first 2 of 3 patients in a group have a DLT (see Section 5.6.2.1), the MTD will have been exceeded (see Section 5.6.2.1) and a cohort will be enrolled to evaluate DKN-01 at a dose of

300 mg (±paclitaxel, depending on group assignment). If none of the 3 treated patients in a group develop a DLT after a minimum of one cycle of treatment, enrollment into the group will proceed according to the planned schedule. If a DLT is observed in 1 of the 3 patients in a group, up to an additional 3 patients will be enrolled and treated. If no further DLTs are observed within the expanded group of 6, enrollment into the group will proceed. If ≥2 of 6 patients within a group experience a DLT, the MTD will have been exceeded and a cohort will be enrolled to evaluate DKN-01 at a dose of 300 mg (±paclitaxel, depending on group assignment).

For the Rollover Treatment Phase, patients remain on the same dose and schedule as they received in the previous study part.

3.2. Study Periods

The study has 6 distinct periods, as follows:

3.2.1. Screening

Potentially eligible patients will sign informed consent prior to undergoing any study-related procedures. Patients will undergo Screening assessments for protocol eligibility within 28 days of study entry, as outlined in Table 6.

Fresh tumor tissue samples are required to be collected from all patients during Screening for genomic cancer profiling (i.e., CTNNB1 mutation and Wnt-signaling mutation), gene expression levels (e.g., RNA-Seq), DKK1 expression (e.g., RNAscope in situ hybridization), immunohistology, infiltrating immune cells and additional IHC staining (DKK1 and associated downstream elements, [e.g., β-catenin]). Although fresh biopsy is preferred, an archived specimen collected within 3 months of C1D1 may be acceptable, with the prior approval of the Medical Monitor.

This basket study is enriching for activating β-catenin mutations and/or Wnt signaling alterations, whereby approximately 50% of all evaluable patients enrolled in each group, in Stage 1 and in Stage 1 and 2 combined (Groups 1-4) and in Groups 5 and 6, are required to have an activating β-catenin mutation (CTNNB1 mutation) or other Wnt signaling alteration (e.g., LRP5/6, APC, AXIN1/2, GSK3B, RNF43, ZNRF3, RSPO2/3, FBXW7, ARID1A, or CBP/CREBBP; see full list in Appendix 12.6), based on testing of the Screening tumor tissue sample or previously documented alteration by a Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory.

To allow-for real-time testing of Screening tumor tissue samples, the Screening period may be extended to 42 days, with results obtained and confirmed to be positive before the performance of additional Screening procedures. Note that all other Screening assessments must be performed within 28 days before C1D1.

Patients with prior documentation of a known activating β-catenin mutation (CTNNB1 mutation) or other Wnt signaling alteration by a CLIA-accredited laboratory will be permitted to enroll based on this documentation. In such patients, a Screening tumor sample will be collected and analyzed centrally; however, confirmatory results are not required for study enrollment.

Groups 1-4 employ a 2-stage design conducted separately for each group. For each monotherapy group (Groups 1 and 3), once 6 evaluable patients are enrolled who do not have activating β-catenin mutation and/or Wnt signaling alterations, Stage 1 enrollment for that group will continue only with patients with activating β-catenin mutation and/or Wnt signaling alterations. For Group 2, once 10 evaluable patients are enrolled who do not have activating β -catenin mutation and/or Wnt signaling alterations, Stage 1 enrollment for that group will continue only with patients with activating β-catenin mutation and/or Wnt signaling alterations. For combination therapy Group 4, once 8 evaluable patients are enrolled who do not have activating β-catenin mutation and/or Wnt signaling alterations, Stage 1 enrollment for that group will continue only with patients with activating β-catenin mutation and/or Wnt signaling alterations. At any time for Groups 1, 3, or 4, once 10 evaluable patients who do not have a documented activating β-catenin mutation and/or other Wnt signaling alteration have been enrolled in a group, enrollment in that group will continue only with patients with activating β-catenin mutation (CTNNB1 mutation) or other identified Wnt signaling alteration. At any time for Group 2, once 15 evaluable patients who do not have a documented activating β-catenin mutation and/or other Wnt signaling alteration have been enrolled, enrollment in that group will continue only with patients with activating β-catenin mutation (CTNNB1 mutation) or other identified Wnt signaling alteration.

3.2.2. Study Treatment Period

The Study Treatment Phase includes either DKN-01 monotherapy or DKN-01 in combination with paclitaxel; patients will be assigned to receive monotherapy or combination therapy at the Investigator's discretion. Patients who initially start combination therapy but subsequently discontinue paclitaxel may continue to receive DKN-01 as monotherapy during the Treatment Period.

Patients are to begin study treatment as soon as possible (and preferably within 24 hours) after completion of all screening procedures and confirmation of study eligibility. Study visits will be performed as outlined in Table 6.

During the Treatment Period, tumor measurements are to be performed using the same radiographic methods used during Screening. Tumor response, including PD, is to be assessed by the Investigator within ±7 days of the first study drug dose in every other cycle, starting in C3, and at the End of Treatment (EOT) Visit, using RECIST 1.1.

The severity of adverse events (AEs) will be graded according to the United States National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

3.2.3. Rollover Treatment Phase

The Rollover Treatment Phase will permit patients who are still experiencing clinical benefit continued access to study drug(s) until they meet discontinuation criteria as per Section 6.4.1. Study visits will be performed as outlined in Table 7.

3.2.4. Study Treatment Discontinuation

All patients will continue study treatment in the Treatment Phase until development of radiographically-documented PD or unacceptable toxicity or another discontinuation criterion is met, as determined by the Investigator. All patients will return for an EOT Visit approximately 30 days (+7 days) after the last treatment administration in the Treatment Period. The reason for discontinuation from study treatment will be documented in the electronic case report form (eCRF).

3.2.5. Progressive Disease Follow-up Phase

To ensure accuracy and completeness for the disease response-related endpoints, patients who permanently discontinued study treatment prior to PD will continue to be followed up in the PD follow-up phase until radiographically documented PD. During this PD follow-up period, efficacy assessments for disease response and PD per RECIST 1.1 will be performed every 8 weeks [see Table 6 (Table 7 for Rollover Treatment Phase only)]. Patients are expected not to start any other anti-cancer therapy during the PD follow-up phase prior to radiographically documented PD; however, if alternate therapy is started, patients will continue to be followed for radiologic progression even after starting subsequent therapy. After radiographically-documented PD, all patients will be followed for survival in the Survival Follow-up Phase.

3.2.6. Survival Follow-up Phase

After discontinuation of treatment and documentation of PD, all patients will be followed in the Survival Follow-up Phase for survival until death, withdrawal of consent, loss to follow-up, implementation of the rollover treatment phase, or closure of the study by the Sponsor. Survival follow-up will occur 4 times per year (every 12 weeks [±14 days]) after the EOT visit or end of PD follow-up phase, as applicable, and may be conducted via telephone or office visit. During survival follow-up, the following information will be collected: survival and subsequent anti-cancer therapies.

3.3. Study Termination

The study may be prematurely terminated if, in the opinion of the Investigator or Leap Therapeutics, Inc. (Leap), there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the Investigator or Leap 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.
- Availability of an open label extension study of DKN-01 trials, under which patients who are participating in a study with DKN-01 and who in the opinion of the investigator are receiving clinical benefit could continue to receive access to DKN-01 as a monotherapy or in combination.

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

4. STUDY POPULATION

The study population will consist of a confirmed diagnosis of recurrent EEC or recurrent platinum-resistant/refractory EOC, primary peritoneal or fallopian tube cancer, or recurrent carcinosarcoma (MMMT).

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

4.1. Number of Patients

A maximum of 124 evaluable patients are planned to be enrolled, with up to 21 evaluable patients in each of treatment Groups 1, 3, and 4, up to 31 evaluable patients in Group 2, up to 10 evaluable patients in Group 5, and up to 20 evaluable patients in Group 6.

4.2. Inclusion Criteria

Patients may be included in the study if they meet all of the following inclusion criteria during Screening prior to first dose of study drug.

Epithelial Endometrial Cancer

1. Must have a histologically confirmed diagnosis (by either primary surgical specimen or biopsy for recurrence) of recurrent previously treated EEC.

Epithelial Ovarian Cancer

2. Must have a histologically confirmed diagnosis (by either primary surgical specimen or biopsy for recurrence) of recurrent platinum-resistant/refractory EOC, primary peritoneal, or fallopian tube cancer (i.e., disease recurrence within 6 months of completion or progression during platinum-based chemotherapy).

Carcinosarcoma/Malignant Mixed Mullerian Tumors (Groups 5-6)

3. Must have a histologically confirmed diagnosis (by either primary surgical specimen or biopsy for recurrence) of recurrent uterine or ovarian carcinosarcoma (MMMT).
4. Patient must have had only 1 prior chemotherapeutic regimen for management of recurrent or advanced carcinosarcoma that may have included chemotherapy (including in adjuvant setting with refractory or disease recurrence within 6 months), chemotherapy and radiotherapy, and/or consolidation/maintenance therapy.

General

5. Must be refractory or intolerant to at least one prior standard therapy(ies) for metastatic or locally advanced disease (see Inclusion Criterion #4 for Groups 5-6).
    a. If prior therapy consisted of palliative chemoradiation therapy, it will be considered one line of therapy.
    b. Prior treatment with paclitaxel as part of a definitive therapy regimen is acceptable provided the patient is not intolerant of paclitaxel.
    c. Patients who are not eligible to receive paclitaxel will be allowed to receive single agent DKN-01.

6. Tumor tissue for mandatory pre-treatment and on–treatment evaluation (fresh biopsy during Screening preferred; archived specimen (≤3 months) may be acceptable with prior approval from the Medical Monitor).
7. One or more tumors measurable on radiographic imaging as defined by RECIST 1.1.
8. Ambulatory and ≥18 years of age.
9. ECOG performance status (PS) of 0 or 1.
    a. PS of 2 on the ECOG scale may be eligible upon the review and approval of the Medical Monitor.
10. Estimated life expectancy of at least 3 months, in the judgment of the Investigator.
11. Disease-free of active second/secondary or prior malignancies for ≥2 years with the exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or breast.
12. Acceptable liver function:
    a. Total bilirubin ≤2.0 × upper limit of normal (ULN).
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × ULN. If liver metastases are present, then ≤ 5 × ULN is allowed.
13. Acceptable renal function:
    a. Creatinine normal for age: if serum creatinine is abnormal for age the patient must have a calculated creatinine clearance ≥30 mL/min using the Cockcroft and Gault Method (Cockroft and Gault 1976).
14. Acceptable hematologic status:
    a. Granulocyte ≥1500 cells/mm^3.
    b. Hemoglobin ≥9 g/dL (transfusion permitted within 30 days of study entry).
    c. Platelet count ≥75,000 cells/mm^3.
15. Acceptable coagulation status:
    a. Prothrombin time (PT)/partial thromboplastin time (PTT) ≤ 1.2 x ULN (unless receiving anticoagulation therapy, in which case eligibility will be based upon International Normalized Ratio [INR], see below).
    b. If receiving anticoagulant: INR ≤ 3.0 and no active bleeding, (i.e., no clinically significant bleeding within 14 days prior to first dose of study therapy).
16. Females of child-bearing potential and male partners of female 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 become pregnant or suspect she is pregnant while participating in the study, the Investigator should be immediately informed.

17. Reliable and willing to make themselves available for the duration of the study and are willing to follow study-specific procedures.
18. Provided written informed consent prior to any study-specific procedures.

Rollover Treatment Phase

19. Received DKN-01 either as a monotherapy or in combination with paclitaxel in this study and is tolerating study drug(s) and currently displaying clinical benefit, in the Investigator's opinion.

4.3. Exclusion Criteria

Patients with any of the following characteristics will be ineligible for study entry:

1. Any of the following pure histologies of endometrial or ovarian cancer: germ cell, sex cord stroma, or sarcoma.
2. New York Heart Association Class III or IV cardiac disease, myocardial infarction within the past 6 months, or unstable arrhythmia.
3. Have Fridericia-corrected QT interval (QTcF) >470 msec, or history of congenital long QT syndrome. Any ECG abnormality that in the opinion of the Investigator would preclude safe participation in the study; patients with pacemakers where QTc is not a reliable measure will require an evaluation by a cardiologist to exclude co-existing cardiac conditions which would prohibit safe participation in the study.
4. Active, uncontrolled bacterial, viral, or fungal infections, within 7 days of study entry requiring systemic therapy.
5. Known to be human immunodeficiency virus (HIV) positive, have hepatitis B surface antigen (HBSAg), or hepatitis C antibodies (HCAb) unless hepatitis C virus ribonucleic acid (HCV RNA) undetected/negative.
6. History of major organ transplant (i.e., heart, lungs, liver, or kidney).
7. History of autologous/allogenic bone marrow transplant.
8. Serious nonmalignant disease that could compromise protocol objectives in the opinion of the Investigator and/or Sponsor.
9. Pregnant or nursing.
10. History of osteonecrosis of the hip or evidence of structural bone abnormalities in the proximal femur on magnetic resonance imaging (MRI) scan that are symptomatic and clinically significant. Degenerative changes of the hip joint are not exclusionary. Screening of asymptomatic patients is not required.
11. Symptomatic central nervous system (CNS) malignancy or metastasis. Patients with treated CNS metastases are eligible provided their disease is radiographically stable, asymptomatic, and they are not currently receiving corticosteroids and/or anticonvulsants. Screening of asymptomatic patients without a history of CNS metastases is not required.

12. Known osteoblastic bony metastasis. Screening of asymptomatic patients without a history of metastatic bony lesions is not required.

Medication-Related

13. Treatment with surgery or chemotherapy within 21 days prior to study entry (42 days for nitrosoureas or mitomycin C).
14. Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to study entry.
15. Clinically significant peripheral neuropathy at the time of study entry. Patients with pre-existing peripheral neuropathy will be allowed to receive single agent DKN-01.
16. History of hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor® EL (polyoxyethylated castor oil). Patients who exhibit these hypersensitivities will be eligible to receive single agent DKN-01.
17. Prior radiation therapy within 14 days prior to study entry.
18. Currently receiving any other investigational agent or received an investigational agent within last 30 days of study entry.
19. Previously treated with an anti-DKK1 therapy.
20. Significant allergy to a pharmaceutical therapy that, in the opinion of the Investigator, poses an increased risk to the patient.

Lifestyle-Related

21. Active substance abuse.

5. STUDY TREATMENTS

5.1. Clinical Trial Materials

5.1.1. 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 Leap 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 Leap or its designee in the pharmacy manual.

5.1.2. Paclitaxel

TAXOL® (paclitaxel) Injection is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to IV infusion. TAXOL® is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL[1] (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP (Bristol-Myers Squibb Company, 2011).

Paclitaxel will be provided using commercial supplies.

5.2. Blinding, Packaging and Labeling

5.2.1. Blinding and Breaking the Blind

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

5.2.2. 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.

5.3. Method of Assigning Patients to Treatment

Patients who meet all eligibility criteria, as defined in Section 4.2 and Section 4.3, will be enrolled. Patients who are considered eligible for paclitaxel, based on the Investigator's judgement, may be assigned to a combination therapy group, based on their primary diagnosis. Patients who are not considered eligible to receive paclitaxel, based on the Investigator's judgement, will be enrolled to a monotherapy group, based on their primary diagnosis.

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[1] Cremophor® EL is the registered trademark of BASF Aktiengesellschaft. Cremophor® EL is further purified by a Bristol-Myers Squibb Company proprietary process before use.

Before each patient's enrollment into the study, an eligibility check may be conducted between the investigational site and Leap to confirm that each patient meets all enrollment criteria. Note that tumor tissue must be collected during Screening (fresh biopsy preferred; archived specimen [≤3 months] may be acceptable with prior approval from Medical Monitor) for a patient to be eligible for enrollment in the study. Upon confirmation of eligibility, the Sponsor or designee will confirm the identification number assignment and group for each patient.

5.4. 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.

5.5. 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 in the 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.

5.6. 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 Leap 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.

5.6.1. DKN-01 Administration

DKN-01 is a large molecular weight protein that will be administered at a dose of 300 mg (Groups 1-4) and 600 mg (Groups 5 and 6) as an IV infusion over a minimum of 30 minutes and up to a maximum of 2 hours on D1 and 15 of each 28-day cycle without interruption.

5.6.2. Paclitaxel Administration

For patients receiving combination therapy, paclitaxel will be administered at a dose of 80 mg/m^2 via IV infusion over 1 hour on D1, 8, and 15 of each 28-day cycle according to standard clinical practice and as per the prescribing information (Bristol-Myers Squibb Company, 2011).

Standard of care premedication for paclitaxel will be given prior to each paclitaxel infusion (e.g., dexamethasone 20 mg PO 12 to 6 hours prior; diphenhydramine 50 mg IV 30 to 60 minutes prior; and cimetidine or ranitidine 50 mg IV 30 to 60 minutes prior) (Bristol-Myers Squibb Company, 2011).

On D1 and 15 of each cycle, DKN-01 will be administered first followed by paclitaxel as separate infusions.

For Groups 5 and 6, 3 patients in each group will initially be enrolled in a safety run-in phase. If the first 2 of 3 patients in a group have a DLT (see Section 5.6.2.1), the MTD will have been exceeded (see Section 5.6.2.1) and a cohort will be enrolled to evaluate DKN-01 at a dose of 300 mg (±paclitaxel, depending on group assignment). If none of the 3 treated patients in a group develop a DLT after a minimum of one cycle of treatment, enrollment into the group will proceed according to the planned schedule. If a DLT is observed in 1 of the 3 patients in a group, up to an additional 3 patients will be enrolled and treated. If no further DLTs are observed within the expanded group of 6, enrollment into the group will proceed. If ≥2 of 6 patients within a group experience a DLT, the MTD will have been exceeded and a cohort will be enrolled to evaluate DKN-01 at a dose of 300 mg (±paclitaxel, depending on group assignment).

5.6.2.1. Dose-Limiting Toxicity Determination and Maximum Tolerated Dose/ Recommended Phase 2 Dose Definition

A DLT is defined as an AE during C1 that is possibly related to the study drug(s) and fulfills any one of the following criterion using the NCI CTCAE version 5.0.

- Grade 4 neutropenia lasting ≥ 5 days or Grade 3 or 4 neutropenia with fever and/or infection
- 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 including the clinical sequelae [e.g., 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.

Patients in Group 6 must have completed 100% of the DKN-01 doses and 75% of the paclitaxel doses in C1 to be evaluable for DLT.

Furthermore, in any study part, if a patient experiences a TEAE meeting the definition of DLT in the first cycle of treatment, he/she will be discontinued from study treatment.

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.

The RP2D is defined as the MTD or up to the highest planned dose level evaluated in Groups 5-6 without identification of the MTD.

5.6.3. Rollover Treatment Phase

The dose and schedule of study drug(s) will remain the same as per the previous study part.

6. TREATMENT OF PATIENTS

6.1. Criteria for Initiation of a New Treatment Cycle

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

- Absolute neutrophil count (ANC) resolved to baseline grade or ≤Grade 1 (≥1500/mm^3).
- Platelet count ≥75×10^9/L.
- Liver associated enzymes/function (e.g., AST, ALT, alkaline phosphatase [ALP], bilirubin) ≤Grade 1 or resolved to baseline grade.
- Any other drug-related AEs that may have occurred resolved to ≤Grade 1 severity or baseline grade.

If these conditions are not met on D1 of a new cycle, 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.

If, in the opinion of the Investigator, a patient is receiving clinical benefit from continued treatment with DKN-01 alone or in combination with paclitaxel, patients may continue therapy until developing documented PD or otherwise meeting criteria for treatment discontinuation (Section 6.4.1).

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

6.1.1. Criteria for Treatment on Days 8 and 15 of a Treatment Cycle

Treatment may be administered on D8 and 15 for patients meeting the following criteria:

- ANC ≥1000 cells/mm^3.
- Platelet count ≥75×10^9/L.
- Liver associated biochemical abnormalities must resolve to ≤Grade 1 or baseline grade.

Refer to Section 6.2.2 for instructions for paclitaxel dose modifications for the management of peripheral neuropathy as well as neutropenia and thrombocytopenia within a cycle.

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

6.2.1. DKN-01 Dosing and Dose Adjustments

DKN-01 will be administered via IV infusion on D1 and 15 in each 28-day treatment cycle.

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 grade. 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 grade (see Table 1).

Table 1 DKN-01 Dose Adjustments for Groups 1-4

Toxicity Occurrence	DKN-01
First*	Restart at 300 mg after toxicity resolves to ≤Grade 1 or baseline grade.
Second	Restart at reduced dose of 150 mg after toxicity resolves to ≤Grade 1 or baseline grade.
Third	Restart at reduced dose of 75 mg after toxicity resolves to ≤Grade 1 or baseline grade.
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.

Table 2 DKN-01 Dose Adjustments for Groups 5 and 6

Toxicity Occurrence	DKN-01
First*	Restart at 600 mg after toxicity resolves to ≤Grade 1 or baseline grade.
Second	Restart at reduced dose of 300 mg after toxicity resolves to ≤Grade 1 or baseline grade.
Third	Restart at reduced dose of 150 mg after toxicity resolves to ≤Grade 1 or baseline grade.
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.

For patients who experience an infusion reaction to DKN-01, all attempts should be made to obtain blood samples for determination of anti-DKN-01 antibody (immunogenicity sample) and serum DKN-01 levels as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event or just prior to the start of new therapy, whichever comes first. In addition, these samples may be used for determination of PcD markers.

DKN-01-related adverse reactions and infusion reactions are to be managed as described in Appendix 12.5 and Appendix 12.4, respectively.

6.2.2. Paclitaxel Dosing and Dose Adjustments

For patients receiving combination therapy, paclitaxel is administered via IV infusion on D1, 8, and 15 of each treatment cycle. The paclitaxel dose is to be modified for peripheral neuropathy and for neutropenia and thrombocytopenia as described in Table 3 and Table 4, respectively.

Table 3 Paclitaxel Dose Modifications for Peripheral Neuropathy

Grade	Mgmt/Next Dose Paclitaxel
Grade 1-2, tolerable	No change in dose.
Grade 2, intolerable	Hold until ≤ tolerable Grade 2. Resume at reduced dose.
Grade 3-4	Hold until ≤Grade 2. Resume at reduced dose.
Recommended management: consider medications for neuropathy.	

Table 4 Paclitaxel Dose Modifications for Neutropenia and Thrombocytopenia

Laboratory Value	Management/Next Dose Paclitaxel
Neutropenia	
Day 8 or 15 of cycle:	Hold until ≥1000 cells/mm^3, no change in dose.
The use of growth factors is permitted	
Thrombocytopenia	
Day 8 and 15 of cycle:	Hold until ≥75×10^9/L, no change in dose.
Grade 3-4	Hold until ≥75×10^9/L. Resume at reduced dose, if indicated.
A platelet goal of 50×10^9/L should be considered for those on anticoagulation.	

Recommendations for the management of other toxicities considered to be paclitaxel-related are summarized in Table 5.

Table 5 Paclitaxel Dose Adjustments

Toxicity Occurrence	Paclitaxel
First*	Restart at 80 mg/m^2 after toxicity resolves to ≤Grade 1 or baseline grade (Days 1, 8, and 15 per cycle)
Second	Restart at 70 mg/m^2 after toxicity resolves to ≤Grade 1 or baseline grade (Days 1, 8, and 15 per cycle)
Third	Restart at 60 mg/m^2 after toxicity resolves to ≤Grade 1 or baseline grade (Days 1, 8, and 15 per cycle)
Fourth	Discontinue

*If the toxicity is judged to be significant in the opinion of the Investigator and the Investigator does not wish to dose at the same dosing level, he/she may contact the Medical Monitor to consider a 1 dose reduction level with the first occurrence of toxicity.

If, in the opinion of the Investigator, a patient is receiving clinical benefit from treatment with the combination of DKN-01 plus paclitaxel but has a compelling clinical reason after C2 to discontinue treatment with paclitaxel, the patient will be permitted to continue in the study with DKN-01 monotherapy at the discretion of the treating clinician. Patients can continue therapy until they meet criteria for discontinuation (Section 6.4.1).

6.2.3. Dose Delays

The start of a new cycle may be delayed up to 28 days (for toxicities only) to allow sufficient time for recovery from the previous cycle. Patients who do not recover from toxicity within 28 days will be discontinued from the study and undergo EOT procedures.

Missed doses will not be made up.

Supportive care use of transfusion for symptomatic anemia or hemoglobin <8 g/dL and of colony-stimulating factors for neutropenia is encouraged per established guidelines.

A treatment delay at the start of a cycle (Day 1) of no more than 7 days, because of holidays, weekends, inclement weather, or other justifiable events, will be permitted and not considered as a protocol violation. If a delay of therapy is ≥28 days is necessary, the patient must be removed from the study.

6.3. Duration of Study Participation and Treatment

A patient's duration of study participation will include a Screening Period, a Treatment Period of repeating 28-day cycles, and a Post-Treatment Follow-up Period. The total duration of participation for a patient is dependent upon the patient's response to treatment as well as toxicity to study drugs. If, in the opinion of the Investigator, a patient is receiving clinical benefit from treatment with the combination of DKN-01 plus paclitaxel but has a compelling clinical reason after C2 to discontinue treatment with paclitaxel, the patient will be permitted to continue in the study with DKN-01 monotherapy at the discretion of the treating clinician. Patients can continue therapy until they meet criteria for discontinuation (Section 6.4.1).

Patients enrolled in the rollover treatment phase will continue to receive the same dose and schedule of study drug(s) as per the previous study part.

Upon discontinuing DKN-01, patients undergo EOT assessments and are followed up for AEs for 30 days after the last DKN-01 dose.

After completion of the EOT visit, patients without radiographically-documented PD will continue to be followed up in the PD follow-up phase until radiographically documented PD. During this PD follow-up period, efficacy assessments for disease response and PD per RECIST 1.1 will be performed every 8 weeks [see Table 6 or Table 7 (Rollover Treatment Phase only)]. Patients are expected not to start any other anti-cancer therapy during the PD follow-up phase prior to radiographically documented PD; however, if alternate therapy is started, patients will continue to be followed for radiologic progression even after starting subsequent therapy.

After discontinuation of treatment and documentation of PD, all patients will be followed in the Survival Follow-up Phase for survival until death, withdrawal of consent, loss to follow-up, or closure of the study by the Sponsor. Survival follow-up will occur 4 times per year (every 12 weeks [±14 days]) after the 30 days post treatment discontinuation visit or end of PD follow-up phase, as applicable, and may be conducted via telephone or office visit. During survival follow-up, the following information will be collected: survival and subsequent anti-cancer therapies.

6.4. Withdrawal and Replacement of Patients

6.4.1. 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 EOT 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.
- Availability of an open label extension study of DKN-01 trials, under which patients, who are participating in a study with DKN-01 and who in the opinion of the investigator are receiving clinical benefit could continue to receive access to DKN-01 as a monotherapy or in combination
- Dosing delay of ≥28 days.
- Development of radiographically-documented PD, as determined by the Investigator using RECIST 1.1 (Appendix 12.2).
- With the consent of the patient or the legally authorized representative the Investigator may determine that limited data collection may be continued (e.g., through medical record review) for the duration of the study after a patient has withdrawn.

6.4.2. Replacement of Study Patients

Patients who discontinue from the study will not be replaced.

6.5. Concomitant Medications, Therapies and Supportive Care

No other chemotherapy, immunotherapy, hormone therapy, or any other type of therapy (including herbal or natural supplements) for treatment of cancer or experimental drugs will be permitted while the patients are on this study. In addition, any disease progression requiring other forms of specific antitumor therapy will also necessitate discontinuation from the study. Appropriate documentation for all forms of premedications, supportive care, and concomitant medications must be captured on the case report form.

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

All concomitant medications should be recorded in the eCRF throughout the patient's participation in the study, from the time of provision of informed consent through the EOT visit.

7. STUDY ASSESSMENTS

The Schedule of Assessments for the study is provided in Table 6 in Appendix 12.1. For the Rollover Treatment Phase of the study assessments are outlined in Table 7 in Appendix 12.1. Detailed descriptions of the study assessments to be conducted during this study are described in the following sub-sections.

7.1. Clinical Procedures and Safety Assessments

7.1.1. 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.

7.1.2. 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 on C1D1 to confirm continued study eligibility.

7.1.3. 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.

7.1.4. Physical Examination

A complete physical examination (general appearance, head/ears/eyes/nose/throat [HEENT], lungs/chest, heart, abdomen, lymph nodes, musculoskeletal, extremities, and neurological examination) will be conducted at the time points designated in Table 6, (see Table 7 for Rollover Treatment Phase). During Screening, the physical examination is to include measurement of height.

Abbreviated (i.e., symptom-directed) physical examinations will be conducted at the time points designated in Table 6 (see Table 7 for Rollover Treatment Phase) to address any complaints or concerns verbalized by the patient at all other study visits.

7.1.5. Vital Signs and Weight

Vital signs are to be measured at the time points designated in Table 6, (see Table 7 for Rollover Treatment Phase). 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.

7.1.6. Electrocardiograms

A 12-lead ECG will be obtained at the time points designated in Table 6, (see Table 7 for Rollover Treatment Phase). 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.

7.1.7. 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 6, (see Table 7 for Rollover Treatment Phase). 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.

7.1.8. 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.

Refer to Section 6.1 and Section 6.1.1 for laboratory criteria required to initiate a new treatment cycle and for subsequent study drug doses within a cycles.

Clinical laboratory evaluations are to be performed at the time points designated in Table 6 (see Table 7 for Rollover Treatment Phase). Final clinical laboratories are to be performed at the EOT visit.

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-to-lymphocyte ratio (NLR) also is to be determined. It is acceptable to use the automated differential for complete blood count (CBC).

Chemistry

Sodium, potassium, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), 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.

Urinalysis

Specific gravity, pH, protein, glucose, ketones, blood, and urine leukocyte esterase.

Coagulation Studies

PT, PTT, and INR.

Pregnancy Testing

Serum or urine pregnancy testing is to be performed for women of childbearing potential. If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. On C1D1, the pregnancy test may be performed within 72 hours before the study drug dose; the results must be available and confirmed to be negative before administration of the first study drug dose. Pregnancy testing is to be repeated during the study any time pregnancy is suspected.

Pregnant and breastfeeding women must not take DKN-01; hence the study investigator may need to test to confirm that a patient is postmenopausal. A woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months; or women with documented plasma follicle-stimulating hormone level >35μlU/mL). Women who are using oral, implanted or injectable contraceptive hormones, an intrauterine device, barrier methods (diaphragm,

condoms, spermicidal) to prevent pregnancy, practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of childbearing potential.

CA 125

Blood samples for measurement of CA125 are to be collected at the time points designated in Table 6.

Other Clinical Laboratory Tests

Blood samples for measurement of vitamin D and thyroid-stimulating hormone are to be collected at the time points designated in Table 6.

7.1.9. Concomitant Medications / Procedures Review

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

7.1.10. Adverse Event Monitoring

Each patient must be carefully monitored for the development of any AEs, including infusion-related AEs (see Section 7.1.11), throughout the study from signing of the informed consent through 30 days after the last dose of DKN-01, when EOT procedures are performed. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?"), and from signs and symptoms detected during each examination, from laboratory evaluation, observations of study personnel, patient diary, and spontaneous reports from patients.

During post-treatment follow-up, any SAEs that 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 8 of this protocol.

7.1.11. 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 12.3 and Appendix 12.4.

7.1.11.1. Infusion-related Reactions

The NCI CTCAE, version 5.0, definition of infusion-related reactions will be used in this study (see Appendix 12.3), 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.

For patients who experience an infusion reaction to DKN-01, all attempts should be made to obtain blood samples for determination of anti-DKN-01 antibody (immunogenicity sample) and serum DKN-01 levels as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event or just prior to the start of new therapy, whichever comes first. In addition, these samples may be used for determination of PcD markers.

Guidelines for the management of DKN-01 infusion-related reactions are summarized in Appendix 12.4.

7.2. Blood Sample Collection for Pharmacokinetics, Pharmacodynamics, and Exploratory Assessments

Blood samples are to be collected for PK, PcD, and exploratory assessments as indicated in the following subsections at the time points designated in Table 6. After processing of the samples for the protocol-specified assays, any remaining biological material (whole blood, serum, plasma) is to be stored for future exploratory analyses, as deemed appropriate. In the rollover treatment phase blood sample for pharmacokinetics, pharmacodynamics, and exploratory assessments will not be collected.

7.2.1. Blood Sample Collection for DKK1

Blood samples will be collected for determination of total DKK1 (includes DKK1/DKN-01 complex) in serum at the time points designated in Table 6. Free serum DKK1 levels may be estimated.

Serum levels of DKK1 will be measured using a validated Enzyme-linked Immunosorbent Assay (ELISA), designed to perform in the presence of DKN-01.

7.2.2. Pharmacokinetic Samples

Blood samples will be collected for the assessment of serum DKN-01 concentrations at the time points designated in Table 6. Instructions for the collection and handling of blood samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Serum concentrations of DKN-01 will be assayed using a validated method at a laboratory designated by the Sponsor.

Prior to analysis, the samples will be stored at a facility designated by the Sponsor. Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last patient visit for the study.

Any remaining serum from the samples collected for PK may be pooled and used for exploratory metabolism work, as deemed appropriate.

7.2.3. Samples for Immunogenicity Research

Blood samples will be collected for assessment of antibodies to DKN-01 (i.e., ADA) at the time points designated in Table 6. The blood sample collected for immunogenicity will be separated

into serum and divided into 2 tubes, one (A) for screening assay and the other (B) for storage for potential evaluation in a functional/cell-based assay.

ADA will be assessed using a validated assay (Qualitative Affinity Capture Elution [ACE] ELISA), which is tolerant to high concentrations of free drug (DKN-01).

If any patient is found to be ADA-positive at the EOT visit, the patient will be monitored monthly (if feasible) until serum samples are determined to be ADA-negative.

Samples may be stored for a maximum of 2 years following last patient visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to DKN-01. The duration allows the Sponsor to respond to regulatory requests related to DKN-01.

7.2.4. Samples for Exploratory Biomarkers

Blood samples for exploratory biomarkers relevant to DKN-01 and/or the study indication will be collected at the time points specified in Table 6.

Samples may be stored for a maximum of 2 years following last patient visit for the study at a facility selected by the Sponsor.

7.3. Tumor Tissue Samples

Fresh tumor tissue samples are required to be collected from all patients during Screening for genomic cancer profiling (i.e., CTNNB1 mutation and Wnt-signaling mutation). Although fresh biopsy is preferred, an archived specimen collected within 3 months of study entry may be acceptable, with the prior approval of the Medical Monitor.

Approximately 50% of all evaluable patients enrolled in each group, in Stage 1 and in Stage 1 and 2 combined (Groups 1-4) and in Groups 5 and 6, are required to have an activating β-catenin mutation (CTNNB1 mutation) or other Wnt signaling alteration (e.g., LRP5/6, APC, AXIN1/2, GSK3B, RNF43, ZNRF3, RSPO2/3, FBXW7, ARID1A, or CBP/CREBBP; see full list in Appendix 12.6), based on testing of the Screening tumor tissue sample by a CLIA-accredited laboratory. Once 50% of evaluable patients without a documented β-catenin mutation or other Wnt signaling alteration have been enrolled within a group in Stage 1 (or in Stage 1 and 2 combined, or in Groups 5 and 6), then only patients with activating β-catenin mutation (CTNNB1 mutation) or other identified Wnt signaling alteration, based on testing of the Screening tumor tissue sample by a CLIA-accredited laboratory, will be eligible for enrollment in that group (see Section 3.1 for details). (To allow for real-time testing of Screening tumor tissue samples, the Screening period may be extended to 42 days in such cases, with results obtained and confirmed to be positive before the performance of additional Screening procedures. Note that all other Screening assessments must be performed within 28 days before C1D1.)

Patients with prior documentation of a known activating β-catenin mutation (CTNNB1 mutation) or other Wnt signaling alteration by a CLIA-accredited laboratory will be permitted to enroll based on this documentation. In such patients, a Screening tumor sample will be collected and analyzed centrally; however, confirmatory results are not required for study enrollment.

Fresh tumor tissue samples also will be obtained from all patients at C2D1 ±7 days. The same lesion biopsied during Screening is to be biopsied at C2D1 ±7. The target lesion(s) should not be biopsied. If a repeat biopsy is required during study participation, a sample of the biopsy will be submitted for evaluation.

For patients who discontinue from the study prior to C2D1, a tumor tissue sample is to be obtained at the EOT visit.

Exploratory analyses will include gene expression levels (i.e., RNA-Seq), DKK1 expression (e.g., RNAscope in situ hybridization), immunohistology, infiltrating immune cells and additional IHC staining (e.g., DKK1 and associated downstream elements, [e.g., β-catenin]) on tumor tissue relative to safety and efficacy outcomes.

Tumor blocks or partial blocks will be sectioned and may be returned to the Investigator at last patients visit or before if requested.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the Sponsor. The samples and any data generated from them can only be linked back to the patient by Investigator site personnel. The duration allows the Sponsor to respond to regulatory requests related to the study drug.

Samples will be destroyed according to a process consistent with local regulation.

7.4. Efficacy and Response Assessments

Response and evaluation of PD will be determined according to RECIST v 1.1 (Eisenhauer et al. 2009) (Appendix 12.2). Refer to the Schedule of Assessments [Table 6, (see Table 7 for Rollover Treatment Phase)] for details regarding the timing of specific efficacy measures.

For baseline tumor measurements, all sites of disease should be imaged by computed tomography (CT)/positron emission tomography (PET). With the approval of the Medical Monitor, if the anatomic region cannot be adequately imaged by CT/PET, CT or MRI may be used instead. Baseline imaging studies may be performed within 28 days before C1D1.

Tumor measurements are to be repeated within ±7 days of the first study drug dose in every other cycle, starting in C3, and at the EOT visit (±7 days) until radiographically documented PD. Repeat assessments should use the same radiographic methods as used at baseline (Appendix 12.2).

To confirm objective responses, all lesions should be radiologically assessed, and the same radiologic method used for the initial response determination should be repeated at a minimum of 4 weeks following the initial observation of an objective response, using the sample method that was used at baseline. If a patient is discontinued from the study, repeat radiology assessments may be omitted if clear clinical signs of progressive disease are present.

7.5. Post-Treatment Follow-up and Mortality Assessments

After completion of the EOT visit, patients without radiographically-documented PD will continue to be followed up in the PD follow-up phase until radiographically documented PD. During this PD follow-up period, efficacy assessments for disease response and PD per RECIST 1.1 will be performed every 8 weeks [see Table 6 (see Table 7 for Rollover Treatment Phase)]. Patients are expected not to start any other anti-cancer therapy during the PD follow-up phase

prior to radiographically documented PD; however, if alternate therapy is started, patients will continue to be followed for radiologic progression even after starting subsequent therapy.

After discontinuation of treatment and documentation of PD, all patients will be followed in the Survival Follow-up Phase for survival until death, withdrawal of consent, loss to follow-up, implementation of the rollover treatment phase, or closure of the study by the Sponsor. Survival follow-up will occur 4 times per year (every 12 weeks [±14 days]) after the 30 days post treatment discontinuation visit or end of PD follow-up phase, as applicable, and may be conducted via telephone or office visit. During survival follow-up, the following information will be collected: survival and subsequent anti-cancer therapies.

8. ADVERSE EVENTS

8.1. Definitions, Documentation, and Reporting

8.1.1. 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 (e.g., 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 (e.g., 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 maternal or paternal exposures to study drug should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

8.1.2. 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, i.e., 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 (e.g., 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.

8.2. 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 (e.g., "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 Leap or its designee of any SAE within 24 hours of Investigator awareness of the event via a Leap-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 Leap, or it's designee in accordance with 21 CFR § 312.32. Patients will be monitored for AEs from signing of the informed consent form (ICF) to 30 days after the last dose of DKN-01.

All SAEs that occur during the course of the study 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 Leap or its designee).

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)/Independent Ethics Committees (IEC). If there are serious, unexpected adverse drug experiences associated with the use of the study drug, Leap 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 5.0, 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.

Progressive disease (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.

8.3. Monitoring of Adverse Events and Period of Observation

AEs and SAEs will be recorded starting at time of patient consent up to and including 30 days after administration of the last dose of DKN-01. 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 the EOT procedures are performed, which the Investigator considers to be related to study drug, must be reported to Leap 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 Leap 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 Leap or designee. Any clinically significant findings from ECGs, laboratory, or vital sign measurements that result in a diagnosis should be reported to Leap or its designee. Investigators will be instructed to report to Leap 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.

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

This is a proof-of-concept basket study designed primarily to seek information on the safety, PK, and efficacy of DKN-01 in combination with paclitaxel and as DKN-01 monotherapy in patients with recurrent EOC or EEC with and without activating β-catenin mutation and/or Wnt signaling alterations, or carcinosarcoma (MMMT). A maximum of 124 evaluable patients (combination regimen plus monotherapy regimen) will be enrolled in the study. This is an exploratory open-label study with 6 groups. Groups 1-4 employ a 2-stage study design conducted separately for each group. Up to 21 evaluable patients are enrolled in each of Groups 1, 3, and 4 and up to 31 evaluable patients in Group 2. Groups 5 and 6 are exploratory in nature and will have up to 10 and 20 evaluable patients enrolled and dosed at the RP2D, respectively.

The sample sizes for Groups 5 and 6 are based on practical considerations and clinical judgement to obtain sufficient information on the safety, initial clinical effectiveness, and PK data in the carcinosarcoma groups at a DKN-01 dose exceeding 300 mg.

The sample size of Groups 1 through 4 employ a 2-stage study design and were calculated as follows: For each monotherapy group (Groups 1 and 3) after 12 evaluable patients are enrolled (Stage 1), an additional 9 evaluable patients will be enrolled in that group (Stage 2) if 1 or more patients respond (i.e., experience CR or PR). If there are no responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group. If the group continues to Stage 2, a total of 21 evaluable patients will be studied for that group. The group will be considered successful if ≥3 treated patients respond. This design is applied to each monotherapy group separately and is based on a 2-stage Simon Minimax design for a total of 21 evaluable patients (null hypothesis that ORR ≤5% versus the alternative hypothesis that ORR ≥20% with alpha=0.080 and power=0.803).

For combination therapy Group 2, after 20 evaluable patients are enrolled (Stage 1), an additional 11 evaluable patients will be enrolled in that group (Stage 2) if 3 or more patients respond (i.e., experience CR or PR). If there are fewer than 3 responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group. If the group continues to Stage 2, a total of 31 evaluable patients will be studied for that group. The group will be considered successful if ≥6 treated patients respond. This design is applied to combination therapy Group 2 separately and is based on a 2-stage Simon Minimax design for a total of 31 evaluable patients (null hypothesis that ORR ≤12% versus the alternative hypothesis that ORR ≥25% with alpha=0.150 and power=0.802).

For combination therapy Group 4, after 16 evaluable patients are enrolled (Stage 1), an additional 5 evaluable patients will be enrolled in that group (Stage 2) if 2 or more patients respond (i.e., experience CR or PR). If there are fewer than 2 responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group. If the group continues to Stage 2, a total of 21 evaluable patients will be studied for that group. The group will be considered successful if ≥4 treated patients respond. This design is applied to combination therapy Group 4 separately and is based on a 2-stage Simon Minimax (Simon 1989) design for a total of 21 evaluable patients (null hypothesis that

ORR ≤10% versus the alternative hypothesis that ORR ≥25% with alpha=0.149 and power=0.803).

There are no formal comparisons planned between groups. Any statistical results will be interpreted in the perspective of the exploratory nature of the study.

9.2. Randomization

There is no randomization in this open-label Phase 2 study.

9.3. Populations for Analysis

Several study populations will be used for analysis, as follows:

- Evaluable Analysis Set (EAS): All patients who received any amount of DKN-01 and have at least one evaluable post-baseline RECIST tumor response assessment or were discontinued due to toxicity. The EAS will be the primary population for analyses of ORR, ODCR, PFS, DoR, DoCR, DoCB, and TTP.
- Full analysis set (FAS): All enrolled patients who receive any amount of DKN-01. The FAS will be used for analyses of OS, TTTF, sensitivity analysis of select tumor-related endpoints, and exploratory endpoints.
- Safety population, defined as all enrolled patients who receive any amount of study treatment (either DKN-01 or paclitaxel). All safety analyses will be based on this population. The safety population and FAS are identical, unless a patient received paclitaxel but did not receive DKN-01.
- A Per-Protocol (PP) subset may also be used to analyze 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: All enrolled patients who receive at least a single dose of DKN-01 and have sufficient data to determine PK parameters.

9.4. 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).

9.5. Interim Analyses

Interim analyses will be conducted after Stage 1 for Groups 1-4. No interim analyses are planned for Groups 5 and 6. For each monotherapy group (Groups 1 and 3), after 12 evaluable patients are enrolled (Stage 1), an additional 9 evaluable patients will be enrolled in that group (Stage 2) if 1 or more patients respond (i.e., experience CR or PR). If there are no responses, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group.

For combination therapy Group 2, after 20 evaluable patients are enrolled (Stage 1), an additional 11 evaluable patients will be enrolled in that group (Stage 2) if 3 or more patients respond (i.e.,

experience CR or PR). If there are fewer than 3 responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group.

For combination therapy Group 4, after 16 evaluable patients are enrolled (Stage 1), an additional 5 evaluable patients will be enrolled in that group (Stage 2) if 2 or more patients respond (i.e., experience CR or PR). If there are fewer than 2 responses in Stage 1, then preliminary anti-tumor activity in the group will be rejected and no further patients will be enrolled in that group.

9.6. Statistical Methods

9.6.1. General Methods

Summaries will be tabulated for each group and within each group, where applicable, by presence of Wnt signaling alterations and/or CTNNB1 activating mutations. Selected parameters may also be summarized by dose and will be detailed in the SAP.

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 confidence intervals (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.

9.6.2. 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

9.6.3. 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.

9.6.4. Efficacy Analysis

Efficacy data will be summarized for each group. Selected summaries may also be done within each group, as applicable, by presence of Wnt signaling alterations and/or CTNNB1 activating mutations, and by subgroups as described in the SAP.

All efficacy endpoints are secondary for Group 5 and Group 6.

9.6.4.1. Primary Efficacy Endpoint and Analysis (Groups 1-4)

For the purpose of the 2-stage design in Groups 1-4, the ORR is considered the primary efficacy endpoint. The ORR is defined as the proportion of patients with BOR of PR or CR according to RECIST 1.1. The proportion of patients with ORR in the EAS, along with a 95% CI, based on the Clopper-Pearson interval, will be reported. Secondary analyses of ORR described above may be repeated in FAS, treating missing BOR as a non-responder. ORR at each visit and best overall response will also be summarized using the EAS. Secondary analyses of ORR may be repeated in the PP set.

9.6.4.2. Secondary Efficacy Endpoints and Analysis (Groups 1-4)

Secondary efficacy variables in the study include:

- ***Objective disease control rate (ODCR)*** is defined as the percentage of patients with BOR of CR, PR, or SD. The analysis of ODCR will be performed using the EAS and conducted in the same manner as ORR. Similar to ORR, analysis of ODCR may be repeated in the FAS and PP set.
- ***Overall survival (OS)*** is defined as the time from first dose of study drug until date of death due to any cause. Patients without documentation of death at the time of analysis will be censored as of the date the patient was last known to be alive, or the data cut-off date, whichever is earlier. Overall survival (OS) will be performed in the FAS using Kaplan-Meier methods.
- ***Progression-free survival (PFS)*** is defined as time from first dose of study drug to first documentation of PD (per RECIST 1.1) or death due to any cause. Analysis of PFS will be performed in the EAS and may be repeated in the FAS and PP set.

  Patients who do not experience PD and are alive will be censored at the time of last evaluable tumor assessment. Patients who do not experience PD and start new anti-cancer therapy will be censored at the last evaluable tumor assessment on or prior to the time the new anti-cancer therapy. For analyses conducted in the FAS, patients with no evaluable post-baseline tumor assessments will be censored at the time of receipt of first study drug. Patients who are lost to follow-up for assessment of PD will be censored at their last evaluable tumor assessment. Additional details for censoring will be specified in the SAP and will be based on the Food and Drug Administration, Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, dated May 2007. The analysis of PFS will be based on Kaplan-Meier methods.

- ***Time to progression (TTP)*** is defined as time from first dose of study drug to first documentation of PD (per RECIST 1.1). Analysis of TTP will be performed in the EAS and may be repeated in the FAS and PP set.

  Patients who do not experience PD will be censored at the time of last evaluable tumor assessment. Patients who do not experience disease progression and start new anti-cancer therapy will be censored at the last evaluable tumor assessment on or prior to the time the new anti-cancer therapy was begun. For analyses conducted in the FAS, patients with no evaluable post-baseline tumor assessments will be censored at the time of receipt of first study drug. Patients who are lost to follow-up for assessment of PD will be censored at their last evaluable tumor assessment. Additional details for censoring will be specified in the SAP. The analysis of TTP will be based on Kaplan-Meier methods.

- ***Duration of response (DoR)*** includes patients with an objective disease response (PR or CR) and is defined as the time from the first tumor assessment that supports the patient's objective disease response to the time of PD or death due to any cause. Patients who do not experience PD or death at the time of analysis will be censored using the same rules as described for PFS. The analysis of DOR will be performed in the EAS using Kaplan-Meier methods.

- ***Duration of CR (DoCR)*** includes patients with a CR and is otherwise defined and analyzed similarly to DoR.

- ***Duration of clinical benefit (DoCB)*** includes patients with a BOR of CR, PR, or SD and is defined as the time from the first tumor assessment of CR, PR or SD to the time of PD or death due to any cause. Patients who do not experience PD or death at the time of analysis will be censored using the same rules as described for PFS. The analysis of DoCB will be performed in the EAS using Kaplan-Meier methods.

- ***Time to treatment failure (TTTF)*** is defined as time from first dose of study drug to discontinuation of DKN-01 for any reason including PD, toxicity, and death. Patients without documentation of death at the time of analysis will be censored as of the date the patient was last known to be alive, or the data cut-off date, whichever is earlier. Time to treatment failure (TTTF) will be performed in the FAS using Kaplan-Meier methods.

9.6.4.3. Secondary Efficacy Endpoints and Analysis (Groups 5-6)

Secondary efficacy endpoints in each independent study group (Groups 5-6) are:

- ORR (i.e., BOR of CR + PR), as assessed by the Investigator using RECIST 1.1.
- ODCR (i.e., CR+PR+SD > 6 weeks), as assessed by the Investigator using RECIST 1.1.
- OS, defined as the time from first study drug dose (i.e., C1D1) to death from any cause.
- PFS, defined as the time from first study drug dose (C1D1) to first radiographically-documented PD, as determined using RECIST 1.1, or death due to any cause.
- TTP, defined as the time from first study drug dose (C1D1) until the date of first radiographically-documented PD, as determined using RECIST 1.1.

- DoR, defined as the time from initial response (≥PR) until radiographically-documented PD or death; PD is defined using RECIST 1.1.
- DoCR, defined as the time from initial CR until radiographically-documented PD or death; PD is defined using RECIST 1.1.
- DoCB, defined as the time from the first tumor assessment of CR, PR or SD to the time of PD or death due to any cause; PD is defined using RECIST 1.1.
- TTTF, defined as the time from first study drug dose (C1D1) until the date of treatment discontinuation of DKN-01 for any reason, including PD, toxicity, and death.

9.6.5. Safety Analysis

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

Adverse event 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 and DKN-01 in combination with paclitaxel by group and overall.

Safety analyses will include presentations of the following:

- 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

For Groups 5 and 6, the following analysis will be presented:

- DLTs

9.6.5.1. Study Drug Exposure

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

9.6.5.2. 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 30 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.

Incidence of TEAEs, 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 by group. A summary of TEAEs of CTCAE Grade 3 or higher will also be provided by group. The number and percent of patients with infusion-related reactions will be summarized by group, overall, and by visit.

No formal hypothesis-testing analysis of TEAE incidence 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.

9.6.5.3. 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 by group. 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 by group.

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

9.6.5.4. Other Safety Parameters

Concomitant medications and procedures will be summarized by group. Vital signs, ECG results, and shifts from baseline in ECOG PS will be summarized descriptively over time by group. These data and physical examination results will be provided in data listings.

9.6.6. Pharmacokinetic Analyses

Pharmacokinetic analyses will be conducted on patients in the PK Analysis Set, defined as all enrolled patients who have received at least a single dose of DKN-01 and have sufficient data to determine PK parameters.

The C_{max}, T_{max}, and AUCs will be reported, as feasible.

Data may be pooled with data from other studies to refine the previously developed population PK and/or PK/PcD models, or to conduct further modeling activities.

9.6.7. Immunogenicity Analyses

Details regarding immunogenicity analyses will be provided in the SAP.

9.6.8. Analysis of Exploratory Endpoints

Exploratory analysis will be evaluated for the following exploratory endpoints:

- DKK1 concentration in serum and plasma.
- Tumor genetics, gene expression levels (e.g., RNA-Seq), DKK1 expression (e.g. RNAscope in situ hybridization), immunohistology, infiltrating immune cells and additional IHC staining (DKK1 and associated downstream elements, [e.g., β-catenin]) on tumor tissue relative to safety and efficacy outcomes.

Additional details will be provided in the SAP.

9.6.9. 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.

10. ADMINISTRATIVE REQUIREMENTS

10.1. 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.

10.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see Appendix 12.7). 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.

10.3. 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).

10.4. 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 Leap 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.

10.5. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by Leap, 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 Leap. 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. Leap 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 Leap, 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.

10.6. Direct Access to Source Data

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

The study will be monitored by Leap 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 Leap after the clinical phase of the study has been completed or, if authorized, disposed of at the study site and documented (see Section 5.4).

Regulatory authorities, the IEC/IRB, and/or the clinical quality assurance group of Leap 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.

10.7. Case Report Form Completion

Leap 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.

10.8. Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained until the Investigator is notified by the Sponsor that this is no longer required. If the Investigator withdraws from the responsibility of

keeping the study records, custody must be transferred to a person willing to accept the responsibility. Leap must be notified in writing if a custodial change occurs.

10.9. Liability and Insurance

Leap 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.

10.10. Publication of Study Findings and Use of Information

All information regarding DKN-01 supplied by Leap 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 Leap. The Investigator is obligated to provide Leap 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 Leap, 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 Leap. A pre-publication manuscript is to be provided to Leap at least 30 days prior to the submission of the manuscript to a publisher. Similarly, Leap will provide any company-prepared manuscript to the investigators for review at least 30 days prior to submission to a publisher.

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12. APPENDICES

12.1. Schedule of Assessments

The schedule of study assessments is presented in Table 6.

Table 6 Schedule of Assessments

Procedure	Screening (Within 28 Days of C1 D1)[1]	Treatment Period						EOT (30 Days Post Tx Discon-tinuation)	PD Follow-up (Q8 weeks[3])	Survival Follow-up (Q12 weeks[4])
		Cycle 1			≥Cycle 2					
		C1 D1/ Baseline	C1D8	C1D15	D1	D8[2]	D15			
Visit Window	-	-	± 1D	± 1D	± 1D	± 1D	± 1D	+ 7D	± 7D	± 14D
Informed consent	X									
Medical history	X									
Cancer history, including treatment history[5] and, if available, genomics	X									
Demographics	X									
Tumor tissue collection/biopsy	X[6,7]				X[8]					
Height	X									
Complete physical examination	X							X		
Abbreviated physical examination		X		X	X		X			
Weight	X	X			X			X		
Body surface area		X			X					
Vital signs	X	X			X			X		
Electrocardiogram	X	X			X			X		
ECOG performance status	X	X			X			X		
Laboratory sample collection										
Hematology[9]	X[10]	X		X	X		X	X		
Neutrophil-to-lymphocyte ratio (NLR)	X[10]	X								
Coagulation studies[9]	X[10]									
Clinical chemistries[11]	X[10]	X		X	X		X	X		
CA125	X[10]	X			X			X		
Vitamin D	X[10]	X						X		
TSH	X[10]	X			X			X		
Urinalysis[12]	X[10]	X			X			X		
Pregnancy testing[13]	X[10]	X			X			X		
PK[14]		X	X	X	X			X		

Procedure	Screening (Within 28 Days of C1 D1)[1]	Treatment Period						EOT (30 Days Post Tx Discon-tinuation)	PD Follow-up (Q8 weeks[3])	Survival Follow-up (Q12 weeks[4])
		Cycle 1			≥Cycle 2					
		C1 D1/ Baseline	C1D8	C1D15	D1	D8[2]	D15			
Visit Window	-	-	± 1D	± 1D	± 1D	± 1D	± 1D	+ 7D	± 7D	± 14D
ADA[15]		X			X			X		
Serum DKK1	X	X			X			X		
Plasma samples for exploratory biomarker analysis		X			X			X		
Study drug administration[16]										
Pre-treatment[17]		X	X	X	X	X	X			
DKN-01 monotherapy		X		X	X		X			
Combination therapy:										
DKN-01[18]		X		X	X		X			
Paclitaxel[18]		X	X	X	X	X	X			
Tumor imaging[19]	X				X			X	X	
Disease response assessment[20]					X			X	X	
Adverse events, including infusion-related AEs		X	X	X	X	X	X	X		
Concomitant medications		X	X	X	X	X	X	X		
Survival and subsequent therapies								X	X	X

Table footnotes:

1 To allow-for real-time testing of Screening tumor tissue samples, the Screening period may be extended to 42 days in such cases, with results obtained and confirmed to be positive before the performance of additional Screening procedures. All other Screening assessments must be performed within 28 days before C1D1.

2 After completion of Cycle 2, subsequent D8 visits can be conducted over the phone with patients in the monotherapy groups.

3 Imaging studies, tumor assessments, and disease response assessment should be performed as scheduled every 8 weeks (± 7 days) following first dose of study therapy until radiographically-documented progression of disease, even if therapy is delayed. PD Follow-up phase only applies to patients who discontinue study treatment without documented PD.

4 All patients will be followed in the Survival Follow-up phase for survival until death, withdrawal of consent, loss to follow-up, implementation of the rollover treatment phase, or closure of the study by the Sponsor. Long-term follow-up will occur 4 times per year (every 12 weeks ±14 days) after the 30 days post treatment discontinuation visit or PD follow-up phase discontinuation visit, as applicable.

5 Cancer treatment history is to include documentation of prior chemotherapy, radiation therapy, surgery, and use of blood products, including red cell and platelet transfusions and growth factors within the previous 3 months.

6 Note that fresh tumor tissue samples are required to be collected from all patients during Screening for genomic cancer profiling. Although fresh biopsy is preferred, an archived specimen collected within 3 months of study entry may be acceptable, with the prior approval of the Medical Monitor.

7 This basket study will enrich for Wnt signaling alterations whereby approximately 50% of all patients enrolled require an activating β-catenin mutation (CTNNB1 mutation) or other Wnt signaling alteration (e.g., LRP5/6, APC, AXIN1/2, GSK3B, RNF43, ZNRF3, RSPO2/3, FBXW7, ARID1A, or CBP/CREBBP; see full list in Appendix 12.6). Once 50% of patients (i.e., 10 patients) without a documented β-catenin or other Wnt signaling alteration have been enrolled within a group, enrollment in that group will continue only with patients with activating β-catenin mutation (CTNNB1 mutation) or other identified Wnt signaling alteration.

8 Fresh tumor tissue samples will be obtained from all patients at C2D1 ±7 days. The same lesion biopsied during Screening is to be biopsied at C2D1 ±7 days. The target lesion(s) should not be biopsied. If a repeat biopsy is required during study participation, a sample of the biopsy will be submitted for evaluation. Patients who discontinue prior to the C2D1 visit are to have a biopsy performed at the EOT visit. Exploratory analyses will include tumor genetics, gene expression levels (e.g., RNA-Seq), DKK1 expression (e.g., RNAscope in situ hybridization), immunohistology, infiltrating immune cells and additional IHC staining to evaluate DKK1 and DKK1 associated downstream elements (e.g., β-catenin) on tumor tissue relative to safety and efficacy outcomes. If a repeat biopsy is required during study participation, a sample of the biopsy will be submitted for evaluation.

9 Hematology includes hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), leukocytes (WBC), neutrophils, segmented and banded, lymphocytes, monocytes, eosinophils, basophils, and platelets. It is acceptable to use the automated differential for complete blood count (CBC). Coagulation studies include prothrombin time (PT)/partial thromboplastin time (PTT) and international normalized ratio (INR).

10 If Screening safety laboratory tests are obtained ≤72 hours of C1D1 to confirm eligibility, safety labs should be repeated on C1D1 but do not need to be resulted prior to dosing. If Screening laboratory tests are obtained ≥72 hours prior to C1D1, then all safety laboratory tests need to be repeated on C1D1 to confirm eligibility. All pre-treatment laboratory tests are to be obtained with 24- 48 hours of D1 dosing.

11 Clinical chemistry includes sodium, potassium, total and direct bilirubin, lactate dehydrogenase (LDH), ALP, ALT, AST, blood urea nitrogen (BUN), creatinine, creatine kinase, uric acid, calcium, glucose (random), albumin, cholesterol, serum chloride, phosphorus, carbon dioxide, and total protein.

12 Urinalysis includes specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase.

13 Serum or urine pregnancy testing is to be performed for women of childbearing potential. If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. On C1D1, the pregnancy test may be performed within 72 hours before the study drug dose; the results must be available and confirmed to be negative before administration of the first study drug dose. Pregnancy testing is to be repeated during the study any time pregnancy is suspected.

14 Blood samples for serum PK are to be collected on C1D1 pre-infusion, post-infusion, and then 24 hours (1 day), and 168 hours (7 days) post-infusion. Thereafter, such samples are to be collected pre- and post-infusion on D1 of each cycle and a final sample is to be collected at the EOT visit. Please use the following windows when scheduling blood samples for PK: C1D1 pre-infusion: - 60-minute window; C1D1 post infusion: ± 5-minute window; 24 hours (1 day): random draw during Day 2; 168 hours (7 days): ± 1 day; C1D15 pre-infusion: -60 minute window

15 Blood samples for serum ADA/immunogenicity are to be collected pre-infusion on C1D1, and then pre-infusion on D1 of every other cycle beginning with C3 (C5, C7, C9, etc) and at the EOT visit. If any patient is found to be ADA-positive at the EOT visit, the patient will be monitored monthly (if feasible) until serum samples are determined to be ADA-negative. If a patient has an infusion reaction, all attempts should be made to obtain an immunogenicity and PK sample as close to the onset of the event as possible, at the resolution of the event and 30 days following the event.

16 For patients receiving combination therapy, study drug is to be administered in the following order: premedications→ DKN-01 → paclitaxel.

17 Premedication for paclitaxel (will be given prior to each paclitaxel infusion as per local standard of care. Suggested premedications include dexamethasone 20 mg orally [PO] 12 to 6 hours prior; diphenhydramine 50 mg IV 30 to 60 minutes prior; and cimetidine or ranitidine 50 mg IV 30 to 60 minutes prior) or equivalents.

18 DKN-01 will be administered IV over a minimum of 30 minutes and up to a maximum of 2 hours given on days 1 and 15 of each cycle without interruption plus paclitaxel administered IV over 1 hour on Days 1, 8, and 15 of each 28-day cycle according to standard clinical practice. Standard of care premedication for paclitaxel will be given prior to DKN-01. For patients receiving combination therapy, DKN-01 will be administered first followed by paclitaxel.

19 Baseline imaging studies may be performed within 28 days before C1D1. For baseline tumor measurements, all sites of disease should be imaged by CT/PET. With the approval of the Medical Monitor, if the anatomic region cannot be adequately imaged by CT/PET, CT or MRI may be used instead. Tumor measurements are to be repeated within ±7 days of the first study drug dose in every other cycle, starting in C3, and at the EOT Visit until radiographically documented progression of disease. Repeat assessments should use the same radiographic methods as used at Baseline.

20 Disease response is to be assessed by the Investigator using RECIST 1.1 (Eisenhauer et al., 2009) within ±7 days of the first study drug dose in every other cycle, starting in Cycle 3 and at the EOT Visit following first dose of study therapy until radiographically documented PD.

The schedule of study assessments for Rollover Treatment Phase is presented in Table 7.

Table 7 Schedule of Assessments- Rollover Treatment Phase

	Treatment Period			EOT (30 Days Post Tx Discon-tinuation)	PD Follow-up (Q8 weeks[3])	Survival Follow-up (Q12 weeks[4])
	≥Cycle 2					
Procedure	**D1**	**D8[2]**	**D15**			
Visit Window	**± 1D**	**± 1D**	**± 1D**	**+ 7D**	**± 7D**	**± 14D**
Informed consent[1]						
Complete physical examination				X		
Abbreviated physical examination	X		X			
Weight	X			X		
Body surface area	X					
Vital signs	X			X		
Electrocardiogram	X			X		
ECOG performance status	X			X		
Laboratory sample collection						
Hematology[5]	X		X	X		
Coagulation studies[5]						
Clinical chemistries[6]	X		X	X		
Urinalysis[7]	X			X		
Pregnancy testing[8]	X			X		
Study drug administration[9]						
Pre-treatment[10]	X	X	X			
DKN-01 monotherapy	X		X			
Combination therapy: DKN-01[11] Paclitaxel[11]	 X X	 X	 X X			
Tumor imaging [12]	X			X	X	
Disease response assessment[13]	X			X	X	
Adverse events, including infusion-related AEs	X	X	X	X		
Concomitant medications	X	X	X	X		
Survival and subsequent therapies				X	X	X

Table footnotes:

1 Prior to starting treatment in the Rollover Treatment Phase patient are be consented to the corresponding consent form.

2 After completion of Cycle 2, subsequent D8 visits can be conducted over the phone with patients in the monotherapy groups.

3 Imaging studies, tumor assessments, and disease response assessment should be performed as scheduled every 12 weeks (± 7 days) following first dose of study therapy until radiographically-documented progression of disease, even if therapy is delayed. PD Follow-up phase only applies to patients who discontinue study treatment without documented PD.

4 All patients will be followed in the Survival Follow-up phase for survival until death, withdrawal of consent, loss to follow-up, or closure of the study by the Sponsor. Long-term follow-up will occur 4 times per year (every 12 weeks ±14 days) after the 30 days post treatment discontinuation visit or PD follow-up phase discontinuation visit, as applicable.

5 Hematology includes hemoglobin, hematocrit, erythrocyte count (RBC), mean cell volume (MCV), mean cell hemoglobin concentration (MCHC), leukocytes (WBC), neutrophils, segmented and banded, lymphocytes, monocytes, eosinophils, basophils, and platelets. It is acceptable to use the automated differential for complete blood count (CBC). Coagulation studies include prothrombin time (PT)/partial thromboplastin time (PTT) and international normalized ratio (INR). All pre-treatment laboratory tests are to be obtained with 24- 48 hours of D1 dosing.

6 Clinical chemistry includes sodium, potassium, total and direct bilirubin, lactate dehydrogenase (LDH), ALP, ALT, AST, blood urea nitrogen (BUN), creatinine, creatine kinase, uric acid, calcium, glucose (random), albumin, cholesterol, serum chloride, phosphorus, carbon dioxide, and total protein. All pre-treatment laboratory tests are to be obtained with 24- 48 hours of D1 dosing.

7 Urinalysis includes specific gravity, pH, protein, glucose, ketones, blood, and leukocyte esterase. All pre-treatment laboratory tests are to be obtained with 24- 48 hours of D1 dosing.

8 Serum or urine pregnancy testing is to be performed for women of childbearing potential. If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy testing is to be repeated during the study any time pregnancy is suspected.

9 For patients receiving combination therapy, study drug is to be administered in the following order: premedications→ DKN-01 → paclitaxel.

10 Premedication for paclitaxel (will be given prior to each paclitaxel infusion as per local standard of care. Suggested premedications include dexamethasone 20 mg orally [PO] 12 to 6 hours prior; diphenhydramine 50 mg IV 30 to 60 minutes prior; and cimetidine or ranitidine 50 mg IV 30 to 60 minutes prior) or equivalents.

11 DKN-01 will be administered IV over a minimum of 30 minutes and up to a maximum of 2 hours given on days 1 and 15 of each cycle without interruption plus paclitaxel administered IV over 1 hour on Days 1, 8, and 15 of each 28-day cycle according to standard clinical practice. Standard of care premedication for paclitaxel will be given prior to DKN-01. For patients receiving combination therapy, DKN-01 will be administered first followed by paclitaxel.

12 Tumor measurements are to be repeated within ±7 days every 12 weeks, and at the EOT Visit until radiographically documented progression of disease. Repeat assessments should use the same radiographic methods as used at Baseline.

13 Disease response is to be assessed by the Investigator using RECIST 1.1 (Eisenhauer et al., 2009) within ±7 days every 12 weeks and at the EOT Visit following first dose of study therapy until radiographically documented PD.

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 (e.g., 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 (e.g., 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 examination 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 (i.e., 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 fludeoxyglucose-positron emission tomography (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 – unevaluable

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 – unevaluable.

[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, (i.e., 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 Unevaluable 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. NCI-CTCAE v 5.0 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 (e.g., antihistamines, NSAIDS, narcotics, I.V. fluids); prophylactic medications indicated for ≤ 24 hrs	Prolonged (e.g., 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% O2	Hypotension managed with one pressor; hypoxia requiring ≥40% O2	Life-threatening consequences; pressor or ventilator support indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.					

12.4. 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.

12.5. 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 • Blood or mucus in stool with or without fever • Peritoneal signs consistent with bowel perforation • Ileus	**Moderate:** • 4 to 6 stools/day over baseline • Abdominal pain • Blood or mucus in stool	• Withhold DKN-01 • Administer antidiarrheal treatment while etiology is investigated.	Symptoms Resolve to ≤Grade 1 or baseline (Section 6.2): • Resume DKN-01 as per Table 1 if symptoms have improved to mild severity or resolution.
	Severe or life-threatening: • 7 stools/day over baseline • Peritoneal signs consistent with bowel perforation • Ileus • Fever	• Permanently discontinue DKN-01 • Rule out bowel perforation • Consider endoscopic evaluation	
Liver			
Elevations in liver function tests: • AST >2.5 x ULN • ALT >2.5 x ULN • Total bilirubin >1.5 x ULN	**Moderate:** • AST or ALT >2.5 to <5.0 x ULN and/or • Total bilirubin >1.5 to <3.0 x ULN	• 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 (Section 6.2): • Resume DKN-01 as per Table 1 if liver function tests are <2.5 x ULN or return to BL and bilirubin is <1.5 x ULN or returns to BL. Symptoms Ongoing: • If AST or ALT elevation continues to be >5 x ULN OR total bilirubin > 3 x ULN, see below.
	Severe or life-threatening • AST or ALT >5.0 x ULN and/or • Total bilirubin >3.0 x ULN	• Permanently discontinue DKN-01 • Rule out infectious or malignant causes • Increase frequency of liver function test monitoring until resolution	

System Monitoring	Severity	Management	Follow-up
Skin			
• Pruritus • Rash	**Moderate** • Non-localized rash (diffuse, <50% of skin surface	• Withhold DKN-01 • Administer topical corticosteroids if there is no improvement of symptoms within 1 week.	Symptoms Resolve to ≤Grade 1 or baseline (Section 6.2): • Resume DKN-01 as per Table 1 if dermatitis resolves or improves to mild (localized) symptoms. Symptoms Ongoing: • If symptoms worsen, see below.
	Severe or life-threatening • Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous or hemorrhagic manifestations	• Permanently discontinue DKN-01 • Administer systemic corticosteroid therapy	
Neurologic			
Monitor for symptoms of motor or sensory neuropathy • Unilateral or bilateral weakness • Sensory alterations • Paresthesia .	**Moderate** • Moderate symptoms, clinically detectable with no impact on ADLs	• Withhold DKN-01 • Introduce appropriate medical intervention	Symptoms Resolve to ≤Grade 1 or baseline (Section 6.2): • Resume DKN-01 as per Table 1 when symptoms resolve or return to BL Symptoms Ongoing: • If symptoms worsen, see below
	Severe or life-threatening • Severe symptoms (impact on ADLs) or life threatening	• Permanently discontinue DKN-01 • Institute appropriate medical intervention	
Endocrine			
• Fatigue • Headache • Mental status changes • Abdominal pain • Unusual bowel habits • Hypotension • Abnormal thyroid function tests and/or serum chemistries	**Moderate to life-threatening** • Document signs and/or symptoms of dysfunction • Endocrinopathies requiring hormone replacement or medical intervention • AEs requiring hospitalization, urgent medical intervention or interfering with ADLs	• Withhold DKN-01 • 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 (Section 6.2): • Resume DKN-01 as per Table 1 when: • Patient is stable on hormone-replacement therapy (as indicated) Symptoms Ongoing: • Permanently discontinue DKN-01

12.6. Wnt Signaling Alterations

ZNRF3

RSPO2

RNF43

CTNNB1

AXIN1

APC

WISP3

TNKS2

TNKS

TERT

SOX9

SOX2

SLIT2

PAX5

NOTCH1

MLL2

LTK

LRP1B

LRP

GSK3B

GREM1

FOXP1

FBXW7

FAM123B

CREB

CDH20

CDC73

ARID1A

APCDD1

12.7. 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.

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