Leap Therapeutics, Inc.

Protocol

- **Protocol Title:** A Phase 2, Multicenter, Open-Label Study of DKN-01 in Combination with Tislelizumab ± Chemotherapy a First-Line or Second-Line Therapy in Adult Patients with Inoperable, Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (**DisTinGuish**)
- **Version:** 6.0, 29 June 2023
- **Protocol Identifier:** DEK-DKK1-P205
- **NCT04363801**

CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Phase 2, Multicenter, Open-Label Study of DKN-01 in Combination with Tislelizumab ± Chemotherapy as First-Line or Second-Line Therapy in Adult Patients with Inoperable, Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (**DisTinGuish**)
Protocol Identifier:	DEK-DKK1-P205
Phase:	2
Investigational Product(s):	DKN-01 (Leap Therapeutics, Inc.) Tislelizumab (BGB A317) (BeiGene, Ltd.)
Indication:	Inoperable, locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma
IND Number:	[redacted] (Leap Therapeutics, Inc.) [redacted] (BeiGene, Ltd.)
EU CT Number	2023-504940-32-00
Sponsor:	Leap Therapeutics, Inc. 47 Thorndike Street, Suite B1-1 Cambridge, MA 02141 Sponsor Signatory [redacted]
Original Protocol Version 1.0:	19 March 2020
Protocol Version 2.0:	12 April 2021
Protocol Version 3.0:	31 August 2021
Protocol Version 4.0:	27 May 2022
Protocol Version 5.0:	16 November 2022
Protocol Version 5.1 Germany Specific:	29 March 2023
Protocol Version 6.0:	29 June 2023

FINAL PROTOCOL APPROVAL SHEET

A Phase 2, Multicenter, Open-Label Study of DKN-01 in Combination with Tislelizumab ± Chemotherapy as First-Line or Second-Line Therapy in Adult Patients with Inoperable, Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (**DisTinGuish**)

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Date

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INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2, Multicenter, Open-Label Study of DKN-01 in Combination with Tislelizumab ± Chemotherapy as First-Line or Second-Line Therapy in Adult Patients with Inoperable, Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (**DisTinGuish**)

Protocol Identifier: DEK-DKK1-P205

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Instructions for Investigator: Please SIGN and DATE this signature page prior to implementation of this Sponsor-approved protocol. PRINT your name, title, and the name and address of the center in which the study will be conducted.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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Name of Sponsor/Company: Leap Therapeutics, Inc.	
Investigational Product:	DKN-01 (Leap Therapeutics, Inc.) Tislelizumab (BGB-A317) (BeiGene, Ltd.)
Title of Study:	A Phase 2, Multicenter, Open-Label Study of DKN-01 in Combination with Tislelizumab ± Chemotherapy as First-Line or Second-Line Therapy in Adult Patients with Inoperable, Locally Advanced or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (**DisTinGuish**)
Protocol Identifier:	DEK-DKK1-P205
Phase of Development:	2

Number of Patients: Approximately 232 participants (hereafter referred to as patients) will be enrolled to ensure a minimum of 220 evaluable patients. Expected enrollment in each cohort as follows:

- Part A: Approximately 24 patients with treatment-naïve inoperable, locally advanced or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma will be enrolled to ensure 20 evaluable patients.
- Part B: Approximately 48 patients with previously treated inoperable, locally advanced or metastatic Dickkopf-1 (DKK1)-high G/GEJ adenocarcinoma will be enrolled to ensure 40 evaluable patients.
- Part C: Approximately 160 patients with treatment-naïve inoperable, locally advanced or metastatic G/GEJ adenocarcinoma will be randomized and enrolled in 2 treatment groups to ensure 80 evaluable patients per treatment group.

Study Centers: Approximately 55 centers, including, but not limited to the United States, Republic of Korea, Germany, and United Kingdom.

Part A and Part B:

Primary Study Objective:

- To characterize the safety and tolerability of DKN-01 in combination with tislelizumab ± CAPOX (capecitabine + oxaliplatin) in patients with inoperable, locally advanced or metastatic G/GEJ adenocarcinoma.

Secondary Study Objectives:

- Part A: To estimate the objective response rate (ORR) of patients with inoperable, locally advanced or metastatic G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab + CAPOX as a first-line therapy using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
- Part B: To estimate the ORR of patients with inoperable, locally advanced or metastatic DKK1-high G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab as a second-line therapy using RECIST v1.1.
- Part A: To estimate duration of response (DoR), duration of complete response (DoCR), progression-free survival (PFS), overall survival (OS), duration of clinical benefit (DoCB), durable clinical benefit (DCB), disease control rate (DCR), and time to response (TTR) in

patients with inoperable, locally advanced or metastatic G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab + CAPOX as a first-line therapy.

- Part B: To estimate DoR, DoCR, PFS, OS, DoCB, DCB, DCR, and TTR in patients with inoperable, locally advanced or metastatic DKK1-high G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab as a second-line therapy.

Exploratory Study Objectives:

- To characterize the pharmacokinetics (PK) of DKN-01.
- To characterize the PK of tislelizumab.
- To assess the immunogenicity of DKN-01.
- To assess the immunogenicity of tislelizumab.
- To assess predictive, prognostic, and/or pharmacodynamic biomarkers and clinical characteristics including any association between response, survival, or other clinical outcomes and DKN-01 in combination with tislelizumab ± CAPOX.
- To evaluate biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivative) samples obtained before, during, and/or after treatment with DKN-01 in combination with tislelizumab ± CAPOX including assessment of association of these biomarkers with clinical outcomes to DKN-01 + tislelizumab ± CAPOX.
- To evaluate exposure-response relationships if the available data permit.
- Part A: To estimate the ORR, BOR, DCB rate and DCR using iRECIST in patients with inoperable, locally advanced or metastatic G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab + CAPOX as first-line therapy continuing treatment beyond the initial assessment of progressive disease.
- Part B: To estimate the ORR, BOR, DCB rate and DCR using iRECIST in patients with inoperable, locally advanced or metastatic DKK1-high G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab as a second-line therapy continuing treatment beyond the initial assessment of progressive disease.

Safety Endpoint:

- Incidence of treatment-emergent adverse events (TEAEs), Grade ≥3 TEAEs, treatment-related TEAEs, treatment-emergent serious adverse events (TESAEs), treatment-related TESAEs, and TEAEs leading to study drug discontinuation.

Other Key Safety Endpoints:

- Incidence of treatment-emergent Grade 3/4 clinical laboratory abnormalities.
- Incidence of treatment-emergent immune-related adverse events (irAEs).
- Incidence of Grade 3/4 and serious treatment-emergent irAEs.
- Incidence of Grade 3/4 and serious infusion-related reactions.
- Changes from baseline in clinical laboratory parameters (serum chemistry and hematology).
- Changes from baseline in vital signs and electrocardiogram (ECG) parameters.
- Shift from baseline in Eastern Cooperative Oncology Group (ECOG) performance status.

Efficacy Endpoints:

- ORR (the proportion of patients with best overall response of complete response [CR] + partial response [PR]), as assessed by the Investigator using RECIST v1.1.

- DoR, defined as the time from initial response (CR or PR) until radiographically documented progressive disease or death due to any cause; progressive disease is defined using RECIST v1.1.
- DoCR, defined as the time from initial CR until radiographically documented progressive disease or death due to any cause; progressive disease is defined using RECIST v1.1.
- PFS, defined as the time from first study drug dose (i.e., C1D1) to first radiographically documented progressive disease, as determined using RECIST v1.1, or death due to any cause.
- OS, defined as the time from first study drug dose (i.e., C1D1) to death due to any cause.
- DoCB, defined as the time from the first study drug dose (i.e., C1D1) to the time of progressive disease, as determined using RECIST v1.1, or death due to any cause in patients who had a best overall response of CR, PR, or SD of ≥6 weeks.
- DCB, defined as DoCB ≥180 days. Patients who have best overall response of PD or those having clinical benefit but DoCB lasting <180 days will be considered as "non-DCB."
- DCR (i.e., CR+PR+ SD at ≥6 weeks), as assessed by the Investigator using RECIST v1.1.
- TTR, defined as the time from the first study drug dose to the assessment date of the BOR of either CR or PR.

Exploratory Endpoints:

- Summary of serum concentrations of DKN-01 or tislelizumab at specified timepoints.
- Incidence of antidrug antibodies (ADAs) to DKN-01 or tislelizumab.
- Predictive, prognostic, and/or pharmacodynamic biomarkers including any association between response, survival, or other clinical outcomes and DKN-01 in combination with tislelizumab ± CAPOX.
- Biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivative) samples obtained before, during, and/or after treatment with DKN-01 in combination with tislelizumab ± CAPOX. Biomarkers may include, but are not limited to:
  - DKK1 tumor expression in mRNA by ISH
  - Programmed cell death protein ligand-1 (PD-L1) expression in the tumor microenvironment by IHC
  - circulating tumor deoxyribonucleic acid (ctDNA)
  - serum DKK1.
- Exposure-response relationships for DKN-01 as data permit.
- iORR = (number of patients with iCR + iPR)/all patients) based on the Investigator assessment and following iRECIST for patients continuing treatment beyond the initial assessment of progressive disease.

Part C:

Primary Study Objective:

- To assess whether the addition of DKN-01 to the combination of tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6 [leucovorin calcium, fluorouracil, and oxaliplatin]) improves PFS according to the RECIST v1.1 as assessed by the Investigator in patients with advanced DKK1-high and overall G/GEJ adenocarcinoma compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.

Secondary Study Objectives:

- To estimate the objective response rate (ORR) according to RECIST v1.1 as assessed by the Investigator, the duration of response (DoR), and overall survival (OS) in advanced DKK1-high and overall G/GEJ adenocarcinoma patients treated with DKN-01 in combination with tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.
- To assess whether the addition of DKN-01 to the combination of tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) improves PFS and ORR according to RECIST v1.1 as assessed by the Investigator in patients with CPS ≥5 or CPS <5 advanced DKK1-high and overall G/GEJ adenocarcinoma compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.
- To characterize the frequency of toxicity ≥Grade 3 treatment-related adverse events (TRAE) associated with each of the treatment arms.

Exploratory Study Objectives:

- To assess whether the addition of DKN-01 to the combination of tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) improves the duration of complete response (DoCR), duration of clinical benefit (DoCB), durable clinical benefit (DCB), disease control rate (DCR) and time to response (TTR) in advanced DKK1-high and overall G/GEJ adenocarcinoma patients compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.
- To characterize the PK of DKN-01.
- To characterize the PK of tislelizumab.
- To assess the immunogenicity of DKN-01.
- To assess the immunogenicity of tislelizumab.
- To assess predictive, prognostic, and/or pharmacodynamic biomarkers and clinical characteristics including any association between response, survival, or other clinical outcomes of DKN-01 in combination with tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.
- To evaluate exposure-response relationships if the available data permit.
- To estimate the ORR, BOR, DCB rate, and DCR using iRECIST in patients with inoperable, locally advanced or metastatic DKK1-high and overall G/GEJ adenocarcinoma treated with the combination of tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) ± DKN-01 as first-line therapy continuing treatment beyond the initial assessment of progressive disease.
- To assess the concordance between Investigator assessment and central imaging assessment for primary and secondary efficacy analyses.
- To assess the concordance between tumor area positivity (TAP) and CPS PD-L1 expression for primary and secondary efficacy analyses.
- To evaluate differences between backbone chemotherapy regimens (CAPOX vs mFOLFOX6) in combination with tislelizumab ± DKN-01 for primary and secondary efficacy analyses.

Primary Endpoint:

- PFS, as determined by the Investigator per RECIST v1.1, of DKN-01 plus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) versus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) in DKK1-high and in all patients.

Secondary Endpoints:

- ORR, as determined by the Investigator per RECIST v1.1, of DKN-01 plus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) versus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) in DKK1-high and all patients.
- DoR, as determined by the Investigator per RECIST v1.1, of DKN-01 plus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) versus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) in DKK1-high and all patients.
- OS with DKN-01 plus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) versus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) in DKK1-high and in all patients.
- Incidence of ≥Grade 3 treatment-related adverse events (TRAEs).

Exploratory Endpoints:

- DoCR using RECIST v1.1.
- DoCB as determined using RECIST v1.1, is defined as the time from the date of randomization to the time of progressive disease or death due to any cause, in patients who had a best overall response of complete response (CR), partial response (PR), or stable disease (SD) of ≥6 weeks.
- DCB, defined as DoCB ≥180 days. Patients who have best overall response of PD or those having clinical benefit but DoCB lasting < 180 days will be considered as "non-DCB."
- DCR (i.e., CR+PR+SD at ≥6 weeks), as assessed by the Investigator using RECIST v1.
- TTR, defined as the time from the date of randomization to the assessment date of the first instance of an overall response of CR or PR.
- Summary of serum concentrations of DKN-01 at specified timepoints.
- Summary of serum concentrations of tislelizumab at specified timepoints.
- Incidence of anti-drug antibodies (ADAs) to DKN-01.
- Incidence of ADAs to tislelizumab.
- Serum DKK1, change since baseline at specified timepoints (applicable for patients who received DKN-01).
- Exposure-response relationships for DKN-01 as data permit.
- Biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivative) samples obtained before, during, and/or after treatment with DKN-01 plus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) versus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6). Biomarkers may include, but are not limited to:
  - DKK1 tumoral mRNA expression by Chromogenic situ hybridization (CISH).
  - Programmed cell death protein ligand-1 (PD-L1) expression by IHC.
  - Genetics from tumor specimens or circulating tumor deoxyribonucleic acid (ctDNA).
  - Serum and plasma for proteomics and additional scientific analyses.

- iORR = (number of patients with iCR + iPR)/all patients) based on the Investigator assessment and following iRECIST for patients continuing treatment beyond the initial assessment of progressive disease.
- A concordance comparison between Investigator assessment and central imaging assessment for primary and secondary efficacy analyses will be performed.
- A concordance comparison between CPS and TAP will be performed, including additional scientific analysis in patients with TAP ≥5 or TAP <5 advanced DKK1-high and overall G/GEJ adenocarcinoma compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.

Study Design:

This is a Phase 2 open-label, multicenter study to be conducted concurrently in 3 parts (non-randomized Parts A and B and a randomized Part C).

- **Part A** will enroll G/GEJ adenocarcinoma patients who have received no prior systemic treatment in the locally advanced/metastatic setting (first-line treatment).
- **Part B** will enroll patients who received only 1 prior systemic treatment, which must consist of a platinum and/or fluoropyrimidine–based therapy (± human epidermal growth factor receptor 2 [HER2] therapy if applicable) for locally advanced/metastatic DKK1-high G/GEJ adenocarcinoma (second-line treatment).
- **Part C** will enroll G/GEJ adenocarcinoma patients who have received no prior systemic treatment in the locally advanced/metastatic setting (first-line treatment).

In Parts A and B, approximately 72 adult patients with inoperable, histologically confirmed locally advanced or metastatic G/GEJ adenocarcinoma with measurable disease (RECIST v1.1) requiring therapy will be enrolled in the study.

Both Parts A and B are designed to evaluate safety, tolerability, and efficacy of the combination therapy of IV DKN-01 and tislelizumab ± CAPOX in G/GEJ adenocarcinoma patients. Treatment continues in repeating 21-day cycles until patient meets criteria for discontinuation or is no longer deriving clinical benefit. Parts A and B will be enrolled concurrently. A review by the Safety Review Team (SRT) will occur in each study part after the first 5 patients have completed Cycle 1.

Part C is the open-label, randomized, controlled, 2-arm portion of the study to evaluate the efficacy and safety of tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) ± DKN-01 in adult patients with inoperable, histologically confirmed locally advanced or metastatic G/GEJ adenocarcinoma with measurable disease (RECIST v1.1) requiring therapy. Approximately 160 patients will be randomized in a 1:1 ratio to receive either DKN-01 in combination with tislelizumab and chemotherapy regimen (CAPOX or mFOLFOX6) (n=80) or tislelizumab in combination with chemotherapy regimen (CAPOX or mFOLFOX6) (n=80). Patients will be assigned to treatment using a central stratified block randomization scheme. Patients will be stratified at randomization by the following factors:

- DKK1 RNAscope tumor percentage score (TPS) (≥20% vs <20%)
- PD-L1 immunohistochemistry Combined Positive Score (CPS) (≥5 vs <5)

Randomization may occur up to 3 calendar days prior to C1D1.

For Part C, a review by the SRT will occur after the first 5 patients on each chemotherapy regimen (CAPOX and mFOLFOX6) have completed Cycle 1 from both the experimental group (i.e., DKN-01 in combination of tislelizumab and chemotherapy regimen) and the control group (i.e., tislelizumab in combination with chemotherapy regimen (CAPOX or mFOLFOX6). Enrollment will continue during

the safety data review without pause.

The study consists of a Pre-Screening Period (Part B only), a Screening Period, a Treatment Period, and a Follow-up Period. The Follow-up Period includes a follow-up visit approximately 30 days after the last dose of study drug and provides for additional long-term follow-up for disease progression (if the patient discontinued study drug for a reason unrelated to progressive disease) and for subsequent therapies and death (in all patients).

Part A – First-Line Treatment

Part A patients will receive IV DKN-01 (300 mg) on Days 1 and 15, IV tislelizumab (200 mg) on Day 1, IV oxaliplatin (130 mg/m^2) on Day 1, and oral capecitabine (1000 mg/m^2 twice daily [BID]) on Days 1-15 of each 21-day cycle for a total of 28 doses per cycle. Part A is restricted to patients who have not had prior systemic therapy for locally advanced or metastatic disease. Patients may have received prior neoadjuvant or adjuvant therapy as long as it was completed without disease recurrence for at least 6 months. A review by the SRT will occur after the first 5 patients have enrolled and completed Cycle 1. Enrollment in the other ongoing cohorts may continue during the SRT review.

Part B – Second-Line Treatment

Part B patients will receive IV DKN-01 (300 mg or 600 mg) on Days 1 and 15 and IV tislelizumab (200 mg) on Day 1 of each 21-day cycle.

Part B has 2 components:

The first 24 patients (Part B1) will receive DKN-01 300 mg.

The next 24 patients (Part B2) will receive DKN-01 600 mg.

Patients enrolled in Part B are required to have DKK1-high (H-score ≥35) G/GEJ adenocarcinoma (pre-screen biopsy) and must have had only 1 prior systemic therapy for locally advanced/metastatic disease (platinum and/or fluoropyrimidine-based therapy; ± HER2 therapy if applicable). Patients may have received prior neoadjuvant or adjuvant therapy. A review by the SRT will occur after the first 5 patients in each of Part B1 and B2 have enrolled and completed Cycle 1.

It is anticipated that Part B2 will enroll following the completion of enrollment of all patients in Part B1. Enrollment in the other ongoing cohorts (e.g., Part A) may continue during the SRT review.

Part C – First-Line Treatment

Part C patients will be randomized using a central stratified block randomization scheme into one of 2 groups: patients in the experimental group will receive DKN-01 in combination with tislelizumab and chemotherapy regimen (CAPOX or mFOLFOX6) and patients in the control group will receive only tislelizumab in combination with chemotherapy regimen (CAPOX or mFOLFOX6). The randomization will use the following stratification factors:

- DKK1 RNAscope TPS (≥20% vs <20%)
- PD-L1 immunohistochemistry CPS (≥5 vs <5)

Note: To avoid unnecessary delays which could impact patient care, during the Screening Period patients, who in the opinion of the Investigator are unable to wait more than 2 weeks to start treatment, may receive one cycle of chemotherapy (CAPOX or mFOLFOX6) prior to randomization while awaiting biomarker results. Patients meeting these requirements should be discussed with the Medical Monitor.

Once DKK1 and PD-L1 results from the central laboratory are received and the patient has been confirmed to meet all other eligibility requirements, the patient will be randomized to receive either DKN-01 in combination with tislelizumab and chemotherapy (CAPOX or mFOLFOX6) or

tislelizumab in combination with chemotherapy (CAPOX or mFOLFOX6). The chemotherapy regimen administered during Screening must be equivalent to that following randomization.

The enrollment assumptions will be monitored during the enrollment period; thus sample size and timeline could be adjusted accordingly.

Patients in both groups receiving the CAPOX chemotherapy regimen will receive tislelizumab (200 mg, IV) on Day 1 of each 21-day cycle. The CAPOX regimen will include oxaliplatin 130 mg/m^2 on Day 1 and capecitabine 1000mg/m^2 BID on Days 1-15 of each 21-day cycle for a total of 28 doses. Patients in the experimental group will receive DKN-01 (600 mg, IV) on Day 1 of each cycle. For Cycle 1 only, an additional loading dose of DKN-01 (600 mg, IV) will be administered on Day 15. Patients in the control group will not receive DKN-01 treatment.

Patients in both groups receiving the mFOLFOX6 chemotherapy regimen will receive tislelizumab (400 mg, IV) every 6 weeks starting on C1D1 and continuing every third 14-day cycle (e.g., C4D1, C7D1, etc.). The mFOLFOX6 regimen will be administered every 14 days and includes leucovorin calcium (folinic acid) 400 mg/m^2 IV on Day 1, fluorouracil 400 mg/m2 IV bolus on Day 1 followed by fluorouracil 2400 mg/m^2 IV continuous infusion over 48 hours, and oxaliplatin 85 mg/m^2 IV on Day 1. Patients in the experimental group will receive DKN-01 (400 mg, IV) on Day 1 of each cycle. For Cycle 1 only, an additional loading dose of DKN-01 (400 mg, IV) will be administered on Day 8. Patients in the control group will not receive DKN-01 treatment.

For Part C, a review by the SRT will occur after the first 5 patients on each chemotherapy regimen (CAPOX and mFOLFOX6) have completed Cycle 1 from both the experimental group (i.e., DKN-01 in combination of tislelizumab and chemotherapy regimen) and the control group (i.e., tislelizumab in combination with chemotherapy regimen [CAPOX or mFOLFOX6]). Enrollment will continue during the safety data review without pause.

Safety Assessments:

Safety will be evaluated by assessment of adverse events (AEs), ECOG performance status, vital signs, ECG, physical examinations, ADA, and clinical laboratory values.

Toxicities will be graded and documented according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v5.0 guidelines).

The Investigator will determine grade, severity, seriousness, and relationship of the event to the study treatment.

Efficacy Assessments:

Radiological Assessment

Radiological assessment of tumor-response status will be performed approximately every 6 weeks (± 7 days) after C1D1 for the first 24 weeks, then every 9 weeks (± 7 days) after 24 weeks based on RECIST v1.1. Tumor response will be assessed by the Investigator.

Tumor response and progression will also be assessed using the Immune-related Response Criteria (iRECIST), 2017 for any patients continuing treatment after the initial assessment of progressive disease using RECIST 1.1.

Patients should have the same radiographic imaging modality used throughout the study (at baseline and at subsequent assessments) in order to provide uniformity of radiographic assessments.

After first documentation of response (CR or PR), confirmation of tumor response should occur at a minimum of 4 weeks after the first response or at the next scheduled assessment time point. Radiological images will be read locally and then sent to a central imaging vendor (Part C only). The

Sponsor may have the central imaging vendor perform an independent evaluation of some or all of the radiological images in Part C.

Tumor Biopsy

A tumor sample (fresh biopsy [preferred] or archived specimen) will be obtained from all patients during Pre-screening (Part B only) and Screening and will be sent to the Sponsor-designated central laboratory.

For Part B, the biopsy sample (fresh [preferred] or archival) collected during the Pre-screening period will be used to confirm elevated DKK1 mRNA levels required to meet eligibility criteria for enrollment. A fresh biopsy will be collected during the Screening period from patients who did not undergo a biopsy during the Pre-screening period for evaluation of DKK1 mRNA levels (unless it is clinically contraindicated per Investigator and after consultation with the Medical Monitor) for a retrospective DKK1 mRNA analysis.

For all Part A and B patients with fresh biopsies, the patient's biopsy sample obtained during the Screening Period will be sent to the Sponsor-designated central laboratory for retrospective evaluation of DKK1 expression.

All DKK1 testing will be conducted with a proprietary CISH assay using RNAscope technology at Flagship Biosciences, Inc. Westminster, CO, a CAP-accredited and Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. For Part C, PD-L1 expression will also be conducted by Flagship Biosciences. If the central lab is unable to result a PD-L1 CPS score, historical CPS data can be used provided it was generated using either the 22C3 pharmDx, 28-8 pharmDx or SP263 assays.

For both Parts A and B, PD-L1 expression will be retrospectively assessed if sufficient tumor biopsy tissue is available. In Part A, B, and C, scientific analyses, including microsatellite status (e.g., microsatellite stable [MSS], microsatellite instability-low [MSI-L], or microsatellite instability-high [MSI-H]), genomic profiling, RNA profiling (e.g., RNA-Seq), immunohistology, Epstein Barr virus (EBV), infiltrating immune cells by IHC, and additional IHC analyses may be performed.

For Part C patients, DKK1 testing and PD-L1 expression will be prospectively analyzed to permit stratification prior to randomization. DKK1 expression will be assessed using a Tumor Percentage Score (TPS). TPS has demonstrated significant correlation with H-score in retrospective analysis.

For Part C patients, an on-treatment biopsy is required if clinically feasible at Day 21 (+ 7 days). If possible, this should come from the same lesion used for the Screening analysis. If the original lesion is no longer measurable then a biopsy from another lesion is acceptable. Additional tumor tissue collected at any time during the study per standard of care may be submitted to the central laboratory for evaluation. Any on-treatment biopsy tissue will be sent to the Sponsor-designated central laboratory for evaluation of DKK1 expression and other biomarkers of interest.

An additional biopsy to evaluate the effects of treatment on the tumor tissue may be collected at any time during the study if a repeat biopsy is required clinically and the patient consents to the biopsy.

Duration of Patient Participation and Treatment:

A patient's study participation will include a 28-day Screening period (35 days allowed for imaging in Part C), followed by the study treatment period that will continue until the development of radiographically documented progressive disease, unacceptable toxicity or another discontinuation criterion is met, as determined by the Investigator, or until a patient reaches 2 years of treatment as outlined below (as measured from C1D1). After treatment discontinuation, patients will enter a long term follow-up period. The Sponsor has the right to terminate this study at any time.

If, in the opinion of the Investigator, a Part A patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab plus CAPOX but has a compelling clinical reason after completion of Cycle 2 to discontinue oxaliplatin, capecitabine, and/or tislelizumab treatment, the patient will be permitted to continue in the study with DKN-01 monotherapy or any combination of

DKN-01 + other study drugs (e.g., oxaliplatin, capecitabine and/or tislelizumab) at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part B patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab but has a compelling clinical reason after completion of Cycle 2 to discontinue tislelizumab treatment, the patient will be permitted to continue in the study with DKN-01 monotherapy at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part C (experimental arm only) patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab plus CAPOX/ mFOLFOX6 but has a compelling clinical reason after completion of Cycle 2 to discontinue one or several of the combination agents, e.g., oxaliplatin, capecitabine, leucovorin calcium, fluorouracil, DKN-01, and/or tislelizumab treatment, the patient will be permitted to continue in the study provided at least one of the agents is continued and no new systemic therapies are added at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part C (control arm only) patient is receiving clinical benefit from treatment with the combination tislelizumab plus CAPOX/ mFOLFOX6 but has a compelling clinical reason after completion of Cycle 2 to discontinue one or several of the combination agents, e.g., oxaliplatin, capecitabine, fluorouracil, and/or tislelizumab treatment, the patient will be permitted to continue in the study provided at least one of the agents is continued and no new systemic therapies are added at the discretion of the treating clinician, after discussion with the Medical Monitor.

When a patient reaches 2 years of treatment (as measured from C1D1):

Patients may continue on study drugs beyond 2 years if the Investigator considers this to be in the best interest of the patient based on an assessment of clinical benefit and potential risks. Continuation of study drugs beyond 2 years must be explicitly approved by the Sponsor and will be contingent on the continued availability of tislelizumab and DKN-01. The study assessment and procedure schedule will remain the same.

Patients with confirmed CR, PR, or SD may stop treatment after 2 years if the patient wishes. The decision should be based on the Investigator's evaluation, with the patient's clinical benefit and risk taken into consideration. The Investigator should notify the Sponsor that treatment will be stopped prior to stopping the treatment.

Treatment beyond the initial Investigator-assessed, RECIST v1.1-defined disease progression is permitted provided that the patient has Investigator-assessed clinical benefit and is tolerating the study drugs. Tumor assessment in such patients should continue as planned until study treatment discontinuation.

Patients who discontinue study treatment early for reasons other than disease progression (e.g., toxicity) will continue to undergo tumor assessments every 12 weeks during the PD Follow-up Period until the patient begins a subsequent anticancer treatment, experiences disease progression, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first. After documentation of PD, all patients will be followed approximately every 12 weeks per routine clinical practice during the Survival Follow-up Period for survival until death, withdrawal of consent, or study closure.

Study Population: Adult patients with inoperable, locally advanced or metastatic G/GEJ adenocarcinoma

Eligibility Criteria:

Inclusion Criteria: Patients meeting all of the following criteria will be considered eligible for study entry:

Part A and C only

1. No previous systemic therapy for inoperable, locally advanced or metastatic G/GEJ adenocarcinoma.

    a. Patients may have received prior neoadjuvant or adjuvant therapy as long as it was completed without disease recurrence for at least 6 months since last treatment.

Part B only

2. Documented objective radiographic or symptomatic disease progression following first-line therapy with any platinum and/or fluoropyrimidine-based regimen for unresectable or metastatic disease.

    a. Patients may have received prior neoadjuvant or adjuvant therapy. If progression has occurred within 6 months from last dose of neoadjuvant or adjuvant treatment, this regimen will be considered as 1 line of therapy for advanced disease.
    b. Prior trastuzumab (or biosimilar) treatment is acceptable for patients with history of HER2-positive G/GEJ adenocarcinoma.
    c. Prior therapy with an anti-programmed cell death protein 1 (PD-1), anti-PD-L1 in any treatment setting (including adjuvant/neoadjuvant) is acceptable.

3. Documentation of elevated DKK1 mRNA expression in tumor cells from a fresh tumor biopsy (preferred) or archived tumor biopsy specimen. High DKK1 is defined as an H-score ≥35 in mRNA by ISH conducted in a Sponsor designated central laboratory.

Part C only

4. Documentation of PD-L1 CPS by IHC and DKK1 mRNA expression in tumor cells by ISH from a fresh tumor biopsy (preferred) or archived tumor biopsy specimen conducted in a Sponsor designated central laboratory. If the central lab is unable to result a PD-L1 CPS score, historical CPS data can be used provided it was generated using either the 22C3 pharmDx, 28-8 pharmDx or SP263 assays.

General

5. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments.

6. Age ≥18 years on the day of signing the informed consent (exception: ≥19 years in the Republic of Korea).

7. Histologically proven gastric adenocarcinoma or Siewert I-III GEJ adenocarcinoma.

8. At least one measurable lesion on radiographic imaging as defined by RECIST v1.1.

    a. A lesion in an area subjected to prior loco-regional therapy, including previous radiotherapy, is not considered measurable unless there has been demonstrated progression in the lesion since the therapy as defined by RECIST v1.1.

    b. Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease.

9. Tumor tissue for mandatory pre-treatment evaluation (fresh biopsy [preferred] or archived specimen).

10. ECOG performance status ≤1 within 7 days of first dose of study drug.

11. Acceptable liver function:

a. Parts A and B only

i. Total bilirubin ≤2.0 times upper limit of normal (ULN). Total bilirubin must be <3 × ULN for patients with Gilbert's syndrome.

ii. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 times ULN (if liver metastases are present, then ≤5 × ULN is allowed).

b. Part C only

i. Total bilirubin ≤2.0 times upper limit of normal (ULN).

ii. AST and ALT ≤2.5 times ULN.

1. If liver metastases are present, then ≤5 × ULN is allowed (excluding Republic of Korea).

12. Acceptable renal function:

a. Serum creatinine ≤1.5 × ULN or estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation.

13. Acceptable hematologic status (in the Republic of Korea patients must not have required blood transfusion or growth factor support within 14 days before sample collection at Screening for the following):

a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L.

b. Platelets:

i. Part A and C only: ≥100 × 10^9/L
ii. Part B only: ≥75 × 10^9/L

c. Hemoglobin ≥9 g/dL

14. Acceptable coagulation status:

a. Prothrombin time/activated partial thromboplastin time ≤1.2 × ULN (unless receiving anticoagulation therapy; if receiving anticoagulation therapy, eligibility will be based upon international normalized ratio [INR]) see (b)(i) below

b. INR ≤1.5 (unless receiving anticoagulation therapy)
   i. 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 drugs).

15. Females of childbearing potential must be willing to use a highly effective method of birth control for the duration of the study and for at least 6 months after the last dose of study drugs, and have a negative urine or serum pregnancy test within 7 days before first dose of study drugs.

16. Non-sterile males must be willing to use a highly effective method of birth control for the duration of the study and for at least 6 months after the last dose of study drugs

a. A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility.

b. Males with known "low sperm counts" (consistent with "sub-fertility") are not to be considered sterile for purposes of this study.

Exclusion Criteria: Patients meeting any of the following criteria are not eligible for study entry:

Part A and C only

1. Diagnosis of HER2-positive G/GEJ adenocarcinoma.

2. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction (for those receiving CAPOX in Part C).

3. Prior therapy with an anti-programmed cell death protein 1 (PD-1) or anti-PD-L1 antibody.

Part B only

4. Systemic anti-cancer therapy (e.g., chemotherapy or immunotherapy) within 21 days prior to first dose of study drug.

General

5. Squamous cell or undifferentiated or other histological type of gastric cancer.

6. Prior therapy with an anti-PD-L2 or any other antibody or drug specifically targeting T-cell co-stimulation or coinhibitory checkpoint pathways in any treatment setting (including adjuvant/neoadjuvant) or prior therapy with an anti-DKK1 agent (Part B exception, see entry criterion 2c).

7. Active autoimmune diseases or history of autoimmune diseases that may relapse.

    a. Note: Patients with the following diseases are not excluded and may proceed to further Screening:

        i. Controlled Type I diabetes

        ii. Hypothyroidism (provided it is managed with hormone replacement therapy only)

        iii. Controlled celiac disease

        iv. Skin diseases not requiring systemic treatment (e.g., vitiligo, psoriasis, alopecia)

        v. Any other disease that is not expected to recur in the absence of external triggering factors.

8. Any condition that required treatment with corticosteroids (≥10 mg per day prednisone or equivalent) or other immune suppressive drugs within the 14 days prior to first dose of study drug.

    a. Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded:

        i. Adrenal replacement steroid (dose ≤10 mg daily of prednisone or equivalent)

        ii. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption

        iii. Short course (≤7 days) of corticosteroid prescribed prophylactically (e.g., for contrast dye allergy) or for the treatment of a non-autoimmune condition (e.g., delayed-type hypersensitivity reaction caused by contact allergen).

9. Active leptomeningeal disease or uncontrolled brain metastases. Patients with equivocal findings or with confirmed brain metastases are eligible for the study provided that they are asymptomatic and

radiologically stable without the need for corticosteroid treatment or seizure prophylaxis for ≥4 weeks before first dose of study drug.

10. Any active malignancy ≤2 years before first dose of study drug, with the exception of the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (e.g., resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast).

11. Uncontrolled diabetes or >Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥Grade 3 hypoalbuminemia within 14 days before first dose of study drug.

12. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage within 7 days prior to first dose of study drug (the cytological confirmation of any effusion is permitted).

13. Clinically significant anorexia (CTCAE ≥Grade 2) within 7 days prior to first dose of study drug.

14. History of interstitial lung disease, non-infectious pneumonitis, pulmonary fibrosis, acute lung disease, or uncontrolled systemic diseases.

a. Patients with radiation pneumonitis may be eligible for the study if the radiation pneumonitis has been confirmed as stable (beyond acute phase) without any concerns about recurrence. Patients with severe but stable radiation-induced pneumonitis may be required to undergo routine pulmonary function studies.

15. Severe chronic or active infections requiring systemic antibacterial, antifungal, or antiviral therapy, including tuberculosis infection within 14 days of first dose of study drug.

16. Prior allogeneic stem cell transplantation or organ transplantation.

17. History of severe hypersensitivity reactions to other monoclonal antibodies or any components of study treatment.

18. Known dihydropyrimidine dehydrogenase deficiency.

19. Any of the following cardiovascular risk factors:

a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, within 28 days before first dose of study drug

b. Pulmonary embolism within 28 days before first dose of study drug

c. Any history of acute myocardial infarction within 6 months before first dose of study drug

d. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV within 6 months before first dose of study drug

e. Any event of ventricular arrhythmia ≥Grade 2 in severity within 6 months before first dose of study drug

f. Any history of cerebrovascular accident within 6 months before first dose of study drug

g. Uncontrolled hypertension that cannot be managed by standard anti-hypertension medications within 28 days before first dose of study drug

h. Any episode of syncope or seizure within 28 days before first dose of study drug.

20. Fridericia-corrected QT interval >470 msec (female) or >450 (male), 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.

21. Known to be human immunodeficiency virus (HIV) positive unless HIV ribonucleic acid (RNA) is undetected; known to have active hepatitis B (acute or chronic infection requiring antiviral treatment; hepatitis B surface antigen-positive) or have hepatitis C antibodies unless hepatitis C virus RNA is undetected/negative.

22. Serious nonmalignant disease or other circumstance that could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor.

23. History of osteonecrosis of the hip or have 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 patients is not required.

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

25. History of gastrointestinal perforation and/or fistulae within 6 months prior to first dose of study drug, clinically significant bleeding from the gastrointestinal tract within 1 month prior to first dose of study drug, or clinically significant bowel obstruction (CTCAE ≥Grade 2).

26. Major surgery within 4 weeks of first dose of study drug.

27. Serious psychiatric or medical conditions that could interfere with treatment.

28. Toxicities (as a result of prior anticancer therapy) that have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (e.g., alopecia, neuropathy, and specific laboratory abnormalities).

29. Administration of a live vaccine within 28 days before first dose of study drug.

    a. Note: Seasonal vaccines for influenza or COVID vaccines are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.

30. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug, or affect the explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct.

31. Women who are pregnant or are breastfeeding.

32. Concurrent participation in another therapeutic clinical study.

    a. Note: Concurrent participation in observational or non-interventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.

33. Treatment with radiation therapy within 14 days prior to first dose of study drug.

Investigational Product, Dose, and Mode of Administration:

Part A and B only: The duration for each cycle is 21 days and the study treatment regimens are as follows:

Part	DKN-01	Tislelizumab	Oxaliplatin	Capecitabine
Part A	300 mg IV D1, 15	200 mg IV D1	130 mg/m^2 IV D1	1000 mg/m^2 PO BID D1-D15

Part B1	300 mg IV D1, 15	200 mg IV D1	-	-
Part B2	600 mg IV D1, 15	200 mg IV D1	-	-

Abbreviations: BID = twice daily; D = Day; IV = intravenously; PO = orally.

Part C only: The duration for each cycle is based on the chemotherapy regimen: CAPOX is 21 days and mFOLFOX6 is 14 days. The study regimens are as follows or per institutional standard practice:

Chemo Regimen	DKN-01	Tislelizumab	Oxaliplatin[1]	Capecitabine[1]	Leucovorin calcium[1, 6]	Fluorouracil[1]
Experimental Group						
CAPOX	600 mg IV D1[2]	200 mg IV D1 q 3 weeks	130 mg/m^2 IV D1	1000 mg/m^2 PO BID; D1-D15[3]	-	-
mFOLFOX6	400 mg IV D1[4]	400 mg IV D1 q 6 weeks[5]	85 mg/m^2 IV D1	-	400 mg/m^2 IV D1	400 mg/m2 IV bolus on D1 then 2400 mg/m2 IV continuous infusion over 48 hours D1 and D2
Control Group						
CAPOX	-	200 mg IV D1 q 3 weeks	130 mg/m^2 IV D1	1000 mg/m^{2}PO BID; D1-D15[3]	-	-
mFOLFOX6	-	400 mg IV D1 q 6 weeks[5]	85 mg/m^2 IV D1	-	400 mg/m^2 IV D1	400 mg/m2 IV bolus on D1 then 2400 mg/m2 IV continuous infusion over 48 hours D1 and D2

Abbreviations: BID = twice daily; D = day; IV = intravenously; PO = orally; q = every
[1] Standard dosing regimen per institutional standard of care.
[2] For **Cycle 1 only**, an additional loading dose of DKN-01 (600 mg, IV) will be administered on Day 15.
[3] A total of 28 doses from Day 1 through Day 15
[4] For **Cycle 1 only**, an additional loading dose of DKN-01 (400 mg, IV) will be administered on Day 8.
[5] Administered every 6 weeks starting on C1D1 and continuing every third 14-day cycle (e.g., C4D1, C7D1, etc.).
[6] If leucovorin is unavailable, 200 mg/m2 levo-leucovorin may be used. Study treatment may be administered without either agent if neither are available or that is per institutional standard of care.

DKN-01: DKN-01 will be administered intravenously (IV) without interruption over a minimum of 30 minutes and up to a maximum of 2 hours.

Tislelizumab: Tislelizumab will be administered IV; the initial infusion (C1D1) will be delivered over 60 minutes; if this is well tolerated, then the subsequent infusions (CxD1) may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug.

Oxaliplatin – Part A and C Only: Oxaliplatin will be administered IV according to institutional standard of care.

Capecitabine – Part A and C Only: Capecitabine will be administered orally according to institutional standard of care.

Leucovorin calcium and Fluorouracil – Part C Only: Leucovorin calcium and fluorouracil will be administered IV according to institutional standard of care.

Order of Administration

In Part A, the order of IV administration will be DKN-01, tislelizumab, and then oxaliplatin. Capecitabine may be taken at any time on Day 1.

In Part B, DKN-01 will be administered first, followed by tislelizumab.

In Part C, the order of IV administration in the experimental group will be DKN-01, tislelizumab followed by chemotherapy regimen thereafter.

- For patients receiving CAPOX, the order of IV administration will be DKN-01, tislelizumab, and then oxaliplatin. Capecitabine may be taken at any time on Day 1.
- For patients receiving mFOLFOX6, the order of administration will be DKN-01, tislelizumab, followed by chemotherapy (oxaliplatin, leucovorin, and fluorouracil will be given per institutional SOC guidelines).

In Part C, the order of IV administration in the control group will be tislelizumab followed by chemotherapy regimen thereafter.

- For patients receiving CAPOX, the order of IV administration will be tislelizumab and then oxaliplatin. Capecitabine may be taken at any time on Day 1.
- For patients receiving mFOLFOX6, the order of administration will be tislelizumab, followed by chemotherapy (oxaliplatin, leucovorin, and fluorouracil will be given per institutional SOC guidelines).

Statistical Methods:

Part A and Part B

Sample Size Determination

The sample size for Part A and B of this Phase 2 study is not based on formal statistical calculations as this is a pilot study designed primarily to seek information on the safety, efficacy, and pharmacokinetics/pharmacodynamics of DKN-01 in combination with tislelizumab ± CAPOX. Data collected from previous clinical studies indicates that DKN-01 is well tolerated. It was therefore determined that 20 patients would be sufficient to assess the safety and tolerability of DKN-01 in combination with tislelizumab ± CAPOX in a pilot study.

A maximum of 24 patients (first-line treatment) will be enrolled in Part A to ensure 20 evaluable patients. A maximum of 48 patients (DKK1-high G/GEJ adenocarcinoma, second-line treatment) will be enrolled in Part B to ensure 40 evaluable patients. With a sample size of 20 evaluable patients in Part A, observed ORR rates of 69%, 77%, or 80% would be statistically greater than the 50% expected success rate at a 0.05 one-sided significance level with at least 50%, 80%, or 90% power, respectively. With a sample size of 40 evaluable patients in Part B, observed ORR rates of 42%, 49%, or 53% would be statistically greater than the ≥30% expected success rate at a 0.05 one-sided significance level with at least 50%, 80%, or 90% power, respectively.

It is estimated that approximately 180 patients will be screened to achieve the target of 24 patients enrolled in Part A and 48 patients in Part B.

Part C

Statistical Hypothesis

The primary efficacy endpoint is PFS, and the study is designed to test the superiority of DKN-01 plus tislelizumab and chemotherapy (CAPOX or mFOLFOX6), the experimental treatment, over

tislelizumab and chemotherapy (CAPOX or mFOLFOX6), the control treatment, for DKK1 high and in all patients. The primary analysis will test the following hypotheses:

- Null Hypothesis: The hazard ratio for PFS between experimental and control treatment is equal to one.
- Alternative Hypothesis: The hazard ratio for PFS between experimental and control treatment is less than one.

Sample Size Determination

The sample size for Part C of this Phase 2 study is estimated based on the primary efficacy endpoint PFS as this part of the study is designed primarily to seek information on the efficacy of DKN-01 in combination with tislelizumab and chemotherapy regimen (CAPOX or mFOLFOX6) as compared to the combination of tislelizumab and chemotherapy regimen (CAPOX or mFOLFOX6) alone in DKK1-high patients and in patients regardless of their DKK1 status (all-comers). It is determined that a total of approximately 160 patients (approximately 80 patients in each treatment group) would be sufficient to assess the efficacy of DKN-01 in combination with tislelizumab and chemotherapy for DKK1-high patients and in patients regardless of their DKK1 status.

With a power of 83% and a one-sided Type I error of 10%, a total of 137 PFS events of all-comer patients are required to detect a treatment effect hazard ratio of 0.681 (median PFS for all-comers is 7.7 months in the control arm and 11.3 months in the experimental arm). With a power of 80% and a one-sided Type I error of 10%, a total of 49 PFS events of DKK1-high patients are required to detect a treatment effect hazard ratio of 0.546 (median PFS for DKK1-high patients is 6.5 months in the control arm and 11.9 months in the experimental arm) in DKK1-high patients.

The sample size and power calculations are based on the following assumptions: Assuming a recruitment period of 12 months, a 10% probability of dropping out during the course of the study, a minimum follow-up of 24 months, and approximately 50% of patients will be DKK1-high. If the proportion of DKK1 high patients is not 50%, the power of PFS in DKK1-high patients will vary and may require further evaluation.

For purposes of analysis, the following populations are defined:

	Description
Enrolled	All patients who signed the main study informed consent form (ICF).
Safety Population	For Part A and B: All patients who signed the ICF and received at least 1 dose of DKN-01. This is the primary population for the Safety Analysis. For Part C: The safety population is defined as all patients who are randomized and receive at least one dose of study treatment.
Efficacy	
Intent-to-Treat (ITT) Population	For Part A and B: The intent-to-treat population (full analysis set) is defined to be all patients who enrolled and received at least one dose of DKN-01. For Part C: The intent-to-treat population is defined to be all patients randomized to treatment. Patients will be included in the treatment group assigned at randomization regardless of the actual treatment received.
Modified Intent-to-Treat (mITT) Population	For Part A and B: All patients who received more than one dose of DKN-01. This is the primary population for the efficacy analyses including PFS and OS. For Part C: All randomized patients who receive at least one cycle of study treatment.

Response Evaluable Population	Part A: All patients who received any amount of DKN-01 + tislelizumab + oxaliplatin + capecitabine and have measurable baseline and at least 1 evaluable post-baseline RECIST tumor response assessment. Part B1 and B2: All patients who received any amount of DKN-01 + tislelizumab and have a measurable baseline and at least 1 evaluable post-baseline RECIST tumor response assessment. Part C: All patients who received any amount of tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) ± DKN-01 and have measurable baseline and at least 1 evaluable post-baseline RECIST tumor response assessment.
Per-Protocol (PP) Population	Part A and B: All enrolled patients without important protocol deviations that necessitates exclusion from this population or compliance issues, as applicable. Part C: All patients who are randomized and received the study treatment (tislelizumab + chemotherapy regimen [CAPOX or mFOLFOX6] ± DKN-01) as planned and have no important protocol deviations. The PP population will be used for sensitivity analyses of the primary and secondary objectives.
Pharmacokinetics Population DKN-01	All enrolled patients with available serum-time concentration data from patients dosed with DKN-01.
Pharmacokinetics Population tislelizumab	All enrolled patients with available serum-time concentration data from patients dosed with tislelizumab.
Biomarker population	There is one biomarker population for each of the following biomarkers: - DKK1 tumor expression in messenger RNA (mRNA) by chromogenic in situ hybridization (CISH). - Programmed cell death protein ligand-1 (PD-L1) expression by IHC.

Abbreviations: DKK1 = Dickkopf-1; ICF = informed consent form; PD-L1 = programmed cell death protein ligand 1.

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	anti-drug antibodies
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the drug concentration-time curve from time zero to infinity
BID	twice daily
BSA	body surface area
C1D1	Cycle 1, Day 1 (pattern set for cycle and days [e.g., C1D8, C2D1, etc.])
CAP	College of American Pathologists
CAPOX	capecitabine + oxaliplatin
CI	confidence interval
CISH	chromogenic in situ hybridization
CK	creatine kinase
CK-MB	creatine kinase cardiac isoenzyme
CL	clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum observed serum concentration
CNS	central nervous system
CR	complete response
CPS	Combined positive score
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
D	day
DCB	durable clinical benefit
DCR	disease control rate
DKK1	Dickkopf-1
DoCB	duration of clinical benefit

Abbreviation	Definition
DoCR	duration of complete response
DoR	duration of response
EBV	Epstein Barr virus
EC	esophageal cancer
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FcRn	neonatal Fc receptor
FcγR	gamma fragment crystallizable region receptor
FDG-PET	fludeoxyglucose-positron emission tomography
GCP	Good Clinical Practice
G/GEJ	gastric or gastroesophageal junction
GI	gastrointestinal
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
ICI	Immune checkpoint inhibitor
ICF	informed consent form
ICH	International Council for Harmonisation
IHC	immunohistochemistry
IND	Investigational new drug application
INR	international normalized ratio
irAE	immune-related adverse events
IRB/IEC	Institutional Review Board/Independent Ethics Committee
iRECIST	Immune-related Response Criteria in Solid Tumors
ISH	in situ hybridization
IV	intravenous(ly)
IRT	Interactive Response Technology
Leap	Leap Therapeutics, Inc.
mAb	monoclonal antibody
mFOLFOX6	leucovorin calcium, fluorouracil, and oxaliplatin

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI-H, MSI-L	microsatellite instability-high, microsatellite instability-low
MSS	microsatellite stable
NCI	National Cancer Institute
NE	not evaluable
NK	natural killer
NLR	neutrophil-to-lymphocyte ratio
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein ligand-1
PET	positron emission tomography
PFS	progression-free survival
PI	Principal Investigator
PK	pharmacokinetic
PO	orally
PR	partial response
Q2W	once every 2 weeks
QW	once weekly
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SOC	system organ class
SOD	Sum of Diameters
SRT	Safety Review Team
TAP	Tumor area positivity
TEAE	treatment-emergent adverse event

Abbreviation	Definition
TESAE	treatment-emergent serious adverse event
TMDD	target-mediated drug disposition
TPS	tumor percentage score
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
V_2, V_3	peripheral volume
Vc	central volume
WBC	white blood cells
“X” L	“X” Line of therapy

1. INTRODUCTION

1.1. Background Information on Gastric and Gastroesophageal Junction Adenocarcinoma

The combination of DKN-01 and tislelizumab is being investigated for the treatment of inoperable, locally advanced or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma.

Gastric adenocarcinoma remains one of the most common and deadly cancers worldwide, especially among older males in whom this cancer is more prevalent than women. Based on GLOBOCAN 2018 data, gastric adenocarcinoma is the fifth most common neoplasm and the third most deadly cancer, with an estimated 783,000 deaths in 2018, following only lung and colorectal cancer in overall mortality. About 1 in 12 or 1.8% of all oncological deaths are attributable to gastric adenocarcinoma. The cumulative risk of developing gastric adenocarcinoma from birth to age 74 is 1.87% in males and 0.79% in females worldwide (Bray, Ferlay et al. 2018, Rawla and Barsouk 2019).

According to the National Cancer Institute, there were an estimated 113,054 people living with gastric adenocarcinoma in the United States of America (USA) in 2016. In 2020, it is estimated that there will be 27,600 new cases of gastric adenocarcinoma and an estimated 11,010 people will die of this disease. Gastric adenocarcinoma represents 1.6% of all new cancer cases in the United States (ACS 2020). Adenocarcinoma of the esophagus and GEJ or proximal esophagogastric junction is the fastest growing cancer in the Western population, especially in the USA, rising by 6-fold annually on the background of declining rates of most other cancers (Fenoglio-Preiser, Carneiro et al. 2000, Siewert, Marcus et al. 2000) and 2.5-fold compared with 1970 incidence of GEJ cancers.

The prognosis of patients with gastric cancer may vary based upon the stage of cancer as well as factors such as nodal involvement and direct tumor extension beyond the gastric wall and tumor grade (Nakamura, Ueyama et al. 1992, Siewert, Böttcher et al. 1998, Adachi, Yasuda et al. 2000). The 5-year survival rates for Tumor Node Metastasis stages IA and IB tumors treated with surgery are 94% and 88%, respectively (Zhang, Zhou et al. 2014, Wang, Sun et al. 2015). Overall 5-year survival is approximately 32%. Long remissions are rare in disseminated gastric cancer, and treatments are primarily palliative (NCI 2002).

1.2. Current Treatment of G/GEJ Adenocarcinoma and Unmet Clinical Needs

Management of G/GEJ adenocarcinoma is challenging, as these tumors involve 2 contiguous organs and also straddle the thoracic cavity and abdominal cavity via hiatal opening. Management of G/GEJ adenocarcinomas depends on the stage of the tumor. For early-stage tumors there is a role for endoscopic submucosal dissection, but advanced tumors require multimodality treatment including surgery, chemotherapies, and immunotherapies.

1.2.1. Treatment Modalities

Multimodality approach: The optimal multimodality approach is not well established, but relative benefits of preoperative chemoradiotherapy versus perioperative chemotherapy versus

initial surgery followed by postoperative chemoradiotherapy or chemotherapy have been debated (Ashraf, Hoffe et al. 2015, Lin, Khan et al. 2019, Petrelli, Ghidini et al. 2019, Wagner, Lordick et al. 2020). The approach most adopted clinically for G/GEJ adenocarcinoma includes a combined modality therapy rather than surgery alone and includes preoperative or neoadjuvant therapy for most patients with cT3 or higher, node-positive, or borderline resectable G/GEJ adenocarcinoma who will likely tolerate a combined modality treatment(Ashraf, Hoffe et al. 2015). This approach has been preferred over perioperative chemotherapy (Ashraf, Hoffe et al. 2015). Perioperative chemotherapy can be an alternative option for patients who are unable to tolerate trimodality therapy and when clinical suspicion for occult metastatic disease is high (Cunningham, Allum et al. 2006, Ychou, Boige et al. 2011, Ashraf, Hoffe et al. 2015).

Several chemotherapy regimens have been studied, and options include epirubicin, cisplatin, and 5-fluorouracil (ECF) based on the MAGIC trial (Cunningham, Allum et al. 2006), epirubicin plus cisplatin and capecitabine (ECX) based on the MRC OE05 trial (Alderson, Cunningham et al. 2017), or infusional 5-fluorouracil plus cisplatin (Ychou, Boige et al. 2011); for younger and fit patients, docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil may be an option based on results from the FLOT4-AIO trial (Al-Batran, Hofheinz et al. 2016). Generally, 4 cycles of preoperative chemotherapy are preferred over 6 cycles when ECX or ECF is chosen.

For concurrent chemoradiotherapy, although an optimal regimen is not well established, a doublet rather than single-agent chemotherapy is preferred, and options include 2 courses of cisplatin and 5-fluorouracil (CALGB 9781 trial; [(Tepper, Krasna et al. 2008)]) or low-dose weekly carboplatin plus paclitaxel per results from the Dutch CROSS trial (Shapiro, van Lanschot et al. 2015). The CROSS regimen is most frequently recommended and adopted for this modality of treatment. The optimal dose-fractionation radiotherapy for concurrent chemoradiotherapy is yet to be determined, since many earlier trials were performed before the availability of newer techniques like 3D conformal radiotherapy and intensity-modulated radiotherapy. Modern 3D conformal techniques are preferred to reduce toxicities to vital organs, and regardless of the specific chemotherapy regimen used, a standard dose of radiation for patients treated with concurrent chemotherapy is 50.4 Gy (Herskovic, Martz et al. 1992, Tepper, Krasna et al. 2008).

Surgical treatment options: Surgical management is dictated by the anatomic location of the tumor. Patients with Siewert type I tumors are not candidates for a pure transabdominal approach, and the standard recommended approach is transthoracic en bloc esophagectomy and partial gastrectomy with 2-field lymphadenectomy. Most type II and type III tumors are offered total gastrectomy with a transabdominal/transhiatal resection of the distal esophagus with lymphadenectomy of lower mediastinum and abdominal D2 nodal compartment (Hulscher, van Sandick et al. 2002, Sasako, Sano et al. 2006, Omloo, Lagarde et al. 2007). Patients who are not surgical candidates can be treated with a definitive chemoradiotherapy approach, although it is less desirable as a curative option.

For patients who have undergone surgery after preoperative chemotherapy alone, postoperative chemotherapy is preferred over chemoradiotherapy (Verheij, Jansen et al. 2016). Post-operative radiotherapy is reserved for patients with a histologically positive resection margin. The NCCN guidelines suggest postoperative fluoropyrimidine-based chemoradiotherapy for margin-

positive resection and chemotherapy alone (if used preoperatively) for residual node-positive but margin-negative disease (Verheij, Jansen et al. 2016).

For patients who undergo initial surgery without neoadjuvant therapy, postoperative adjuvant therapy is recommended for margin-positive disease, node-positive disease, or pathologic T3 or higher primary tumor stage (Macdonald, Smalley et al. 2001, Lee, Lee et al. 2012a).

1.2.2. Current Treatment of Gastric and Gastroesophageal Junction Adenocarcinoma and Unmet Clinical Needs

G/GEJ adenocarcinoma represents a major cause of cancer-related deaths (Bray 2018). Recently, several products have been approved globally for the treatment of this disease. The backbone of first-line (1L) systemic therapy includes a fluoropyrimidine and a platinum agent (standard of care) with addition of trastuzumab in human epidermal growth factor receptor 2 (HER2) overexpressing patients (Rogers 2022). Recently the Checkmate-649 trial demonstrated the addition of the anti-PD1 antibody, nivolumab, to 1L standard of care therapy improved overall survival compared with SOC alone, in particular in patients whose tumor have higher programmed death ligand 1 (PD-L1) expression (combined positive score [CPS] ≥5) (Janjigian 2021). After progression on 1L therapy, paclitaxel with or without the anti-VEGFR2 antibody ramucirumab is a global standard for second line (2L) therapy (Wilke 2014). Following the Keynote-059 trial (Fuchs 2018), the anti-PD-1 antibody pembrolizumab demonstrated benefit for third line (3L) patients with PD-L1 positive tumors defined by a combined positive score (CPS) of 1 or greater (CPS ≥1 [Fuchs 2018]). Pre-specified analysis from pembrolizumab-containing trials, including Keynote-061 (2L) and Keynote-062 (1L), have identified subsets of patients more likely to benefit from immune-checkpoint inhibitors (ICI), including those with higher PD-L1 scores (CPS ≥10) and/or microsatellite instable (MSI-H) tumors (Chao 2021; Shitara 2020; Wainberg 2021). However, this represents the minority of patients, and intrinsic resistance to ICI remains a critical unmet need. Discriminatory biomarkers independent of PD-L1 and MSI-H represent a key area of investigation with potential to identify patients more likely to respond to ICIs.

Despite the availability of these products, an unmet medical need remains for treatment of patients with G/GEJ adenocarcinoma, a rare disease. None of the products approved to date for the treatment of gastroesophageal cancers specifically target patients with high Dickkopf-1 (DKK1) expression, a target population for DKN-01.

1.3. Background Information on the Study Drugs DKN-01 and Tislelizumab

Please refer to the latest version of the DKN-01 Investigator's Brochure or Tislelizumab Investigator's Brochure (BeiGene) for the most current information available for DKN-01 and tislelizumab, respectively.

1.3.1. Background Information DKN-01

DKN-01 (formerly known as LY2812176) is a humanized monoclonal antibody (mAb) (immunoglobulin G4 [IgG4]) optimized for neutralizing activity against DKK1 protein. DKN-01 is in development as an anticancer agent and is being studied for treatment of several human malignancies, including G/GEJ adenocarcinoma.

1.3.1.1. Pharmacology of DKN-01

DKN-01 is a potent mAb with neutralizing activity against DKK1, a secreted modulator of Wnt signaling, 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, Tamai et al. 2009, Clevers and Nusse 2012, Clevers, Loh et al. 2014, Sedgwick and D'Souza-Schorey 2016). DKN-01 is in development as an anticancer agent and is being investigated in a variety of solid tumors.

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, Tamai et al. 2009, Clevers and Nusse 2012, Clevers, Loh et al. 2014, Sedgwick and D'Souza-Schorey 2016). DKK1 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 2006, Wang and Zhang 2011, Kimura, Fumoto et al. 2016).

The overexpression of DKK1 in tumors or elevated levels of DKK1 in patient serum has been associated with cancer-promoting activity in many types of cancer. Cancers with tumors that express DKK1 or induce elevated patient serum levels include breast, chondrosarcoma, cholangiocarcinoma, cervical, colorectal, endometrial, esophageal, gastric, glioblastoma, kidney, liver, laryngeal, lung, malignant fibrous histiocytoma, multiple myeloma, osteosarcoma, ovarian, pancreatic, prostate, and urothelial cancer (Kagey and He 2017).

DKK1 has direct tumor effects by increasing tumor growth, metastasis, and angiogenesis and by favoring a stem cell-like phenotype(Smadja, d'Audigier et al. 2010, Thudi, Martin et al. 2011, Krause, Ryan et al. 2014, Malladi, Macalinao et al. 2016). Furthermore, DKK1 has been implicated in promoting an immunosuppressive tumor microenvironment by activating myeloid derived suppressor cells and through the downregulation of natural killer (NK) activating ligands on cancer cells (D'Amico, Mahajan et al. 2016, Malladi, Macalinao et al. 2016).

Anti-DKK1 antibody inhibited the invasive activity and the growth of cancer cells in vitro and suppressed the growth of engrafted tumors in vivo in mice, while tumor tissues treated with anti-DKK1 displayed significant fibrotic changes and a decrease in viable cancer cells without apparent toxicity in mice (Sato, Yamabuki et al. 2010).

Anti-DKK1 neutralizing antibodies have been hypothesized to not only directly impede tumor growth but also promote an antitumor immune response (Kagey and He 2017).

1.3.1.2. Toxicology of DKN-01

Repeat-dose studies have been conducted with DKN-01 in cynomolgus monkeys and Sprague-Dawley rats with doses up to 100 mg/kg administered once weekly for 8 weeks. No noteworthy findings were observed in the monkeys. In 2 studies conducted in Sprague-Dawley rats, histopathological examination revealed epiphyseal femoral head necrosis in control animals and animals that received DKN-01 at the 100 mg/kg dose. The incidence and severity of epiphyseal femoral head necrosis was higher in the male animals that received the 100 mg/kg dose than in control animals; therefore, it is possible that DKN-01 increased the incidence and severity of this finding.

Evaluation of embryofetal developmental effects induced by DKN-01 in rats and rabbits indicated no effects on embryo survival or toxicity; however, at the high dose of 100 mg/kg, malformations or increases in malformations from control levels were observed. Specifically, imperforation of the anal opening occurred in rats, and there was a minimal apparent increase in malformations relating to the vertebral column and ribs in rabbits in the 2 test-article-treated groups. These findings were present in a single control fetus with multiple malformations and were generally seen in the historical background data of the testing facility. Thus, due to the small group size, the etiology of this finding in relation to treatment cannot be conclusively determined.

Studies in DKK1 knockout mice (Mukhopadhyay, Shtrom et al. 2001, Morvan, Boulukos et al. 2006) suggest that blocking DKK1 with a mAb may pose a risk of teratogenesis.

1.3.1.3. Clinical Pharmacology of DKN-01

After single intravenous (IV) administration of DKN-01 to healthy volunteers at doses of 7 to 300 mg, there was an overall trend for increasing half-life with increasing dose, ranging from 11 to 19 days. As expected for IV administration, the increase in maximum observed serum concentration (C_{max}) values were dose proportional while the area under the drug concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) values increased in a greater than dose proportional manner between 7 and 70 mg, suggesting nonlinear clearance, particularly within the 7 to 70 mg dose range. This non-linearity in PK is likely due to target-mediated drug disposition (TMDD).

In patients with cancer, DKN-01 serum levels and exposure metrics (C_{max} and the AUC from time 0 to the last measurable concentration) generally increased in slightly greater than dose proportional manner over a dose range of 75 to 300 mg. However, exposure between 300 to 600 mg was approximately dose proportional. A dosing frequency of once weekly (QW) or once every 2 weeks (Q2W) both resulted in drug accumulation. The degree of accumulation observed was consistent with drug half-life, as well as the observation that drug levels did not appear to have reached steady state within 4 weeks of dose initiation.

After dosing with DKN-01, a dose-dependent and time-dependent increase in mean total serum DKK1 levels was observed, consistent with TMDD. Modeling suggested that this increase was due to the target engagement by DKN-01 to form a DKN-01/DKK1 complex, which was cleared more slowly than free unbound DKK1. Concurrent with complex formation, free levels of DKK1 were modeled to have decreased. Thus, administration of DKN-01 led to a dose and time dependent suppression of free DKK1 concentrations in serum.

Population pharmacokinetic (PK) analysis was conducted using data from 4 studies (Study DEK-DKK1-P100, DEK-DKK1-P101, DEK-DKK1-P102, and DEK-DKK1-P103) comprising 163 patients.

- Study DEK-DKK1-P100
    - Part A included 13 patients with multiple myeloma, advanced solid tumors, or refractory non–small cell lung cancer (NSCLC) who received DKN-01 doses of 75 mg, 150 mg, and 300 mg weekly, and 600 mg every 2 weeks

    - Part B included patients with refractory NSCLC who received a DKN-01 dose of 300 mg every 2 weeks.
- Study DEK-DKK1-P101 included patients with multiple myeloma (MM) who received a DKN-01 dose of 300 mg every 2 weeks.
- Study DEK-DKK1-P102 comprised patients with relapsed or refractory esophageal cancer (EC) or GEJ tumors.
    - Part A – 150 mg every 2 weeks and 300 mg every 2 weeks (patients with relapsed or refractory EC or GEJ tumors)
    - Part B – 300 mg every 2 weeks (patients with relapsed or refractory EC or GEJ tumors
    - Part C – 300 mg every 2 weeks (patients with esophageal or GEJ adenocarcinoma
    - Part D – 300 mg every 2 weeks (patients with esophageal squamous cell cancer)
    - Part E – 300 mg every 2 weeks (patients with gastric adenocarcinoma with Wnt signaling alterations)
    - Patients with advanced or recurrent esophageal, GEJ, or gastric cancer who were not eligible to receive paclitaxel were enrolled as part of a DEK-DKK1-P102 monotherapy sub-study (300 mg every 2 weeks).
- Study DEK-DKK1-P103 comprised patients with advanced carcinoma primary to the intra- or extra-hepatic biliary system or gallbladder.
    - Part A – 150 mg and 300 mg DKN-01 on Day 1 and Day 8 of a 21-day cycle
    - Part B – Patients were treated at the maximum tolerated dose (MTD) of DKN-01 (300 mg). All patients also received gemcitabine 1000 mg and cisplatin 25 mg.

The patient population was predominantly white (~90%) and male (~60%), with an overall baseline median age of 62 years and an overall baseline median weight of 72 kg.

One of the primary objectives of this analysis was to provide plausible DKN-01 PK profiles such that exposure (both C_{max} and AUC) could be calculated at various time points for all studies despite the limited PK sampling. In addition, free DKK1 concentrations could also be inferred from the model, and these values were used elsewhere to explore a possible relationship with clinical efficacy.

The DKN-01/DKK1 population data was best described using a 2-compartment target mediated disposition model with a quasi-equilibrium assumption. Patient characteristics influencing DKN-01/DKK1 PK/PD included serum albumin and height, which affected the DKN-01 elimination rate (k_{el}). Serum albumin was negatively correlated with the DKN-01 elimination rate, and this is frequently observed for other monoclonal antibodies. This relationship may be explained by the action of the neonatal Fc receptor (FcRn), which mediates albumin turnover but protects IgG antibodies from degradation. Lower albumin might reflect decreased efficiency of FcRn catabolic/recycling capability, which may correlate with faster elimination of DKN-01.

Covariates related to body mass composition are probably the most frequently identified and clinically relevant covariates in population PK analyses. This is not surprising, since PK parameters such as clearance and volume are often a function of body size. Body weight is often found to influence a number of general pop-PK model parameters. However, in this study height was found to positively correlate with both DKN-01 elimination (k_{el}), as well as DKN-01 central compartment volume estimates. Finally, a positive correlation was found between the rate of DKN-01/DKK1 complex internalization/elimination and concentrations of baseline DKK1.

1.3.1.4. Prior Clinical Experience with DKN-01

As of 30 December 2019, DKN-01 has been evaluated in 30 healthy subjects and 345 patients with cancer in 6 industry-sponsored clinical studies. All 30 healthy subjects received a single dose of DKN-01. Among the 345 patients with cancer treated with DKN-01, 111 received DKN-01 monotherapy; 7 received DKN-01 in combination with lenalidomide/dexamethasone; 113 received DKN-01 in combination with paclitaxel; 51 patients received DKN-01 in combination with gemcitabine/cisplatin; and 63 received DKN-01 in combination with pembrolizumab. In addition, as controls in 2 clinical studies, 18 healthy subjects received a single dose of placebo and 1 patient with MM received lenalidomide/dexamethasone (Table 1).

Refer to Section 1.6 for an overall benefit-risk assessment.

Table 1: Individual Clinical Studies

Protocol Number	Study Title	Study Status/ Number Subjects or Patients Dosed
I3U-MC-GRCA	A Placebo-controlled, Safety, Tolerability and Pharmacokinetic Parallel Group Study of Single Escalating Doses of LY2812176[a], an Anti-DKK-1 Humanized Antibody, in Subjects with Low Bone Mineral Density	Complete DKN-01: 30 Placebo: 18
DEK-DKK1-P100	A Two-Part, Phase 1, Multicenter, Open-Label, Study of DKN-01 Given Intravenously. Part A: A Dose-Escalation Study in Patients with Multiple Myeloma or Advanced Solid Tumors. Part B: An Expansion Cohort in Patients with Relapsed or Refractory Non-Small Cell Lung Cancer (NSCLC) ClinicalTrials.gov Identifier: NCT01457417	Complete DKN-01: 32
DEK-DKK1-P101	A Pilot Study of DKN-01 and Lenalidomide (Revlimid®)/ Dexamethasone versus Lenalidomide/Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma ClinicalTrials.gov Identifier: NCT01711671	Complete[b] DKN-01+Len/Dex: 7 Len/Dex: 1

Protocol Number	Study Title	Study Status/ Number Subjects or Patients Dosed
DEK-DKK1-P102	A Multi Part, Phase 1, Multi-center, Open-label Study of DKN-01 as a Monotherapy or in Combination with Paclitaxel or Pembrolizumab in Patients with Relapsed or Refractory Esophagogastric Malignancies[c] ClinicalTrials.gov Identifier: NCT02013154	Ongoing (N=151)[1] DKN-01: Monotherapy: 29[1] +Paclitaxel: 59 + Pembrolizumab: 63[c]
DEK-DKK1-P103	A Dose Escalation and Cohort Expansion Study of DKN-01 in Combination with Gemcitabine and Cisplatin in Patients with Advanced Carcinoma Primary to the Intra- or Extra-hepatic Biliary System or Gallbladder ClinicalTrials.gov Identifier: NCT02375880	Complete DKN-01+Gem/Cis: 51
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[d] ClinicalTrials.gov Identifier: NCT03395080	Ongoing DKN-01: Monotherapy: 51 +Paclitaxel: 54

Source: DKN-01 Investigator's Brochure.

[a] DKN-01 was previously named LY2812176.

[b] Twenty patients were planned to be enrolled in Study DEK-DKK1-P101; however, the study was terminated after 8 patients were enrolled due to difficulty in meeting study enrollment target and changing treatment paradigms. Given that the study was terminated prematurely, only safety and PK data for this study are presented in this document; efficacy data are not presented.

[c] Study P102 was amended on 21 July 2017 to include Study Part F, a combination arm of DKN-01 + pembrolizumab.

[d] Study P204 was amended on 13 March 2019 to include a cohort of patients with recurrent carcinosarcoma (malignant mixed Mullerian tumor [MMMT]) to be treated with DKN-01 as monotherapy or DKN-01 + paclitaxel.

1.3.1.4.1. Prior Clinical Experience in Gastroesophageal Cancer

DKN-01 as a monotherapy or in combination with paclitaxel or pembrolizumab was assessed in patients with relapsed or refractory esophagogastric malignancies in a Phase 1, multicenter, open-label study (Study DEK-DKK1-P102).

Study DEK-DKK1-P102 is a Phase 1 nonrandomized, dose-escalating, open label, multi-center study conducted in multiple parts (Parts A through F). In addition, a separate monotherapy sub-study 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, GEJ or gastric cancer with progressive disease requiring therapy are planned to be enrolled in the study. Expected enrollment in each study part was as follows:

- Part A: Up to 12 patients in 2 cohorts of up to 6 patients per cohort
- Parts B, D and E: Up to 20 patients in each part

BeiGene

[1] A total of 29 patients were enrolled into the monotherapy sub-study; however, 1 patient was deleted from the database due to an Informed Consent Form signature issue. The site's Institutional Review Board was notified.

- Part C and Monotherapy Sub-study: Up to 40 patients in each part
- Part F: A maximum of 12 patients (pembrolizumab-naïve and primary-refractory) in the dose-escalation phase. In the expansion phase, sufficient patients (approximately up to 60) to ensure up to 55 evaluable patients at the target dose: up to 40 evaluable pembrolizumab-naïve patients in Group 1 and 15 pembrolizumab-primary refractory patients in Group 2.

Thus, a maximum of approximately 184 patients with advanced refractory or recurrent esophageal, GEJ, or gastric cancer treated with at least one prior regimen with progressive disease requiring therapy were planned to be enrolled in the study and will receive DKN-01 in combination with paclitaxel or pembrolizumab. In addition, it is expected that up to 40 patients with advanced refractory or recurrent esophageal, GEJ, or gastric cancer who are unable to receive paclitaxel or pembrolizumab will be enrolled in the DKN-01 Monotherapy Sub-study. Total study enrollment across all study parts will be up to approximately 224 patients.

A total of 150 patients were enrolled, including 28 patients who received DKN-01 monotherapy; 59 patients who received DKN-01+ paclitaxel, 3 with DKN-01 150 mg and 56 with DKN-01 300 mg; and 63 have received DKN-01+ pembrolizumab, 2 with DKN-01 150 mg and 61 with DKN-01 300 mg. Data from Parts A through E and the Monotherapy Sub-study of this study are final as of 03 September 2019; as of this date, 5 patients from Part F were ongoing in the study rollover protocol.

1.3.1.4.2. Safety Assessment

1.3.1.4.2.1. DKN-01 Monotherapy in Gastroesophageal Cancer Patients (DEK-DKK1-P102)

Among patients treated with DKN-01 as monotherapy (N=28) in the Monotherapy Sub-study, the most common type of treatment-emergent adverse events (TEAEs) were gastrointestinal (GI) disorders (18 patients; 64%) and the most common individual TEAEs were fatigue (13 patients; 46%), anemia (9 patients; 32%), vomiting (8 patients; 29%), dehydration (7 patients; 25%), and nausea (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.

No patient receiving DKN-01 as monotherapy discontinued study drug because of a TEAE.

Among patients who received DKN-01 as monotherapy, 8 (29%) experienced at least 1 SAE, with infections and infestations being the most common type (3 patients; 11%). No individual SAE was reported for >1 patient. All SAEs reported among patients who received DKN-01 as monotherapy were considered by the Investigator to be unrelated to study drug.

One patient receiving DKN-01 monotherapy died due to a TEAE, sudden death, with this event considered unrelated to DKN-01.

1.3.1.4.2.2. Combination Therapy with Paclitaxel in Gastroesophageal Cancer Patients (DEK-DKK1-P102)

Among patients treated with DKN-01 300 mg + paclitaxel (N=56), the most common type of TEAEs were GI disorders (42 patients; 75%) and the most common individual TEAEs were fatigue (30 patients; 54%), anemia (26 patients; 46%), alopecia (19 patients; 34%), neutropenia and peripheral sensory neuropathy (each 32%), 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 fatigue (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-three (59%) of 56 patients treated with DKN-01 300 mg + paclitaxel experienced a DKN-01-related TEAE, most commonly fatigue (14 patients; 25%), diarrhea (7 patients; 13%), nausea, anemia, and decreased appetite (each 5 patients; 9%), and neutropenia (4 patients; 7%).

Seven (13%) patients experienced a DKN-01-related ≥Grade 3 TEAE, including hypophosphatemia (2 patients; 4%) and anemia, leukopenia, monocytosis, neutropenia, and peripheral neuropathy (1 patient; 2%).

DKN-01-related ≥Grade 3 TEAEs reported with DKN-01 150 mg + paclitaxel included single incidences of fatigue and peripheral sensory neuropathy.

Overall, 2 patients receiving DKN-01 + paclitaxel discontinued DKN-01 due to a TEAE, including 1 patient receiving DKN-01 150 mg and 1 patient receiving DKN-01 300 mg. The TEAE leading to DKN-01 discontinuation was peripheral neuropathy/peripheral sensory neuropathy in both cases, with this event considered by the Investigator to be related to both DKN-01 and paclitaxel.

Among the 56 patients who received DKN-01 300 mg + paclitaxel, 21 (38%) 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.

Six patients experienced a Grade 5 TEAE, including aspiration (2 patients) and cardiorespiratory arrest, monocytosis, pulmonary embolism, and respiratory failure (1 patient each).

1.3.1.4.2.3. Combination Therapy with Pembrolizumab in Gastroesophageal Cancer Patients (DEK-DKK1-P102)

Among patients treated with DKN-01 300 mg + pembrolizumab (N=61), the most common type of TEAEs were GI disorders (43 patients; 71%), with the most common individual TEAEs being fatigue (32 patients; 53%), anemia and blood alkaline phosphatase increased (each

21 patients; 34%), hyponatremia (19 patients; 31%), aspartate aminotransferase increased (18 patients; 30%), and decreased appetite (17 patients; 28%).

Only 2 patients were treated with DKN-01 150 mg + pembrolizumab. Two patients intended to be treated with DKN-01 150 mg were inadvertently treated with 300 mg DKN-01 due to site error; neither patient experienced a TEAE. All TEAEs in this arm occurred in 1 patient only; no individual TEAE occurred in both patients in this treatment arm.

Note that no treatment-related immune system disorders or infusion-related reactions, other than 1 case of flushing, have been reported with DKN-01 in combination with pembrolizumab.

Forty (66%) patients receiving DKN-01 300 mg + pembrolizumab experienced at least 1 TEAE considered by the Investigator to be at least possibly related to DKN-01. With the 300 mg dose, the most common DKN-01-related TEAEs were fatigue (11 patients; 18%), aspartate aminotransferase (AST) increased (9 patients; 15%), anemia (6 patients; 10%), alanine aminotransferase (ALT) increased and decreased appetite (each 5 patients; 8%), and nausea (4 patients; 7%).

One (50%) patient receiving DKN-01 150 mg + pembrolizumab experienced TEAEs considered by the Investigator to be at least possibly related to DKN-01, dysphonia and flushing.

Fifteen (25%) patients at the 300 mg dose level experienced a Grade 3 DKN-01-related TEAE. The only such events reported for >1 patient were anemia, AST increased, blood alkaline phosphatase increased, and hypophosphatemia (each 2 patients; 3%).

Four (7%) patients receiving DKN-01 + pembrolizumab discontinued DKN-01 because of a TEAE, including Grade 2 pleural effusion in 1 patient; Grade 3 syncope and Grade 2 orthostatic hypotension in the setting of Grade 2 dehydration in a second patient; Grade 3 abdominal pain in a third patient; and Grade 3 pneumonia in a fourth patient. These events all were considered by the Investigator to be study drug-related.

Among patients who received DKN-01 300 mg + pembrolizumab, 24 (39%) experienced at least 1 SAE, with metabolism and nutrition system disorders being the most common type (7 patients; 12%). The only SAE reported for >1 patient was abdominal pain (4 patients; 7%) and aspiration pneumonia, pneumonia, pulmonary embolism, and sepsis (each 2 patients; 3%). An SAE was considered by the Investigator to be DKN-01-related for 5 (8%) patients; DKN-01-related SAEs included abdominal pain, dehydration, hypophosphatemia, orthostatic hypotension, pleural effusion, pneumonia, and syncope (each 1 patient; 2%).

Four patients experienced a Grade 5 (i.e., fatal) TEAE, including GI hemorrhage in 1 patient and disease progression in the remaining 3 patients; all of these events were considered by the Investigator to be unrelated to study drug.

1.3.1.4.3. Efficacy

Evidence of an antitumor effect of DKN-01 as monotherapy has been observed in patients with NSCLC, esophagogastric cancer, and gynecologic malignancies. Additionally, evidence of an antitumor effect has been observed with DKN-01 in combination with other anti-neoplastic agents in patients with gastroesophageal cancer, biliary tract cancer, and gynecologic malignancies. In particular, DKN-01 has demonstrated durable clinical benefit when used in combination with paclitaxel as a second-line therapy for gastroesophageal cancer.

Further, a study of DKN-01 in combination with pembrolizumab in patients with advanced G/GEJ adenocarcinoma identified a subgroup of patients with DKK1-high tumors with the greatest clinical benefit.

To be evaluable for response according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, patients enrolled in DEK-DKK1-P102 were required to have received at least 1 dose of DKN-01 and have at least 1 evaluable tumor response assessment or have discontinued treatment due to death, toxicity, or clinical progression. As of 30 December 2019, 140 patients treated with DKN-01 300 mg were evaluable for response, including 27 treated with DKN-01 as monotherapy, 54 treated with DKN-01 + paclitaxel, and 59 treated with DKN-01 + pembrolizumab. In addition, 5 patients treated with DKN-01 150 mg, 3 in combination with paclitaxel, and 2 in combination with pembrolizumab, were evaluable for response.

1.3.1.4.3.1. Monotherapy in Gastroesophageal Cancer Patients (DEK-DKK1-P102)

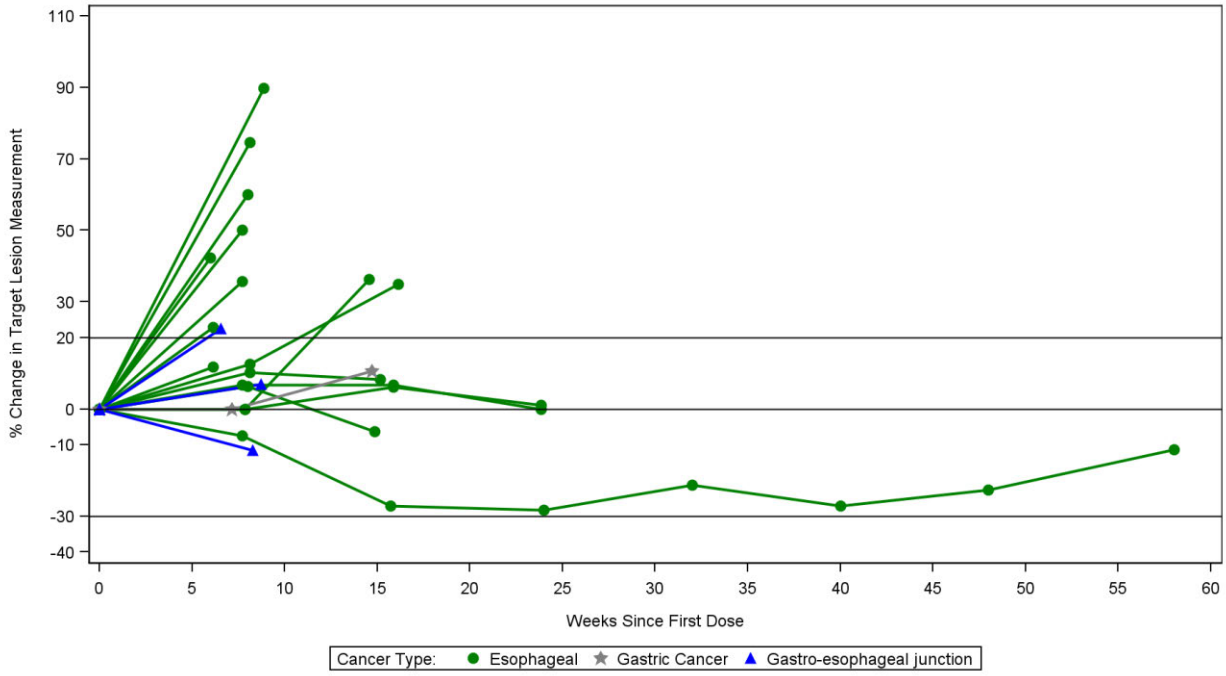
Overall, in Study DEK-DKK1-P102, among the 28 patients who received the DKN-01 monotherapy, 24 were male and 4 were female, and all 28 patients were white. The mean age of patients was 63 years (range 39 to 81 years). Patients were required to have advanced or recurrent gastroesophageal cancer to be eligible for the study; 21 had a primary diagnosis of esophageal cancer, 6 patients had a primary diagnosis of GEJ cancer, and 1 had a primary diagnosis of gastric cancer. The histological type was adenocarcinoma for 23 patients and squamous cell carcinoma for 5 patients. At the time of diagnosis, 17 patients had Stage IV disease, with 9 having Stage III disease, and 2 having Stage II disease. The median time since diagnosis was 17.9 months (range 6.0 to 46.3 months). All 28 patients received prior chemotherapy, with the median number of prior systemic therapy regimens being 3 (range 1 to 7). Overall, 22 (79%) patients had received a prior taxane, 9 (32%) patients had received prior Herceptin (trastuzumab), and 3 (11%) had received a PD-1/PD-L1 inhibitor.

No patient treated with DKN-01 as monotherapy experienced a complete response (CR) or partial response (PR) by Investigator assessment. However, 8 patients had a best response of stable disease (SD), making the disease control rate (DCR) 40% (8 of 20 evaluable patients).

Among all patients in the full analysis set (FAS), median progression-free survival (PFS) was 8.1 weeks (95% confidence interval [CI] 6.3, 11.4), and median overall survival (OS) was 18.7 weeks (95% CI 8.7, 31.0).

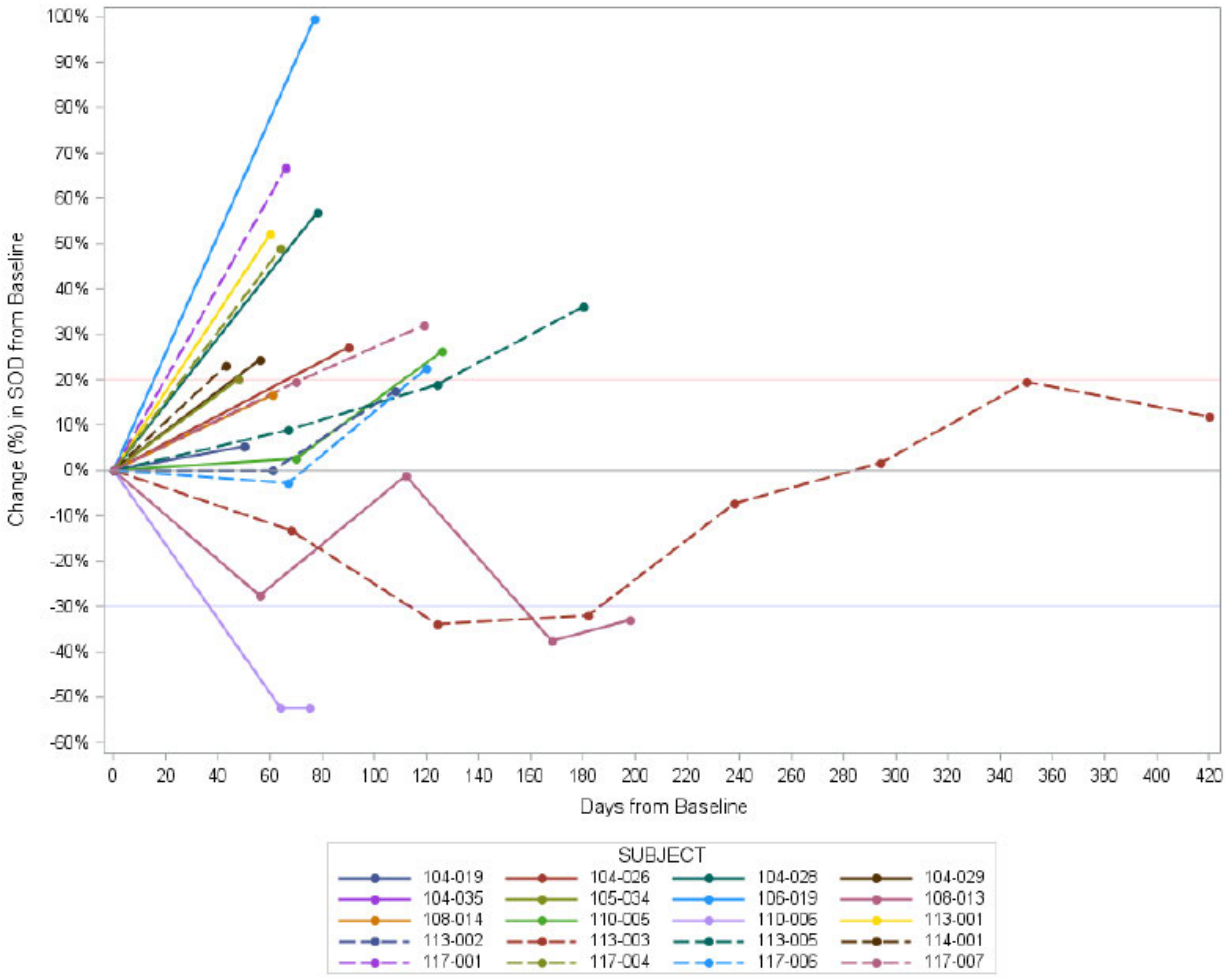
Overall, among the 27 patients treated with DKN-01 300 mg as monotherapy who were evaluable for response, the overall sum of target lesions at baseline was 83.0 mm. Although most patients experienced percent increases from baseline in the sum of target lesion measurements, mean percent decreases were seen, with 1 patient with esophageal cancer experiencing a maximum mean percent decrease from baseline in the sum of target lesion measurements of 27%; this degree change was seen after 4 cycles of therapy (Figure 1).

Figure 1: Spider Plot of Percent Change in Target Lesion Measurements, Based on RECIST v1.1, Among Patients Treated with DKN-01 Monotherapy, by Tumor Type (Evaluable Patients)



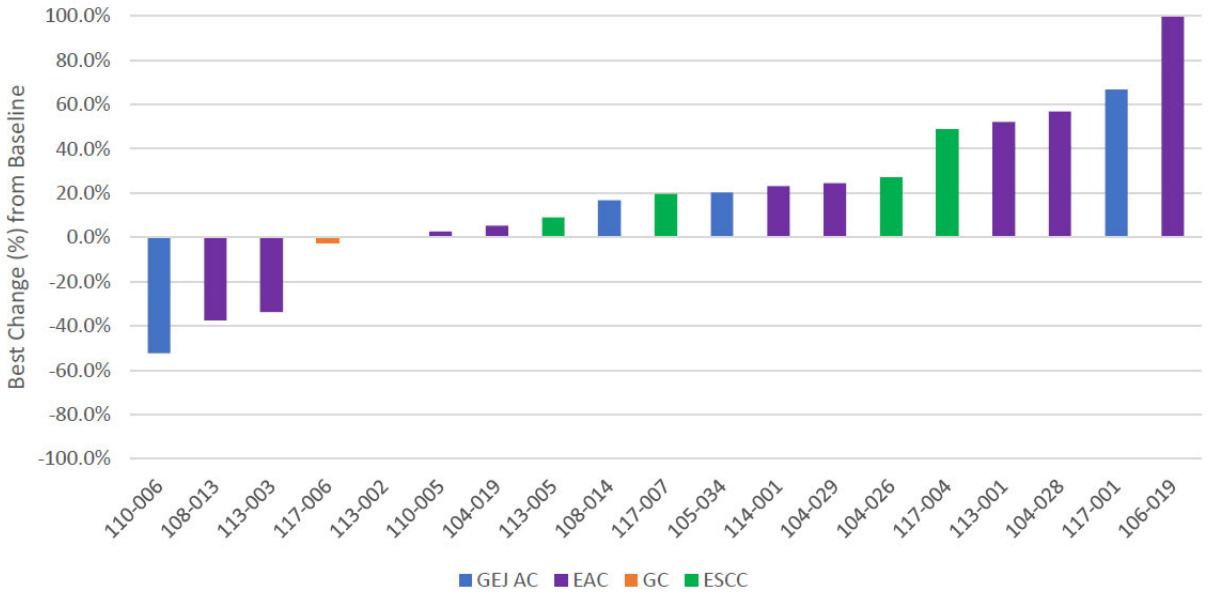
Per protocol, tumor response in this study was to be based on the Investigator's assessment. However, tumor response was assessed centrally, with the central assessment used for supportive analyses. Based on central review, of the 20 patients dosed only with DKN-01 across all malignancy types, 2 out of 20 (10%) had a best individual time point response of PR, 6 out of 20 (30%) had best individual time point response of SD, and 12 out of 20 (60%) had PD. There were no patients with CR (Figure 2, Figure 3).

Figure 2: Sum of Diameters Percent Change from Baseline – Monotherapy (Central Review)



Abbreviations: SOD = sum of the diameters.

Figure 3: Best Percent Change in Sum of Diameters – Monotherapy (Central Review)



Abbreviations: EAC = esophageal adenocarcinoma; ESCC= esophageal squamous cell carcinoma; GEJ AC = gastroesophageal adenocarcinoma; GC = gastric cancer.

1.3.1.4.3.2. Combination Therapy with Paclitaxel in Gastroesophageal Cancer Patients (DEK-DKK1-P102)

Overall, in Study DEK-DKK1-P102, among all 56 patients who received the DKN-01 target dose (300 mg) + paclitaxel, 43 were male and 13 were female, and 48 patients were white. The mean age of patients was 61 years (range 34 to 82 years). Patients were required to have gastroesophageal cancer to be eligible for the study; 29 patients had a primary diagnosis of GEJ cancer and 25 had a primary diagnosis of esophageal cancer; the 2 remaining patients had a diagnosis of gastric cancer. At the time of diagnosis, 30 patients had Stage IV disease, with 18 having Stage III disease, and 8 having Stage II disease. The median time since diagnosis was 15.6 months (range 2.1 to 70.4 months). All 56 patients received prior chemotherapy, with 27 (48.2%) having received a prior taxane, 14 each in the adjuvant/neo-adjuvant setting and metastatic/palliative setting. (Patients may have received such treatment in more than 1 setting.) The median number of prior systemic therapy regimens was 2 (range 1 to 6). Overall, 11 (20%) patients had received prior Herceptin (trastuzumab) and 5 (9%) had received a PD-1/PD-L1 inhibitor.

Three patients received DKN-01 150 mg + paclitaxel, of whom all 3 were white males. The median age was 56 years, with a range of 47 to 73 years. Two patients had a primary diagnosis of GEJ cancer and 1 had a primary diagnosis of esophageal cancer. The median number of prior therapies was 4, and all 3 patients had received a prior taxane.

A summary of efficacy results among treated with DKN-01+paclitaxel in Study P102, by dose and overall, is presented in Table 2.

Table 2: Summary of Efficacy Results in Patients Treated with DKN-01+Paclitaxel in Study DEK-DKK1-P102, Overall and by Dose

Endpoint/Statistic	DKN-01 150 mg + Paclitaxel	DKN-01 300 mg + Paclitaxel Esophageal[a]	DKN-01 300 mg + Paclitaxel GEJ/Gastric	DKN-01 300 mg + Paclitaxel
Evaluable Population[b], n/N (%)				
Objective Response Rate	1/3 (33.3)	4/23 (17.4)	7/26 (26.9)	12/49 (24.5)
Disease Control Rate	3/3 (100)	13/23 (56.5)	15/26 (57.7)	28/49 (57.1)
PFS				
N	3	25	30	55
Median, (95% CI) (Weeks)	18.6 (13.4, 20.1)	11.6 (7.9, 14.7)	11.9 (8.0, 22.6)	11.9 (8.0, 15.7)
OS				
N	3	25	30	55
Median (95% CI) (Weeks)	34.4 (26.3, 89.7)	28.4 (14.7, 33.3)	27.9 (19.0, 39.0)	28.4 (22.6, 33.3)

Source: DKN-01 Investigator's Brochure.
Abbreviations: CI = confidence interval; GEJ = gastroesophageal junction; N = total number of patients treated; n = number of patients within each category; OS = overall survival; PFS = progression-free survival.
[a] Evaluable population excludes 2 non-evaluable patients (non-measurable disease at baseline) and 4 patients without post-baseline assessments (no post-baseline imaging complete).
[b] Patients with non-measurable disease at baseline were excluded from PFS analysis.

DKN-01 + Paclitaxel

In the evaluable population, among patients treated with DKN-01 300 mg + paclitaxel, the objective response rate (ORR) was 24.5% (12/49 patients) and the DCR was 57.1% (28/49).

Among those with G/GEJ cancer treated with DKN-01 300 mg + paclitaxel evaluable for response (N=26), the ORR was 26.9% (7/26), and the DCR was 57.7% (15/26).

The central imaging review reported of the 52 pooled combination therapy patients who received DKN-01 300 mg plus paclitaxel, 9 out of 52 (17.3%) had a best individual time point response of PR, 18 out of 52 (37.5%) had a best individual time point response of SD, and 24 out of 52 (46.1%) had PD. There was a single non-CR/non-PD and there were no patients with CR.

Among patients in the FAS who received DKN-01 300 mg + paclitaxel, median PFS was 11.9 weeks (95% CI, 8.0, 15.7). Among those with G/GEJ cancer, median PFS was 11.9 weeks (95% CI 8.0, 22.6).

Among patients in the FAS who received DKN-01 300 mg + paclitaxel, median OS was 28.4 weeks (95% CI, 22.6, 33.3). Among those with G/GEJ cancer, median PFS was 27.9 weeks (95% CI 19.0, 39.0).

1.3.1.4.3.3. Combination Therapy with Pembrolizumab in Gastroesophageal Cancer Patients (DEK-DKK1-P102)

Part F in Study P102, in which patients receive DKN-01 + pembrolizumab, is ongoing; thus, data are preliminary, based on a database lock on 03 September 2019.

Among 61 patients at the target dose of DKN-01 (300 mg), 55 patients were male and 6 were female. Age ranged from 28 to 81 years. Thirty-two (53%) patients in the target dose group had a primary diagnosis of GEJ cancer, with 22 having esophageal cancer and 7 having gastric cancer. Forty-six patients (75%) had Stage IV disease at diagnosis. The median time since diagnosis was 15 months (range 3 to 68 months). All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at baseline.

Although the numbers of patients in each group were disparate, demographic and baseline disease characteristics among patients with PD-1/PD-L1-naïve and refractory disease (i.e., naïve and refractory groups, respectively) were generally comparable, although, as would be expected, the median time since diagnosis was longer among refractory patients than naïve patients (24.0 months versus 11.8 months, respectively). Similarly, the mean number of prior systemic therapies was higher in the refractory group than in the naïve group (3.6 versus 1.9, respectively). In accordance with the entry criteria, all patients in the refractory group had received prior anti-PD-1/PD-L1 therapy.

A summary of efficacy results in patients treated with DKN-01+pembrolizumab is presented in Table 3.

Table 3: Summary of Efficacy Results Among Patients Treated with DKN-01+Pembrolizumab

	150 mg DKN-01 + Pembro	300 mg DKN-01 + Pembro anti-PD-1/ PD-L1 Naïve ESO	300 mg DKN-01 + Pembro anti-PD-1/ PD-L1 Naïve GEJ/GC	All 300 mg DKN-01 + Pembro anti-PD-1/ PD-L1 Naïve	300 mg DKN-01 + Pembro Primary Refractory to Anti-PD-1/PD-L1	All 300 mg DKN-01 + Pembro
Efficacy Evaluable Population						
Objective Disease Response[a]	0/2	0/17	5/27 (18.5)	5/44 (11.4)	0/9	5/53 (9.4)
95% CI[b]	(0.0, 84.2)	(0.0, 19.5)	(6.3, 38.1)	(3.8, 24.6)	(0.0, 33.6)	(3.1, 20.7)
Objective Disease Control[c]	1/2 (50.0)	4/17 (23.5)	13/27 (48.1)	17/44 (38.6)	4/9 (44.4)	21/53 (39.6)
95% CI[b]	(1.3, 98.7)	(6.8, 49.9)	(28.7, 68.1)	(24.4, 54.5)	(13.7, 78.8)	(26.5, 54.0)

Source: DKN-01 Investigator's Brochure.
Abbreviations: CI = confidence interval; ESO = esophageal; GC= gastric cancer; GEJ = gastroesophageal junction; PD-1 = programmed cell death-1; PD-L1 = programmed cell death ligand-1.
[a] Disease response is the number of patients with a best overall response of CR or PR. Does not require confirmation of response. Denominator only includes patients who are eligible for response evaluation per RECIST v1.1 post baseline.
[b] 95% confidence interval (CI) is calculated based on the exact Clopper-Pearson for binomial proportions.
[c] Disease control is the number of patients with a best overall response of CR, PR, or SD. Does not require confirmation of response or any minimum SD duration. Denominator only includes patients who are eligible for evaluation.

Anti-PD-1/PD-L1 Naïve Patients

Among evaluable patients at the target dose (300 mg), the ORR was 11.4% (5/44) (95% confidence interval [CI] 3.8, 24.6) and the DCR was 38.6% (17/44) (95% CI 24.4, 54.5) in the naïve target dose group.

Among evaluable patients with G/GEJ adenocarcinoma, the ORR and DCR were 18.5% (5/26) (95% CI 6.3, 38.1) and 48.1% (4/26) (95% CI 28.7, 68.1), respectively, in the naïve target dose group.

Central imaging results are not yet available for patients who received DKN-01 + pembrolizumab.

Overall, median PFS was 6.0 weeks (95% CI 5.7, 8.7) in the naïve target dose group, and was 6.9 weeks (95% CI 5.7, 12.0) in those with G/GEJ adenocarcinoma.

Overall, median OS was 20.4 weeks (95% CI 14.4, 31.6) in the naïve target dose group, and was 22.1 weeks (95% CI 14.4, 42.4) in those with G/GEJ adenocarcinoma.

In the 150 mg group, 1 patient was PD-1/PD-L1-naïve; this patient achieved a best response of SD.

Anti-PD-1/PD-L1-Refractory Patients

Among evaluable patients at the target dose (300 mg), the ORR was 0% (0/9) (95% CI 0, 33.6) and the DCR was 44% (4/9) (95% CI 13.7, 78.8) in the refractory target dose group.

Among evaluable patients with G/GEJ adenocarcinoma, the ORR and DCR were 0% (0/5) (95% CI 0, 52.2) and 40.0% (2/5) (95% CI 5.3, 85.3), respectively, in the refractory target dose group.

Overall, median PFS was 6.6 weeks (95% CI 3.0, 12.1) in the refractory target dose groups, and was 6.0 weeks (95% CI 3.0, 13.4) in those with G/GEJ adenocarcinoma.

Median OS was 19.0 weeks (95% CI 10.7, 37.4) the refractory target dose group.

In the 150 mg group, 1 patient was PD-1/PD-L1-refactory; this patient achieved a best response of SD.

1.3.2. Background Information on Tislelizumab

Tislelizumab, also known as BGB-A317 (BeiGene), is a humanized, IgG_4-variant monoclonal antibody against PD-1 under clinical development for the treatment of several human malignancies, including locally advanced unresectable or metastatic G/GEJ adenocarcinoma(Xu, Arkenau et al. 2019).

1.3.2.1. Pharmacology of Tislelizumab

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity [redacted] It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to consistently and dose-dependently enhance the functional activity of human T cells and pre-activated, primary peripheral blood mononuclear cells. Tislelizumab has demonstrated in vivo antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

Tislelizumab is an IgG4-variant antibody [redacted]

[redacted] In vitro assays with tislelizumab suggest either low or no antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), or complement-dependent cytotoxicity (CDC) effects in humans (Labrijn, Buijsse et al. 2009, Zhang, Song et al. 2018). Tislelizumab was specifically engineered to abrogate these potential mechanisms of T-cell clearance and potential resistance to anti-PD-1 therapy.

Please refer to the Tislelizumab Investigator's Brochure (BeiGene) for additional details regarding nonclinical studies of tislelizumab.

1.3.2.2. Toxicology of Tislelizumab

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and cynomolgus monkeys and in a 13-week, repeat-dose toxicology study in cynomolgus monkeys. Tissue cross-reactivity was evaluated in normal frozen tissues from both humans and monkeys. The cytokine release assays were conducted using fresh human whole blood cells. The pivotal toxicology studies were conducted following Good Laboratory Practice regulations. The single-dosing regimens spanned from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeat-dosing regimens spanned to 3-fold higher than the maximum of the intended human doses. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in the human whole-blood assay. The toxicokinetic profile was well characterized, with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The no observed adverse effect level of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study, DEK-DKK1-P205. Please refer to the Tislelizumab Investigator's Brochure (BeiGene) for more detailed information on the toxicology of tislelizumab.

1.3.2.3. Clinical Pharmacology of Tislelizumab

Population PK analysis was conducted using data from 798 patients with solid tumors or classical Hodgkin lymphoma who received doses of 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks, 2.0 and 5.0 mg/kg once every 3 weeks, and 200 mg once every 3 weeks. The PK of tislelizumab was best characterized using a 3-compartmental linear population PK model with linear clearance mechanisms. No time-varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume (V_c), and peripheral volumes (V_2, V_3), were 0.164 L/day, 2.92 L, 0.928 L, and 1.39 L, respectively, with moderate inter-individual variability in CL (32.2%), V_c (16.7%), V_2 (56.6%), and V_3 (94.2%). The volume of distribution at steady state was 5.238 L, which is typical of monoclonal antibodies with limited distribution, which is consistent with a standard immunoglobulin G (IgG) monoclonal antibody (Dirks and Meibohm 2010, Keizer, Huitema et al. 2010, Deng, Jin et al. 2012, Ryman and Meibohm 2017). Based on the population PK analysis, tislelizumab PK was characterized by a terminal half-life

of approximately 25.5 days, which is consistent with other therapeutic IgG monoclonal antibodies.

Population PK analysis demonstrated that baseline age, race/ethnic origin, alanine aminotransferase, aspartate aminotransferase, bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, ECOG performance status, immunogenicity, and sum of products of perpendicular diameters in classical Hodgkin lymphoma patients did not show statistically significant impact on the PK of tislelizumab. Although tumor size, albumin, and tumor type were significant covariates on CL, while body weight, sex, and tumor type were significant covariates on V_c, these covariates are not expected to have a clinically relevant impact on tislelizumab exposure. Exposure-response analysis indicated that there was a lack of clinically significant exposure-response relationships for ORR and safety endpoints across a variety of advanced solid tumors and classical Hodgkin lymphoma for tislelizumab. Population PK analysis supports fixed-dosing across different ethnic groups.

1.3.2.4. Prior Clinical Experience with Tislelizumab

As of 20 May 2019, there were 22 ongoing studies with tislelizumab with over 1705 patients treated. Of these, 13 studies have preliminary data available in the Tislelizumab Investigator's Brochure version 7, 13 September 2019: 7 monotherapy studies, 2 chemotherapy combination therapy studies; and 4 investigational agent combination therapy studies.

Refer to the Tislelizumab Investigator's Brochure (BeiGene) for more detailed information on tislelizumab safety and efficacy data when given as monotherapy or in combination with chemotherapy.

1.3.2.4.1. Pooled Safety Assessment of Monotherapy Studies

A pooled analysis of 7 monotherapy studies was conducted to provide a comprehensive safety assessment separately from combination therapy.

Overall, there were 1273 patients in the pooled monotherapy studies: 1137 patients treated in 5 solid tumor studies and 136 patients treated in 2 hematologic malignancies studies.

Solid tumor studies included the following: BGB-A317_Study_001 (Phase 1a /1b Advanced Solid Tumors), BGB-A317-102 (Phase 1 /2 Advanced Solid Tumors), BGB-A317-204 (Phase 2 Locally Advanced or Metastatic Urothelial Bladder Cancer), BGB-A317-208 (Phase 2 Locally Advanced or Metastatic Urothelial Bladder Cancer), and BGB-A317-209 (Previously Treated Locally Advanced Unresectable or Metastatic Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors). The 2 studies in hematologic malignancies are BGB-A317-203 (Phase 2 Relapsed or Refractory Classical Hodgkin Lymphoma) and BGB-A317-207 (Relapsed or Refractory Mature T- and NK-cell Neoplasms).

Of the 1273 total patients treated, 544 patients (42.7%) remained on study as of 20 May 2019; and 272 patients (21.4%) were still receiving tislelizumab treatment.

Refer to the Tislelizumab Investigator's Brochure (BeiGene) for more detailed information on tislelizumab safety data when given as monotherapy or in combination with chemotherapy.

1.3.2.4.1.1.Pooled Demographics and Baseline Characteristics

Table 4 shows the demographics and baseline characteristics for the patients treated in the pooled monotherapy studies.

Table 4: Demographics, Baseline Characteristics, Treatment Exposure Duration, and Study Follow-up Duration in Pooled Monotherapy Studies

Measure	Overall[a] N = 1273
Age (years)	
Median	59.0
Min, Max	18, 90
Sex, n (%)	
Male	852 (66.9)
Female	421 (33.1)
Race/Ethnic Origin, n (%)	
Asian	807 (63.4)
Black	11 (0.9)
White	405 (31.8)
Missing	2 (0.2)
Other	48 (3.8)
Prior systemic anticancer therapy regimens[b]	
Median	1.0
Min, Max	0, 12
Prior systemic anticancer therapy regimens (grouped)[b], n (%)	
0	271 (21.3)
1	413 (32.4)
2	265 (20.8)
≥3	324 (25.5)
Study treatment exposure duration (months)	
Median	3.58
Min, Max	0.1, 43.6
Study follow-up duration (months)	
Median	8.34
Min, Max	0.1, 47.5

Source: Tislelizumab Investigator's Brochure.

Abbreviations: Max = maximum; Min = minimum; N = total number of patients treated; n = number of patients within each category.
Data cutoff 20 May 2019.
[a] Solid Tumor Studies include: BGB_Study_001, BGB-A317-102, BGB-A317-204, BGB-A317-208, BGB-A317-209 and Hematology Studies include: BGB-A317-203, BGB-A317-207.[b] Only systemic therapies were selected.

Overall, the 1273 patients in the pooled monotherapy analysis had a median treatment exposure duration of 3.58 months (range 0.1 to 43.6) and median study follow-up duration of 8.34 months (range 0.1 to 47.5). Overall, the total pooled monotherapy population had a median age of 59 years and was 66.9% male.

1.3.2.4.1.2.Treatment-Emergent Adverse Events Assessed as Related to Treatment

Of the 1273 total patients treated in the pooled monotherapy studies, 846 (66.5%) experienced at least one treatment-related TEAE. The most commonly occurring TEAEs (≥5% of patients) assessed as related to tislelizumab were increased aspartate aminotransferase (128 patients, 10.1%), increased alanine aminotransferase (123 patients, 9.7%), hypothyroidism (113 patients, 8.9%), rash (96 patients, 7.5%), and pyrexia (94 patients, 7.4%).

Of the 1273 total patients treated in the pooled monotherapy studies, 162 (12.7%) experienced at least one ≥Grade 3 TEAE assessed as related to tislelizumab. The ≥Grade 3 TEAEs that occurred in ≥1% (≥12 patients) in the total study population were increased aspartate aminotransferase (19 patients, 1.5%) and increased alanine aminotransferase (15 patients, 1.2%).

1.3.2.4.1.3.Treatment-Emergent Serious Adverse Events

Of the 1273 total patients treated in the pooled monotherapy studies, 424 (33.3%) experienced at least one treatment-emergent serious adverse event (SAE). The most commonly occurring treatment-emergent SAEs were pneumonia (35 patients, 2.7%), pyrexia (22 patients, 1.7%), and ascites (17 patients, 1.3%).

1.3.2.4.1.4.Immune-Related Adverse Events

Anti-PD-1 therapies are known to cause immune-related adverse events (irAEs) in some patients. Therefore, irAEs have been defined as AEs of special interest in tislelizumab clinical studies and as such are being reported expeditiously and closely monitored.

Immune-related AEs are consistent with an immune-related mechanism or immune-related component for which non-inflammatory etiologies (e.g., infection or tumor progression) have been ruled out. Immune-related AEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. There is a potential temporal relationship between the initiation of treatment with tislelizumab and onset of an irAE that spans a window of days to several months.

All irAEs presented here are assessed as related to study drug by the Investigator and categorized by the BeiGene Safety/Pharmacovigilance team. Certain irAEs have multiple MedDRA terms associated with the same category. Special categories have been created to group patients experiencing these events.

All irAEs that have occurred in ≥1% in the total pooled monotherapy studies are shown in Table 5.

Table 5: Immune-Related Adverse Events of Any Grade Occurring in ≥1% in Pooled Monotherapy Studies

Categories Preferred Term	Total (N = 1273)	
	Any Grade n (%)[a]	**Grade ≥3 n (%)[a]**
Patients with at least one potential immune-related AE[a]	602 (47.3)	121 (9.5)
Immune-related skin adverse reaction	242 (19.0)	11 (0.9)
Rash	97 (7.6)	4 (0.3)
Pruritus	78 (6.1)	0
Pruritus generalised	29 (2.3)	0
Rash maculo-papular	24 (1.9)	1 (0.1)
Immune-related hepatitis	233 (18.3)	51 (4.0)
Aspartate aminotransferase increased	129 (10.1)	21 (1.6)
Alanine aminotransferase increased	124 (9.7)	16 (1.3)
Blood bilirubin increased	74 (5.8)	4 (0.3)
Gamma-glutamyltransferase increased	45 (3.5)	17 (1.3)
Bilirubin conjugated increased	40 (3.1)	3 (0.2)
Immune-related endocrinopathies	187 (14.7)	7 (0.5)
Hypothyroidism	113 (8.9)	0
Hyperthyroidism	47 (3.7)	1 (0.1)
Hyperglycaemia	17 (1.3)	4 (0.3)
Immune-related colitis	75 (5.9)	10 (0.8)
Diarrhoea	66 (5.2)	5 (0.4)
Immune-related pneumonitis	50 (3.9)	30 (2.4)
Pneumonitis	22 (1.7)	9 (0.7)
Lung infection	13 (1.0)	8 (0.6)
Immune-related myositis/rhabdomyolysis/cardiomyopathy	39 (3.1)	7 (0.5)
Blood creatine phosphokinase increased	30 (2.4)	4 (0.3)
Immune-related nephritis and renal dysfunction	33 (2.6)	6 (0.5)
Blood creatinine increased	25 (2.0)	2 (0.2)

Source: Tislelizumab Investigator's Brochure.

Abbreviations: AE = adverse event; N = total number of patients treated; n = number of patients within each category; NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PT = preferred term; SOC = system organ class.
Note: All AEs are coded using Medical Dictionary for Regulatory Activities and graded according to NCI-CTCAE v4.03. Maximum CTCAE grade was selected per patient under each PT. Potential immune-related AE is identified based on a predefined list of AEs and assessed as treatment-related by Investigators.
Sorted in descending order of the number of patients in SOC and PT in Any Grade under Total column.
Data cutoff 20 May 2019.
[a] Percentages are based on the total population.

Of the 1273 total patients for the pooled monotherapy studies, 602 (47.3%) experienced at least one irAE of any grade. The most commonly occurring irAEs of any grade were aspartate aminotransferase increased (129 patients, 10.1%), alanine aminotransferase increased (124 patients, 9.7%), hypothyroidism (113 patients, 8.9%), rash (97 patients, 7.6%), and pruritus (78 patients, 6.1%). Analysis of the total patients with at least one irAE that also was ≥Grade 3 in severity showed that 121 patients (9.5%) experienced such events. The most commonly occurring irAEs ≥Grade 3 in severity were aspartate aminotransferase increased (21 patients, 1.6%), gamma-glutamyltransferase increased (17 patients, 1.3%), alanine aminotransferase increased (16 patients, 1.3%), pneumonitis (9 patients, 0.7%), and lung infection (8 patients, 0.6%).

1.3.2.4.1.5.Infusion-Related Reactions

Infusion-related reactions, including high-grade hypersensitivity reactions, following administration of tislelizumab are common. Of the 1273 total patients in the pooled monotherapy studies, 97 (7.6%) experienced at least one infusion-related reaction of any grade. The most commonly occurring infusion-related reactions of any grade that occurred in the total pooled analysis were pyrexia (50 patients, 3.9%), infusion-related reactions (28 patients, 2.2%), and pruritus (11 patients, 0.9%). There were 6 patients who reported a total of 7 ≥Grade 3 infusion-related reactions in the pooled monotherapy studies (reported events included back pain, hypotension, infusion-related reaction, musculoskeletal chest pain, pyrexia, and rash).

1.3.2.4.1.6.Fatal Adverse Events

A summary of the treatment-emergent fatal AEs that occurred in the pooled monotherapy studies are shown in Table 6.

Table 6: Treatment-Emergent Fatal Adverse Events Regardless of Causality in Pooled Monotherapy Studies

Category	Overall (N = 1273) n (%)
All deaths at data cutoff	641 (50.4)
Death ≤30 days after last dose	105 (8.2)
Primary cause of death	
Adverse event	21 (1.6)
Disease under study	22 (1.7)
Progressive disease	52 (4.1)
Other	10 (0.8)
Death >30 days after last dose	536 (42.1)
Primary cause of death	
Adverse event	14 (1.1)
Disease under study	95 (7.5)
Indeterminate	3 (0.2)
Progressive disease	399 (31.3)
Other	24 (1.9)
Missing	1 (0.1)

Source: Tislelizumab Investigator's Brochure.
Abbreviations: N = total number of patients treated; n = number of patients within each category.
Data cutoff 20 May 2019.

Table 6 shows a total of 105 patients (8.2% of the total population) died ≤30 days after the last study drug dose in the pooled monotherapy studies as of 20 May 2019. Of these 105 patients, there were 21 patients (1.6% of the total population) who had an AE with a fatal outcome ≤30 days after the last study drug dose. Of the 536 patients (42.1% of the total population) who died >30 days after the last study drug dose, 14 patients (1.1% of the total population) died as a result of an AE (refer to the Tislelizumab Investigator's Brochure (BeiGene).

1.3.2.4.1.7.Tislelizumab Safety Summary

For monotherapy, the safety profile of tislelizumab is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to tislelizumab dose level. The safety profile for single-agent tislelizumab is similar to those observed in other PD-1 inhibitors. For combination studies, the safety profile of tislelizumab is generally consistent with use as a single agent and appears to be safe and well tolerated when used in combination with other agents and in multiple different chemotherapy backbones.

1.3.2.4.2. Efficacy Assessment of Tislelizumab

Two phase 2 studies are ongoing in patients with G/GEJ adenocarcinoma.

1.3.2.4.2.1.Study BGB-A317-205

Study BGB-A317-205 is a multi-cohort, Phase 2 study of tislelizumab in combination with standard chemotherapy as first-line treatment in Chinese patients. An esophageal squamous cell carcinoma cohort and a GAC/GEJ adenocarcinoma cohort have been enrolled concurrently. The primary objective of this study is to evaluate the safety and tolerability of tislelizumab in combination with standard chemotherapy. Secondary objectives include the preliminary antitumor efficacy of this combination in this population. Additionally, PK and immunogenicity are being assessed.

As of 20 May 2019, the median treatment exposure duration for patients in Study BGB-A317-205 was 6.58 months (range 0.7 to 18.9), and the median study follow-up duration was 13.47 months (range 0.1 to 19.2).

The Efficacy Evaluable Analysis Set includes all the GAC/GEJ patients who have received at least 1 cycle of the combination therapy, had measurable or evaluable disease at baseline according to RECIST v1.1, and had at least 1 post baseline tumor response assessment unless any clinical progressive disease or death occurred within 10 weeks after the first dose. A summary of tumor response in the efficacy evaluable set is presented in Table 7.

Table 7: Summary of Tumor Response in Study BGB-A317-205 (Efficacy Evaluable Analysis Set)

Category	GAC/GEJ N=13
ORR (CR, PR)	
n (%)	7 (53.8)
(Clopper-Pearson 95% CI)	(25.13, 80.78)
Best Overall Response - Confirmed, n (%)	
Complete response	0
Partial response	7 (53.8)
Stable disease	3 (23.1)
Progressive disease	1 (7.7)
Non-Complete response /Non-Progressive disease[a]	2 (15.4)
DCR (CR, PR, SD, Non-CR/Non-PD)	
n (%)	12 (92.3)
(Clopper-Pearson 95% CI)	(63.97, 99.81)
CBR (CR, PR, durable SD, durable Non-CR/Non-PD) [b]	
n (%)	9 (69.2)
(Clopper-Pearson 95% CI)	(38.57, 90.91)

Abbreviations: CBR = Clinical Benefit Rate; CI = confidence interval; CR = complete response; DCR = disease control rate; GAC/GEJ = gastric and gastroesophageal junction adenocarcinoma; NE = Not Evaluable; OR = Objective Response; ORR = objective response rate; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

[a] 2 patients have only non-target lesions at baseline.

[b] Durable SD or Non-CR/Non-PD: stable disease or Non-CR/Non-PD ≥24 weeks.

OR is based on the confirmed CR or PR according to RECIST v1.1. Patients with no postbaseline response assessment or assessments as NE were considered as non-responders.

The Efficacy Evaluable Analysis Set includes all patients who have received at least 1 dose of the study drug, had measurable or evaluable disease at baseline according to RECIST v1.1, and had at least 1 postbaseline tumor response assessment unless any clinical PD or death occurred within 10 weeks after the first dose.

Data cutoff 20 May 2019.

1.3.2.4.2.2.Study BGB-A317-305

Study BGB-A317-305 is an ongoing randomized, double-blind, placebo-controlled, Phase 3 clinical study comparing the efficacy and safety of tislelizumab plus platinum and fluoropyrimidine versus placebo plus platinum and fluoropyrimidine as first-line treatment in patients with locally advanced unresectable or metastatic G/GEJ adenocarcinoma. Results are not yet available.

1.4. Study Rationale

1.4.1. Rationale for DKN-01 in the Treatment of Gastric and Gastroesophageal Junction Adenocarcinoma

DKN-01 compound is a humanized IgG4 monoclonal antibody targeted against DKK1. DKK1 is a protein that regulates Wnt signaling pathways. Aberrant Wnt signaling is often implicated in cancer, enabling cancer cells to grow and divide and to suppress the immune system. Published data indicates that DKK1 is often overexpressed in many cancers and is associated with worse outcomes, more aggressive tumor growth, and suppression of immune antitumor responses.

A role for DKK1 in maintaining an environment around a tumor that suppresses the immune system's ability to clear the tumor and to prevent metastasis. DKK1 activates the suppressive effects of myeloid-derived suppressor cells, a type of white blood cell that can potently block the ability of other immune cells to attack a tumor. Additional data has shown that metastatic tumor cells with stem cell-like features avoid eradication by the immune system through overexpression of DKK1. DKK1 down-regulates NK cell activating ligands on tumor cells allowing them to remain invisible and evade the immune system. Furthermore, neutralization of DKK1 in preclinical tumor models depends on a functioning immune system and more specifically, NK cells. Through these multiple activities DKK1 helps protect the cancer cells from being targeted by the immune system. Therefore, blocking DKK1 activity has been proposed to stimulate an immune mediated antitumor response. Inhibition of DKK1 has demonstrated antitumor activity in preclinical models. Our hypothesis is that inhibiting DKK1 can generate both a direct antitumor effect, as well as generate an immune antitumor response. Our preclinical and clinical data suggest that a DKK1 neutralizing antibody, DKN-01, is able to effectively synergize with certain chemotherapeutics and checkpoint inhibitors in their antitumor efficacy.

Published studies have also demonstrated a correlation between a worse clinical prognosis for gastric cancer patients with high tumor DKK1 (protein) and/or serum levels (Liu, Li et al. 2016). Furthermore, analysis of DKK1 messenger ribonucleic acid (mRNA) expression from tumors of patients with G/GEJ cancer indicates a worse overall survival for patients with high DKK1 levels (TCGA database – STAD dataset, data on file with the Sponsor). Taken together, these results indicate that DKK1 is a marker for poor prognosis in G/GEJ adenocarcinoma and may identify patients most likely to benefit from a DKK1 neutralizing therapy (Liu, Li et al. 2016).

Previous clinical experience in patients with advanced anti-PD-1/PD-L1 naïve G/GEJ adenocarcinoma in a Phase 1b/2a study of DKN-01 in combination with pembrolizumab demonstrated clinical benefit in patients with elevated tumor DKK1 mRNA expression as assessed retrospectively by an in situ hybridization (ISH) assay (Klempner, Bendell et al. 2020). Tumor DKK1 expression data was available for 31 G/GEJ adenocarcinoma patients and patients within the top tertile (H-score[2] ≥35) were considered DKK1 high. In patients with an evaluable response, the ORR was 50% for the DKK1-high (upper tertile) patients and 0% for the

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[2] H-score (range 0 to 300) was calculated by determining the percentage of cells that were low (1-3 dots), medium (4-9 dots) or high (10=<dots) DKK1 expressors and using the following formula: H-score = 1*(%low)+2*(%medium)+3*(%high)

DKK1-low (bottom and middle tertiles) patients. Furthermore, patients with DKK1-high tumor expression experienced longer progression free (22.1 versus 5.9 weeks) and overall survival (31.6 versus 17.4 weeks) compared with DKK1 low patients, and this effect was independent of PD-L1 CPS. These data support a rationale for treating G/GEJ patients with high DKK1 tumor expression with a DKN-01 anti-PD-1 (tislelizumab) combination.

1.4.2. Rationale for Tislelizumab in the Treatment of Gastric and Gastroesophageal Junction Adenocarcinoma

Increases in PD-1 expression in tumor-infiltrating lymphocytes (TILs) and PD-1 ligand expression in tumor cells were reported in gastric cancer (Wu, Zhu et al. 2006). Recent clinical trials utilizing anti-PD-1 monoclonal antibodies demonstrated significant therapeutic efficacy in, for example, advanced melanoma, refractory NSCLC, and renal cell carcinoma. Anti-PD-1 antibody treatment not only induced higher ORRs but also resulted in a lasting effect on overall survival (Ribas, Puzanov et al. 2015, Weber, D'Angelo et al. 2015). In addition, anti-PD-1 antibodies were also reported to be efficacious in numerous cancer types, including but not limited to, NSCLC, SCLC, RCC, Hodgkin lymphoma, head and neck squamous cell carcinoma, HCC, microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, and urothelial carcinoma.

High levels of FcγR-expressing myeloid derived suppressor cells (e.g., M2 macrophage, myeloid-derived suppressor cells) in tumor tissues predict poor survival of tumor-bearing animals.

However, anti-PD-1 monoclonal antibody treatment may result in Fc-FcγR-mediated ADCC or ADCP depletion of effector T cells (Dahan, Sega et al. 2015, Gul and van Egmond 2015, Makarova-Rusher, Medina-Echeverz et al. 2015, Prieto, Melero et al. 2015, Beers, Glennie et al. 2016). As a no- to low-FcγR-binding agent (which causes minimal ADCC/ADCP effects), tislelizumab may show improved efficacy and reduced toxicity in gastric cancer.

The anti-PD-1 monoclonal antibody tislelizumab has shown antitumor activity in patients with G/GEJ adenocarcinoma in 2 early-phase studies. A report of 207 patients in the Phase 1b portion of a Phase 1a/1b study of single-agent tislelizumab 5 mg/kg every 21 days included 54 patients with gastric cancer (50 with adenocarcinoma) and 54 patients with esophageal cancer (26 with adenocarcinoma)(Deva, Lee et al. 2018). The ORR for gastric cancer patients was 13.0%, with a DCR of 29.6%. The ORR for esophageal cancer patients was 11.1%, with a DCR of 37.0%. PD-L1 expression was assessed retroactively; ORRs were higher in both cohorts for patients whose cancers were PD-L1-positive versus those whose cancers were PD-L1-negative (gastric cancer 22.7% vs 4.3%; esophageal cancer 12.1% vs 5.9%). Treatment-related SAEs were reported in 10 of the 207 patients in the 4 cohorts in this report (4.8%); treatment-related SAEs included pneumonitis in 3 patients and acute hepatitis, dermatitis, diarrhea, increased ALT, increased AST, infusion-related reaction, pyrexia, and vomiting in 1 patient each. Two treatment-related fatalities (acute hepatitis in a patient with HCC and pneumonitis in a patient with NSCLC) had disease-related conditions cited as contributing factors. Results from 15 patients with G/GEJ in a Phase 2b study indicate antitumor activity of the combination of tislelizumab 200 mg and oxaliplatin 130 mg/m^2 on Day 1, and capecitabine 1000 mg/m^2 BID on Days 1 through 15 of a 21-day cycle (Bai, Xu et al. 2019). The ORR among these 15 patients was 46.7% with a DCR of 80%. Responses were durable, with a median PFS of 6.1 months.

Serious adverse events (any cause) occurred in 5 G/GEJ patients (33.3%); all 5 experienced SAEs considered related to both tislelizumab and chemotherapy (Deva, Lee et al. 2018, Bai, Xu et al. 2019).

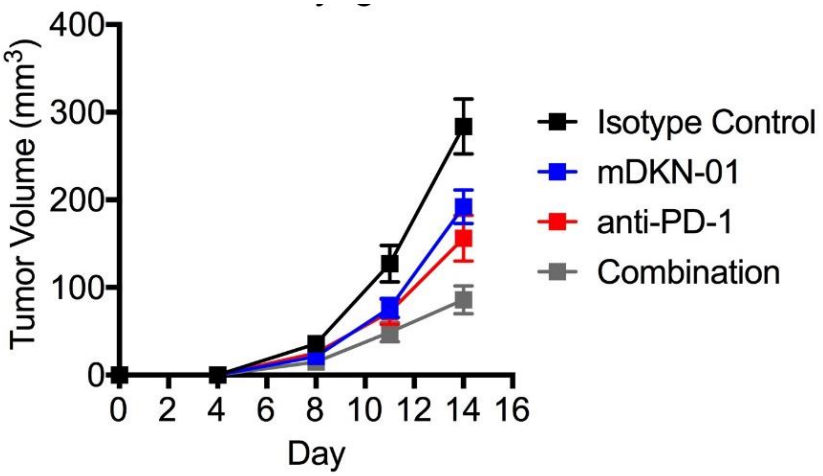
1.4.3. Rationale for the Combination of DKN-01 and Tislelizumab in the Treatment of Gastric and Gastroesophageal Junction Adenocarcinoma

Metastatic tumor cells with stem cell-like features are able to avoid eradication by the immune system through overexpression of DKK1, a protein that regulates Wnt signaling pathways and promotes tumor growth and metastasis (Kagey and He 2017). Blocking DKK1 activity has been proposed to stimulate an immune-mediated antitumor response. DKN-01 is a potent humanized monoclonal antibody with neutralizing activity against DKK1.

Preclinical and clinical data suggest that DKN-01 may effectively synergize with checkpoint inhibitors such as tislelizumab and certain chemotherapeutics in causing tumor cell death and boosting the immune response against the tumor.

The ability of mDKN-01 to have additive activity with an anti-PD-1 antibody was assessed in a B16 syngeneic model (Figure 4). Female B6 mice were inoculated subcutaneously with B16 mouse melanoma cells on Day 0. The following day, twice-weekly treatment with an isotype control (10 mg/kg), mDKN-01 (10 mg/kg), anti-PD-1 antibody (12 mg/kg), or a combination of mDKN-01/anti-PD-1 was initiated. mDKN-01 and anti-PD-1 monotherapy resulted in TGIs of 32% ($p=0.01$) and 45% ($p=0.004$), respectively at Day 14. The combination therapy resulted in a TGI of 70% ($p<0.001$) at Day 14, indicating that additive efficacy was observed.

Figure 4: *In Vivo* Antitumor Activity of Murine Surrogate DKN-01 is Additive with an Anti-PD-1 Antibody



Abbreviations: MTV = mean tumor volume; PD-1 = programmed cell death protein 1; SEM = standard error of the mean; TGI = tumor growth inhibition.
Female B6 (C57BL/6J) mice (15 per group) were inoculated subcutaneously in the right flank with $1x10^5$ B16F0 mouse melanoma cells on Day 0. The following day, twice-weekly intraperitoneally treatment of a IgG2a control (10 mg/kg), a murine surrogate IgG2a DKN-01 (mDKN-01) antibody with a D265A mutation to reduce effector function (10 mg/kg), anti-PD-1 (12 mg/kg), or a combination treatment of mDKN-01/anti-PD-1 was initiated. Tumors were measured every 3-4 days. Mean tumor volumes are plotted. Error bars represent SEM. Percent TGI = [(MTV Control) – (MTV Treated)]/(MTV Control). P-values were calculated using an unpaired T-test.

The use of immunotherapy in the treatment of advanced, solid tumors has recently expanded with the development of monoclonal antibodies that boost the immune response against cancer cells by targeting checkpoint proteins on immune cells, such as PD-1, PD-L2, or cytotoxic T-lymphocyte-associated protein (Gong, Chehrazi-Raffle et al. 2018). Studies in the treatment of esophageal, GEJ and gastric cancers have been conducted with various immunotherapy agents, including tislelizumab, a humanized, IgG4-variant monoclonal antibody against PD-1 (Zayac and Almhanna 2019).

Recent clinical data show improved clinical outcomes in advanced G/GEJ cancer patients with DKK1-high tumors when treated with DKN-01 and anti-PD-1 therapy (pembrolizumab).

1.5. Justification for Dose

1.5.1. Rationale for DKN-01 Dose in Parts A and B

DKN-01 will be administered at a dose of 300 mg (Part A and B1) or 600 mg (Part B2) IV on days (D) 1 and 15 in combination with tislelizumab, ± oxaliplatin and capecitabine in 21-day cycles, as described in Section 3.1.1.2.

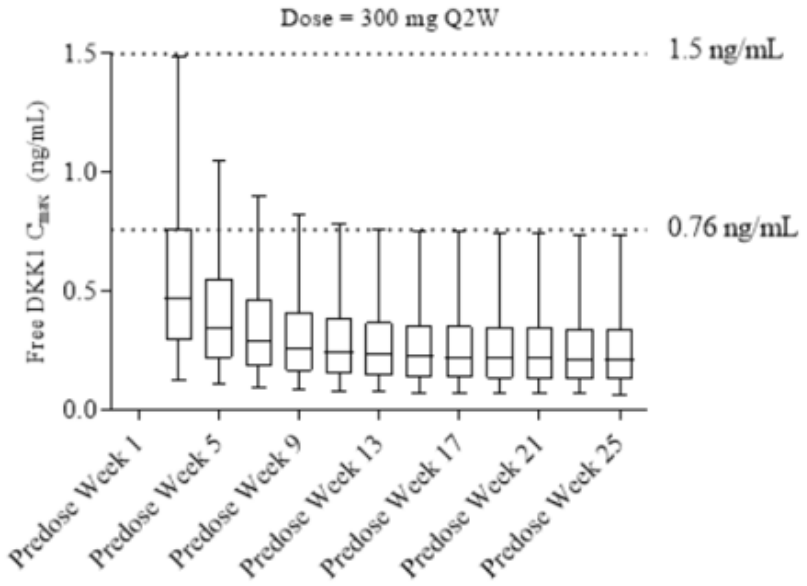
As discussed in Section 1.3.1.1, DKN-01 pharmacology has been associated with a number of direct and indirect effects on tumor growth, metastasis, and angiogenesis. It is thought that the antitumor effects of DKK1 are mediated in large part by binding to and neutralizing DKK1. In order to relate DKK1 neutralization to clinical efficacy, a pharmacokinetic/pharmacodynamic model was developed which could predict both the serum concentrations of DKN-01 and also the resulting free DKK1 serum concentrations (unbound). Higher concentrations of free or

unbound DKK1 equate to a lower degree of neutralization and vice versa. Model simulations were performed which assumed a Q2W dosing schedule and focused on the maximal concentration of free DKK1 achieved (C_{max}) over the dosing interval. As noted, the objective of DKN-01 treatment was to reduce free DKK1 C_{max}. A mean initial patient baseline value for free DKK1 (before treatment) was found to be approximately 5.4 ng/mL. With this value in mind, the model simulations in Figure 5 and Figure 6 demonstrate that the DKK1 C_{max} was substantially reduced (relative to baseline) by a single administration of DKN-01 and continued to decrease over repeat doses. In Figure 5, free DKK1 could be decreased in the majority of patients (>95%), to a maximal value of 1.5 ng/mL after the first 300 mg dose. In addition, after repeat 300 mg Q2W dosing, the highest free DKK1 C_{max} levels declined to approximately 0.8 ng/mL (or less) for 95% of patients. Additional 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.

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 study. In this study, patients were administered DKN-01 at doses of 150 or 300 mg Q2W over a 28-day cycle (Study Parts A-E, and monotherapy). Study Part F was a 21-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 a 21-day cycle. Note that between these 2 studies only the dosing schedule for Q2W P102 was comparable to the initial simulations above. However, in both of these clinical studies modeling fits to DKN-01/DKK1 concentration data showed a dose dependent decrease in free DKK1 C_{max} concentrations. For example, in Study P102, the median free DKK1 C_{max} after the last administered 300 mg DKN-01 dose was 0.52 ng/mL (range 0.14-8.5 ng/mL). This value was comparable to the simulations discussed above and aids in understanding the importance of adequate drug levels to neutralize free DKK1.

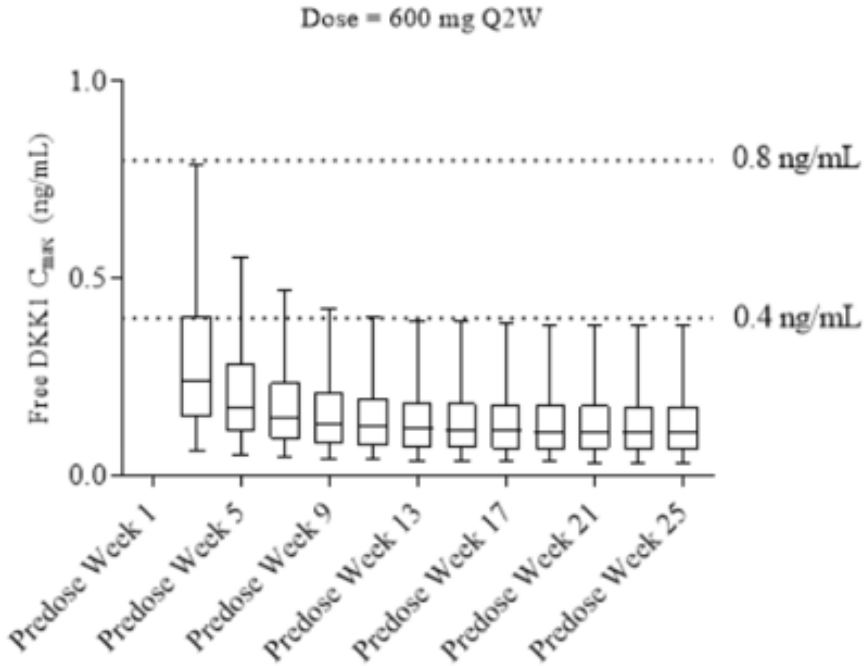
In the P102 study, the relationship between drug levels and PD, SD, and PR patients was examined after a 300 mg dose. Figure 7 plots the individual patient drug trough levels (over a Q2W dosing interval) with PD, SD, or PR. This figure plots results from Part F of Study P102, which had the greatest number of patients with a similar dose of DKN-01, comedication, and cancer type. In Part F there were 63 patients, 33 with PD, 17 showing SD, 5 with a PR, and 8 with no evaluation. In this figure it can be seen that efficacy was associated with a trend of higher drug levels. In summary, the modeling performed supports the idea that higher doses of DKN-01 lead to greater DKK1 neutralization, and higher drug levels which was associated with efficacy. The proposed 300 mg dose is supported by positive results observed in P102, and by extension, a 600 mg dose would lead to higher drug levels, greater free DKK1 suppression and potentially greater efficacy.

Figure 5: Predicted Maximal Free Serum DKK1 (C_{max}) Concentrations after 300 mg DKN-01 IV Dosing Administered Once Every Two Weeks (Q2W)



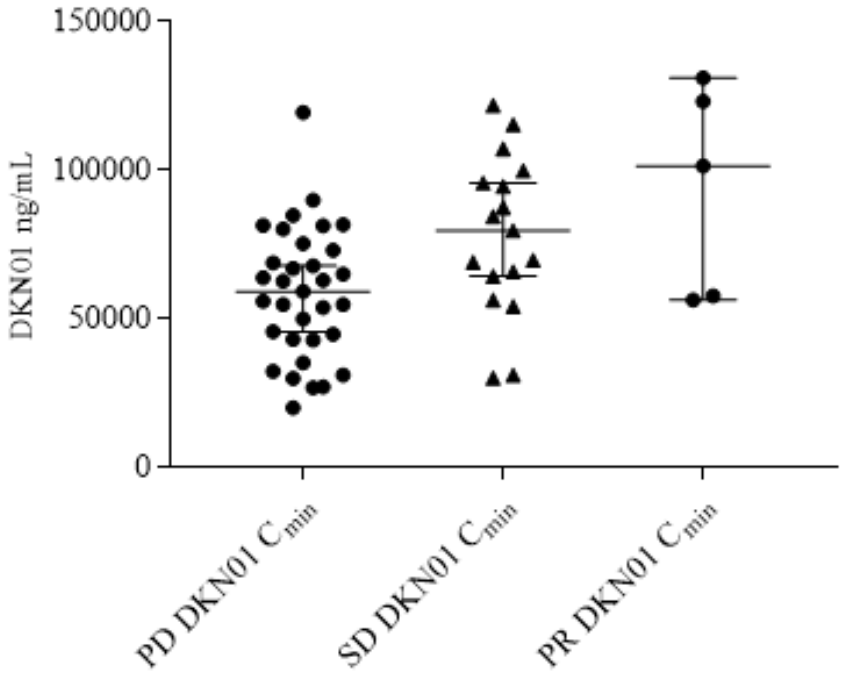
Note: Plot whiskers represent an interval containing 90% of patients.

Figure 6: 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.

Figure 7: Dosing Interval DKN-01 Trough Concentrations (Dose = 300 mg)



1.5.2. Rationale for DKN-01 Dose for Part C

The dosing regimen for both Part C cohorts was informed based on the results of population PK (PopPK) and an Exposure-Response assessment for DKN-01.

Briefly, a PopPK model was developed in January 2022 using data from 369 patients across 6 DKN-01 studies (DEK-DKK1-P100, DEK-DKK1-P101, DEK-DKK1-P102, DEK-DKK1-P103, DEK-DKK1-P204, and DEK-DKK1-P205) involving various tumor types. The PopPK structural model was a 2-compartment model with first-order elimination. Following development of the PopPK model, an exposure-response (E-R) assessment was completed using data from Study P102 Part F (N=46 patients) and from Study P205 (N=36 patients) where all patients were administered DKN-01 at 300mg on D1 and D15 of Cycle 1. Both actual and model predicted exposure metrics, C_{min} on Day 21 prior to the administration of the third dose of DKN-01, and AUC from time 0 to Day 21, at steady state (AUC0-21, ss) were independently evaluated for patients who had disease control (SD) and were protocol responders (PR, or CR) as compared to those who were protocol non-responders. Results of these analyses indicated that a Cycle 1, Day 21 C_{min} ≥60 µg/mL and an AUC0-21, ss >35,000 µg·hr/mL was associated with a greater number of responders suggesting that DKN-01 exposure above these levels may be beneficial.

Using the above described PopPK model predicted DKN-01 parameters, various dosing regimens were simulated to estimate exposures at different doses and schedules. From these simulation, two DKN-01 dosing regimens were estimated to provide adequate target exposures during the first Cycle and over a steady-state Cycle in the majority of patients: 1) 400mg DKN-01 QW for 3 weeks (Cycle 1 only), followed by a 400mg dose Q2W for subsequent cycles, and

2) 600mg DKN-01 on Day 1 and Day 15 (Cycle 1 only), followed by Q3W dosing beginning on Day 21.

For patients in the experimental group for Part C, DKN-01 will be administered at a dose of 600 mg on D1 of each cycle in combination with tislelizumab, oxaliplatin, and capecitabine (CAPOX) in 21-day cycles, or at a dose of 400 mg on D1 of each cycle in combination with leucovorin calcium (folinic acid), fluorouracil, and oxaliplatin (mFOLFOX6) in 14-day cycles as described in Section 3.1.1.3. For Cycle 1 only, an additional dose of DKN-01 will be administered on Day 15 for the CAPOX regimen and on Day 8 for the mFOLFOX6 regimen.

1.5.3. Rationale for Tislelizumab Dose

The clinical fixed dose of tislelizumab 200 mg IV once every 3 weeks was selected based on comparable safety and efficacy profiles between 2 and 5 mg/kg in BGB-A317_Study_001:

- Rates of treatment-related AEs and SAEs observed in patients receiving 2 mg/kg and 5 mg/kg once every 2 weeks and once every 3 weeks were comparable, suggesting no clear dose-dependence across these regimens. Additionally, PK data also shows no relationship between exposure and treatment-emergent irAEs (Wu, Budha et al. 2019a, Wu, Tang et al. 2019b).
- Confirmed response rates in patients treated with tislelizumab on a once every 3 weeks schedule were favorable compared to those treated on a once every 2 weeks schedule. While there are differences in response rates between dose levels, this is more likely a reflection of small sample size and patient heterogeneity than dose response
- Clearance of tislelizumab was not dependent on body weight, and the observed serum exposure of a 200 mg dose fell between serum exposure observed after 2 mg/kg and 5 mg/kg doses. Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg once every 3 weeks
- Exposure-response analysis indicated that there was a lack of clinically significant exposure-response relationships for ORR and safety endpoints across a variety of advanced solid tumors and classical Hodgkin lymphoma for tislelizumab. These findings support 200 mg once every 3 weeks dose regimen for pivotal studies.

Tislelizumab is currently tested in clinical studies at the dose of 200 mg every 3 weeks. The alternate regimen of 400 mg once every 6 weeks is selected by matching dose and exposure (AUC) with the exposure of 200 mg once every 3 weeks regimen. Exposure-response (E-R) assessments of available clinical data from Studies including BGB-A317_Study_001, BGB-A317-102, and BGB-A317-203 suggest no clinically significant relationships observed between tislelizumab exposure and efficacy (CR + PR) or safety across tumor types, and the 400 mg once every 6 weeks regimen is not expected to be clinically different from the 200 mg once every 3 weeks regimen in terms of safety or efficacy outcomes. The higher maximum concentrations (C_{max}) of 400 mg once every 6 weeks regimen compared with the 200 mg once every 3 weeks is well covered by the available safety data at higher doses (10 mg/kg every 2 weeks and 5 mg/kg every 3 weeks were used in Study BGB-A317_Study_001). Additionally, alternative 6-weekly dose administration in adjuvant phase is expected to increase patient compliance in this phase and offer additional convenience for care providers. Recently, the

approval of the use of an extended dosing regimen has also been reported for other PD-1 inhibitors such as nivolumab (240 mg Q2W and 480 mg Q4W) and pembrolizumab (200 mg once every 3 weeks and 400 mg once every 6 weeks), demonstrating the feasibility and utility of this approach (Long et al, 2018; OPDIVO 2014; Lala et al, 2018; Merck Press Release 2019a and 2019b; Ebbinghaus, 2019; Holland, 2019).

In conclusion, the observed clinical activity in patients with advanced tumors, coupled with a manageable safety profile and supportive data, support the proposed tislelizumab dose of 200 mg IV once every 3 weeks and 400 mg IV once every 6 weeks as the recommended dose for pivotal studies. Please refer to the Tislelizumab Investigator's Brochure (BeiGene).

1.6. Benefit-Risk Assessment

Adverse drug reactions identified during clinical studies with DKN-01 include:

- Gastrointestinal disorders including nausea, with or without vomiting, constipation, and diarrhea
- Hematologic abnormalities, including thrombocytopenia, neutropenia, and anemia
- Fatigue.

The identified risks occur more frequently and at higher grade when DKN-01 is given in combination therapy than with DKN-01 monotherapy, as reactions observed with combination therapy, to date, appear influenced by safety of the combination partner (paclitaxel, gemcitabine/cisplatin, or pembrolizumab).

DKN-01 is a clinically active drug that has the potential to benefit adult patients across several different tumor types where there are unmet medical needs. The safety profile has remained favorable across more than 343 oncology patients (including monotherapy, combination therapies).

More than 1273 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥2 mg/kg) with additional patients treated in combination studies. The safety profile is largely consistent with that of other anti-PD-1 antibodies and included mostly mild/moderate AEs. Very few Grade 3/4 irAEs have been observed, and they have been generally reversible and manageable with study drug interruption and/or steroid treatment. These preliminary data from the ongoing Phase 1 and Phase 2 studies show that tislelizumab has been well tolerated in patients with advanced and refractory tumors, including, but not limited to, triple negative breast cancer, NSCLC, cholangiocarcinoma, ovarian, gastric, and HCC, head and neck squamous cell carcinoma, esophageal carcinoma, cervical cancer, colorectal cancer, bladder cancer, melanoma, Merkel-cell carcinoma, thyroid cancer, and RCC. The safety profile for single-agent tislelizumab is similar to those observed in other PD-1 inhibitors. Preliminary data from combination studies show a similar safety profile. The initial data collected in these studies suggest that tislelizumab can result in antitumor activity across a variety of tumor types. Antitumor activity has been observed across the dose ranges evaluated in patients. Therefore, the benefit-risk profile for tislelizumab monotherapy appears to be favorable in oncology population based on preliminary efficacy and safety data.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of the study treatments can be found in the Tislelizumab Investigator's Brochure

(BeiGene) and DKN-01 Investigator's Brochure, and in the local prescribing information for oxaliplatin and capecitabine. These documents will be used as the reference safety information for this clinical study.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Part A and Part B

2.1.1. Study Objectives

2.1.1.1. Primary Objective

- To characterize the safety and tolerability of DKN-01 in combination with tislelizumab ± CAPOX (capecitabine + oxaliplatin) in patients with inoperable, locally advanced or metastatic G/GEJ adenocarcinoma.

2.1.1.2. Secondary Objectives

- Part A: To estimate the ORR of patients with inoperable, locally advanced or metastatic G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab + CAPOX as a first-line therapy using RECIST v1.1.
- Part B: To estimate the ORR of patients with inoperable, locally advanced or metastatic DKK1-high G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab as a second-line therapy using RECIST v1.1.
- Part A: To estimate duration of response (DoR), duration of complete response (DoCR), PFS, OS, duration of clinical benefit (DoCB), durable clinical benefit (DCB), DCR, and time to response (TTR) in patients with inoperable, locally advanced or metastatic G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab + CAPOX as a first-line therapy.
- Part B: To estimate DoR, DoCR, PFS, OS, DoCB, DCB, DCR, and TTR in patients with inoperable, locally advanced or metastatic DKK1-high G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab as a second-line therapy.

2.1.1.3. Exploratory Objectives

- To characterize the PK of DKN-01.
- To characterize the PK of tislelizumab.
- To assess the immunogenicity of DKN-01.
- To assess the immunogenicity of tislelizumab.
- To assess predictive, prognostic, and/or pharmacodynamic biomarkers and clinical characteristics including any association between response, survival, or other clinical outcomes and DKN-01 in combination with tislelizumab ± CAPOX.
- To evaluate biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivative) samples obtained before, during, and/or after treatment with DKN-01 in combination with tislelizumab ± CAPOX including assessment of association of these biomarkers with clinical outcomes to DKN-01+tislelizumab ± CAPOX.
- To evaluate exposure-response relationships if the available data permit.

- Part A: To estimate the ORR, BOR, DCB rate, and DCR using iRECIST in patients with inoperable, locally advanced or metastatic G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab + CAPOX as first-line therapy continuing treatment beyond the initial assessment of progressive disease.
- Part B: To estimate the ORR, BOR, DCB rate, and DCR using iRECIST in patients with inoperable, locally advanced or metastatic DKK1-high G/GEJ adenocarcinoma treated with DKN-01 in combination with tislelizumab as a second-line therapy continuing treatment beyond the initial assessment of progressive disease.

2.1.2. Study Endpoints

2.1.2.1. Safety Endpoint

- Incidence of TEAEs, Grade ≥3 TEAEs, treatment-related TEAEs, treatment-emergent serious adverse events (TESAEs), treatment-related TESAEs, and TEAEs leading to study drug discontinuation.

2.1.2.2. Other Key Safety Endpoints

- Incidence of treatment-emergent Grade 3/4 clinical laboratory abnormalities.
- Incidence of treatment-emergent irAEs.
- Incidence of Grade 3/4 and serious treatment-emergent irAEs.
- Incidence of Grade 3/4 and serious infusion-related reactions.
- Changes from baseline in clinical laboratory parameters (serum chemistry and hematology).
- Changes from baseline in vital signs and electrocardiogram (ECG) parameters.
- Shift from baseline in ECOG performance status.

2.1.2.3. Efficacy Endpoints

- ORR (the proportion of patients with best overall response of CR + PR), as assessed by the Investigator, using RECIST v1.1.
- DoR, defined as the time from initial response (CR or PR) until radiographically documented progressive disease or death due to any cause; progressive disease is defined using RECIST v1.1.
- DoCR, defined as the time from initial CR until radiographically documented progressive disease or death due to any cause; progressive disease is defined using RECIST v1.1.
- PFS, defined as the time from first study drug dose (i.e., C1D1) to first radiographically documented progressive disease, as determined using RECIST v1.1, or death due to any cause.
- OS, defined as the time from first study drug dose (i.e., C1D1) to death due to any cause.

- DoCB, defined as the time from the first study drug dose (i.e., C1D1) to the time of progressive disease, as determined using RECIST v1.1, or death due to any cause in patients who had a best overall response of CR, PR, or SD of ≥6 weeks.
- DCB, defined as DoCB ≥180 days. Patients who have best overall response of PD or those having clinical benefit but DoCB lasting <180 days will be considered as "non-DCB".
- DCR (i.e., CR+PR+ SD at ≥6 weeks), as assessed by the Investigator, using RECIST v1.1.
- TTR, defined as the time from the first dose of study treatment to the assessment date of the BOR of either CR or PR.

2.1.2.4. Exploratory Endpoints

- Summary of serum concentrations of DKN-01 or tislelizumab at specified timepoints.
- Incidence of antidrug antibodies (ADAs) to DKN-01 or tislelizumab.
- Predictive, prognostic, and/or pharmacodynamic biomarkers including any association between response, survival, or other clinical outcomes and DKN-01 in combination with tislelizumab ± CAPOX.
- Biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivative) samples obtained before, during, and/or after treatment with DKN-01 in combination with tislelizumab ± CAPOX. Biomarkers may include, but are not limited to:
  - DKK1 tumor expression in mRNA by ISH
  - Programmed cell death protein ligand-1 (PD-L1) in the tumor microenvironment by IHC
  - circulating tumor deoxyribonucleic acid (ctDNA)
  - serum DKK1.
- Exposure-response relationships for DKN-01 as data permit.
- iORR = (number of patients with iCR + iPR)/all patients) based on the Investigator assessment and following iRECIST for patients continuing treatment beyond the initial assessment of progressive disease.

2.2. Part C

2.2.1. Study Objectives

2.2.1.1. Primary Objective

- To assess whether the addition of DKN-01 to the combination of tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6 [leucovorin calcium, fluorouracil, and oxaliplatin]) improves PFS according to the RECIST v1.1 as assessed by the Investigator, in advanced DKK1-high and overall G/GEJ

adenocarcinoma compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.

2.2.1.2. Secondary Objectives

- To estimate the objective response rate (ORR), according to RECIST v1.1, as assessed by the Investigator, the duration of response (DoR) and overall survival (OS) in advanced DKK1-high and overall G/GEJ adenocarcinoma patients treated with DKN-01 in combination with tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.
- To assess whether the addition of DKN-01 to the combination of tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) improves PFS and ORR, according to RECIST v1.1, as assessed by the Investigator, in patients with CPS ≥5 or CPS <5 advanced DKK1-high and overall G/GEJ adenocarcinoma compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.
- To characterize the frequency of toxicity ≥Grade 3 treatment-related adverse events (TRAE) associated with each of the treatment arms.

2.2.1.3. Exploratory Objectives

- To assess whether the addition of DKN-01 to the combination of tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) improves the duration of complete response (DoCR), duration of clinical benefit (DoCB), durable clinical benefit (DCB), disease control rate (DCR), and time to response (TTR) in advanced DKK1-high and overall G/GEJ adenocarcinoma patients compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.
- To characterize the PK of DKN-01.
- To characterize the PK of tislelizumab.
- To assess the immunogenicity of DKN-01.
- To assess the immunogenicity of tislelizumab.
- To assess predictive, prognostic, and/or pharmacodynamic biomarkers and clinical characteristics including any association between response, survival, or other clinical outcomes of DKN-01 in combination with tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.
- To evaluate exposure-response relationships if the available data permit.
- To estimate the ORR, BOR, DCB rate and DCR using iRECIST in patients with inoperable, locally advanced or metastatic DKK1-high and overall G/GEJ adenocarcinoma treated with the combination of tislelizumab + chemotherapy

regimen (CAPOX or mFOLFOX6) ± DKN-01 as first-line therapy continuing treatment beyond the initial assessment of progressive disease.

- To assess the concordance between Investigator assessment and central imaging assessment for primary and secondary efficacy analyses.
- To assess the concordance between tumor area positivity (TAP) and CPS PD-L1 expression for primary and secondary efficacy analyses.
- To evaluate differences between backbone chemotherapy regimens (CAPOX vs mFOLFOX6) in combination with tislelizumab ± DKN-01 for primary and secondary efficacy analyses.

2.2.2. Study Endpoints

2.2.2.1. Primary Endpoint

- PFS, as determined by the Investigator per RECIST v1.1, of DKN-01 plus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) versus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) in DKK1-high and in all patients.

2.2.2.2. Secondary Endpoints

- ORR, as determined by the Investigator per RECIST v1.1, of DKN-01 plus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) versus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) in DKK1-high and all patients.
- DoR, as determined by the Investigator per RECIST v1.1, of DKN-01 plus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) versus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) in DKK1-high and all patients.
- OS with DKN-01 plus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) versus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) in DKK1-high and in all patients.
- Incidence of ≥Grade 3 treatment-related adverse events (TRAEs).

2.2.2.3. Exploratory Endpoints

- DoCR using RECIST v1.1.
- DoCB as determined using RECIST v1.1, is defined as the time from the date of randomization to the time of progressive disease or death due to any cause in patients who had a best overall response of complete response (CR), partial response (PR), or stable disease (SD) of ≥6 weeks.
- DCB, defined as DoCB ≥180 days. Patients who have best overall response of PD or those having clinical benefit but DoCB lasting <180 days will be considered as “non-DCB”.

- DCR (i.e., CR + PR + SD at ≥6 weeks), as assessed by the Investigator using RECIST v1.1.
- TTR, defined as the time from the date of randomization to the assessment date of the first instance of an overall response of CR or PR.
- Summary of serum concentrations of DKN-01 at specified timepoints.
- Summary of serum concentrations of tislelizumab at specified timepoints.
- Incidence of anti-drug antibodies (ADAs) to DKN-01.
- Incidence of ADAs to tislelizumab.
- Serum DKK1, change since baseline at specified timepoints (applicable for patients who received DKN-01).
- Exposure-response relationships for DKN-01 as data permit.
- Biomarkers from patient-derived tumor tissue(s) and/or blood (or blood derivative) samples obtained before, during, and/or after treatment with DKN-01 plus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) versus tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6). Biomarkers may include, but are not limited to:
    - DKK1 tumoral mRNA expression by Chromogenic situ hybridization (CISH)
    - Programmed cell death protein ligand-1 (PD-L1) expression by IHC
    - Genetics from tumor specimens or circulating tumor deoxyribonucleic acid (ctDNA)
    - Serum and plasma for proteomics and additional scientific analyses.
- iORR = (number of patients with iCR + iPR)/all patients) based on the Investigator assessment and following iRECIST for patients continuing treatment beyond the initial assessment of progressive disease.
- A concordance comparison between Investigator assessment and central imaging assessment for primary and secondary efficacy analyses will be performed.
- A concordance comparison between CPS and TAP will be performed, including additional scientific analysis in patients with TAP ≥5 or TAP <5 advanced DKK1-high and overall G/GEJ adenocarcinoma compared to tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) as a first-line therapy.

3. STUDY DESIGN

3.1. Summary of Study Design

This is a Phase 2 open-label, multicenter study to be conducted concurrently in 3 parts (non-randomized Parts A and B and a randomized Part C).

- Part A will enroll G/GEJ adenocarcinoma patients who have received no prior systemic treatment in the locally advanced/metastatic setting (first-line treatment) (Section 3.1.1.1)
- Part B will enroll patients who received only 1 prior systemic treatment, which must consist of a platinum and/or fluoropyrimidine–based therapy (± HER2 therapy if applicable) for locally advanced/metastatic DKK1-high G/GEJ adenocarcinoma (second-line treatment) (Section 3.1.1.2)
- Part C will enroll G/GEJ adenocarcinoma patients who have received no prior systemic treatment in the locally advanced/metastatic setting (first-line treatment) (Section 3.1.1.3).

In Parts A and B, approximately 72 adult patients with inoperable, histologically confirmed locally advanced or metastatic G/GEJ adenocarcinoma with measurable disease (RECIST v1.1) requiring therapy will be enrolled in the study.

Both Parts A and B are designed to evaluate safety, tolerability, and efficacy of the combination therapy of IV DKN-01 and tislelizumab ± CAPOX in G/GEJ adenocarcinoma patients. Treatment continues in repeating 21-day cycles until patient meets criteria for discontinuation or is no longer deriving clinical benefit. Parts A and B will be enrolled concurrently. A review by the Safety Review Team (SRT) will occur in each study part after the first 5 patients have completed Cycle 1. Refer to Section 7.2.3 for details on the SRT.

Part C is the open-label, randomized, controlled, 2-arm portion of the study to evaluate the efficacy and safety of tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) ± DKN-01 in adult patients with inoperable, histologically confirmed locally advanced or metastatic G/GEJ adenocarcinoma with measurable disease (RECIST v1.1) requiring therapy. Approximately 160 patients will be randomized in a 1:1 ratio to receive either DKN-01 in combination with tislelizumab and chemotherapy regimen (CAPOX or mFOLFOX6) (n=80) or tislelizumab in combination with chemotherapy regimen (CAPOX or mFOLFOX6) (n=80), Patients will be assigned to treatment using a central stratified block randomization scheme. Patients will be stratified at randomization by the following factors:

- DKK1 RNAscope tumor percentage score (TPS) (≥20% vs <20%)
- PD-L1 immunohistochemistry Combined Positive Score (CPS) (≥5 vs <5).

Randomization may occur up to 3 calendar days prior to C1D1.

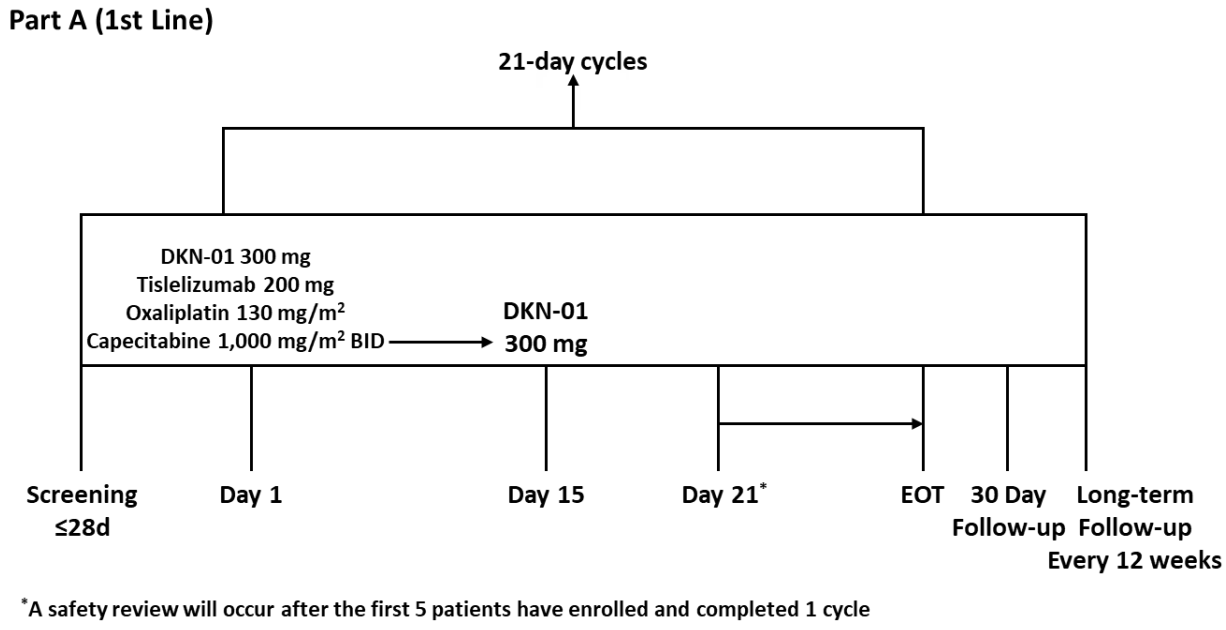
For Part C, a review by the SRT will occur after the first 5 patients on each chemotherapy regimen (CAPOX and mFOLFOX6) have completed Cycle 1 from both the experimental group (i.e., DKN-01 in combination of tislelizumab and chemotherapy regimen) and the control group (i.e., tislelizumab and chemotherapy regimen). Enrollment will continue during the safety data review without pause (refer to Section 7.2.3 for details on the SRT).

3.1.1. Treatment

3.1.1.1. Part A

Part A patients will receive treatment as outlined in Figure 8. Part A is restricted to patients who have not had prior systemic therapy for locally advanced or metastatic disease. Patients may have received prior neoadjuvant or adjuvant therapy as long as it was completed without disease recurrence for at least 6 months. A review by the SRT will occur after the first 5 patients have enrolled and completed 1 cycle. Enrollment in the other ongoing cohorts may continue during the SRT review.

Figure 8: Study Design Part A



Abbreviations: BID = twice daily; EOT = end of treatment.

3.1.1.2. Part B

Part B patients will receive IV DKN-01 (300 mg or 600 mg) on Days 1 and 15 and IV tislelizumab (200 mg) on Day 1 of each 21-day cycle.

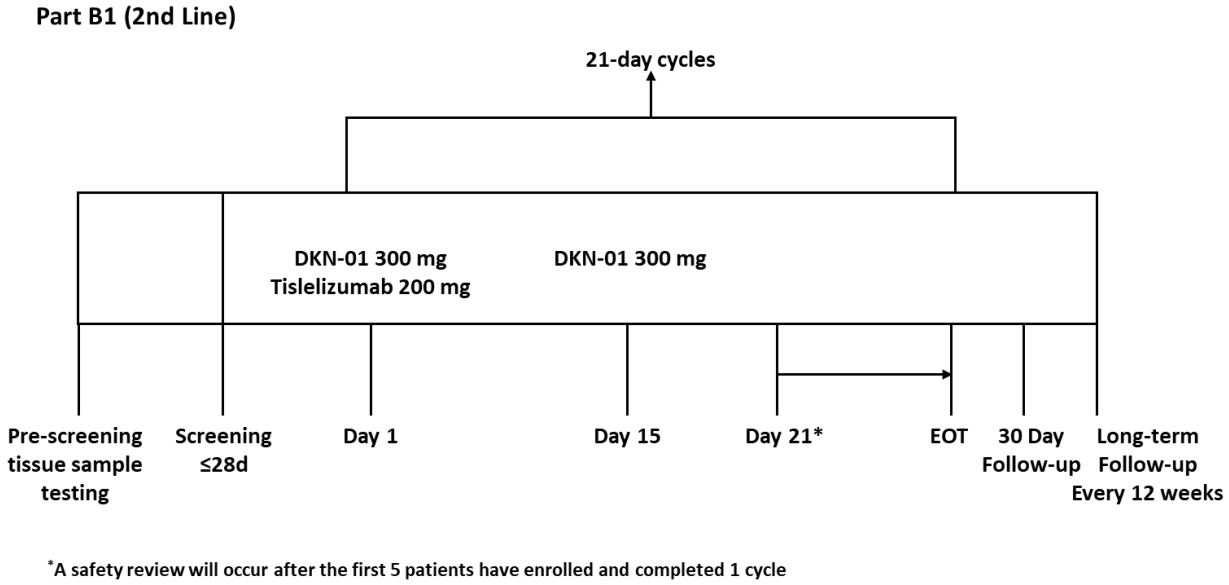
Part B has 2 components:

- The first 24 patients (Part B1) will receive DKN-01 300 mg (Figure 9)
- The next 24 patients (Part B2) will receive DKN-01 600 mg (Figure 10).

Patients enrolled in Part B are required to have DKK1-high (H-score ≥35) G/GEJ adenocarcinoma (pre-screen biopsy) and must have had only 1 prior systemic therapy for locally advanced/metastatic disease (platinum and/or fluoropyrimidine-based therapy; ± HER2 therapy if applicable). Patients may have received prior neoadjuvant or adjuvant therapy (see Section 4.2.2). A safety review will occur after the first 5 patients in each of Part B1 and B2 have enrolled and completed 1 cycle.

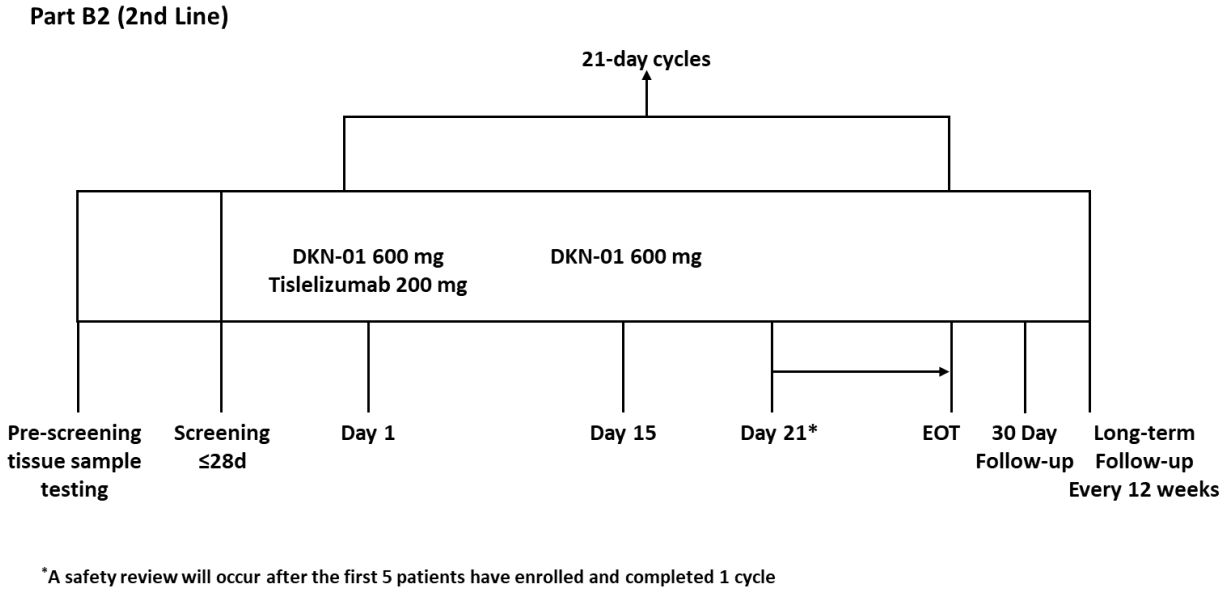
It is anticipated that Part B2 will enroll following the completion of enrollment of all patients in Part B1. Enrollment in the other ongoing cohorts (e.g., Part A) may continue during the SRT review.

Figure 9: Study Design Part B1



Abbreviations: EOT = end of treatment.

Figure 10: Study Design Part B2



Abbreviations: EOT = end of treatment.

3.1.1.3. Part C

Part C patients will be randomized using a central stratified block randomization scheme into one of 2 groups: patients in the experimental group will receive DKN-01 in combination with tislelizumab and chemotherapy regimen (CAPOX or mFOLFOX6) and patients in the control group will receive only tislelizumab in combination with chemotherapy regimen (CAPOX or mFOLFOX6). The randomization will use the following stratification factors:

- DKK1 RNAscope TPS (≥20% vs <20%)
- PD-L1 immunohistochemistry CPS (≥5 vs <5).

Note: To avoid unnecessary delays which could impact patient care, during the Screening Period, patients who in the opinion of the Investigator are unable to wait more than 2 weeks to start treatment, may receive one cycle of chemotherapy (CAPOX or mFOLFOX6) prior to randomization while awaiting biomarker results. Patients meeting these requirements should be discussed with the Medical Monitor.

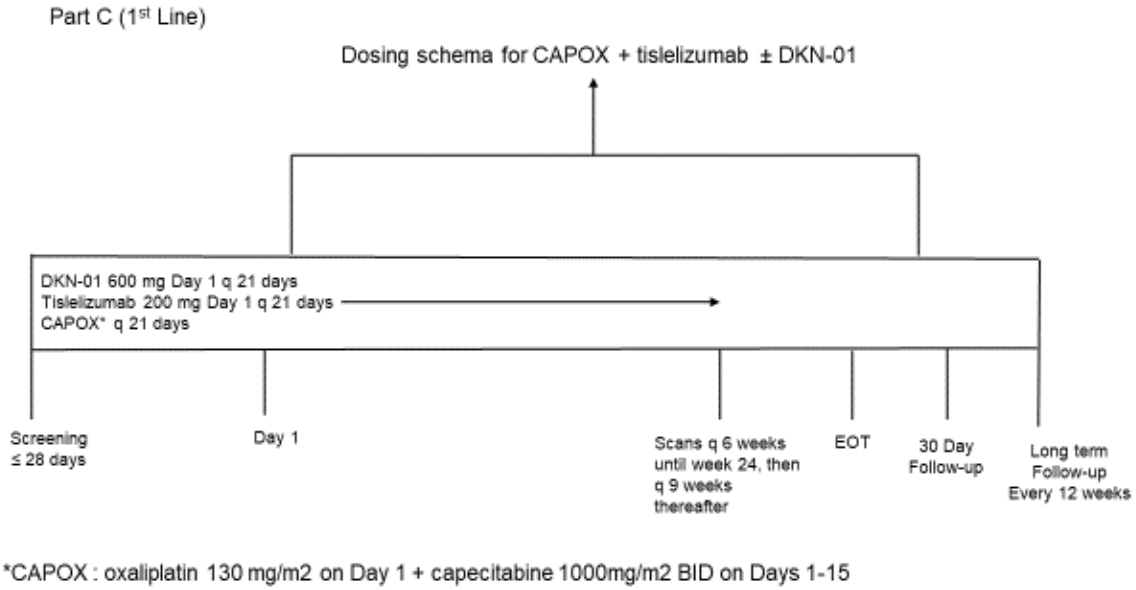
Once DKK1 and PD-L1 results from the central laboratory are received and the patient has been confirmed to meet all other eligibility requirements, the patient will be randomized to receive either DKN-01 in combination with tislelizumab and chemotherapy (CAPOX or mFOLFOX6) or tislelizumab in combination with chemotherapy (CAPOX or mFOLFOX6). If the central lab is unable to result a PD-L1 CPS score, historical CPS data can be used provided it was generated using either the 22C3 pharmDx, 28-8 pharmDx or SP263 assays. The chemotherapy regimen administered during Screening must be equivalent to that following randomization.

Patients in both groups receiving the CAPOX chemotherapy regimen (Figure 11) will receive tislelizumab (200 mg, IV) on Day 1 of each 21-day cycle. The CAPOX regimen will include oxaliplatin 130 mg/m^2 on Day 1 and capecitabine 1000mg/m^2 BID on Days 1-15 of each 21-day cycle for a total of 28 doses. Patients in the experimental group will receive DKN-01 (600 mg, IV) on Day 1 of each cycle. For Cycle 1 only, an additional loading dose of DKN-01 (600 mg, IV) will be administered on Day 15. Patients in the control group will not receive DKN-01 treatment.

Patients in both groups receiving the mFOLFOX6 chemotherapy regimen (Figure 12) will receive tislelizumab (400 mg, IV) every 6 weeks starting on C1D1 and continuing every third 14-day cycle (e.g., C4D1, C7D1, etc.). The mFOLFOX6 regimen will be administered every 14 days and includes leucovorin calcium (folinic acid) 400 mg/m^2 IV on Day 1, fluorouracil 400 mg/m2 IV bolus followed by 2400 mg/m2 continuous infusion over 48 hours and oxaliplatin 85 mg/m^2 IV on Day 1. Patients in the experimental group will receive DKN-01 (400 mg, IV) on Day 1 of each cycle. For Cycle 1 only, an additional loading dose of DKN-01 (400 mg, IV) will be administered on Day 8. Patients in the control group will not receive DKN-01 treatment.

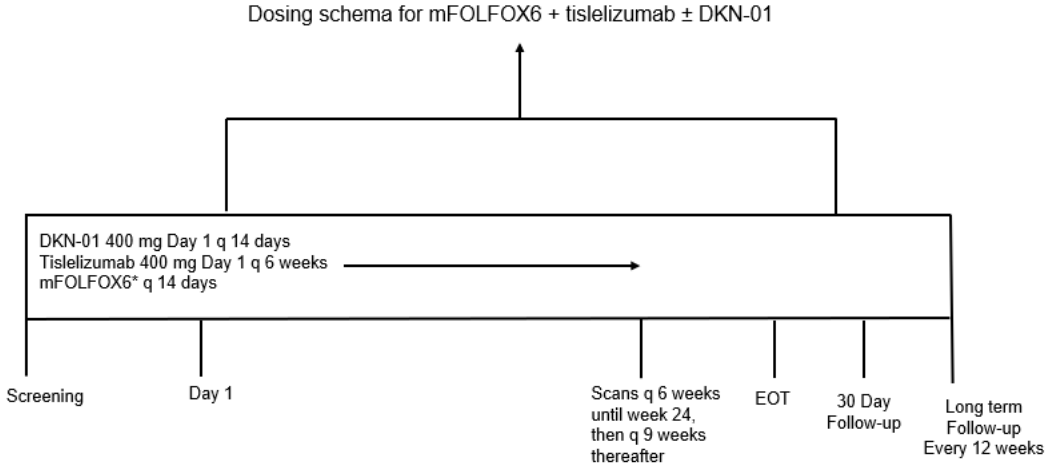
For Part C, a review by the SRT will occur after the first 5 patients on each chemotherapy regimen (CAPOX and mFOLFOX6) have completed Cycle 1 from both the experimental group (i.e., DKN-01 in combination of tislelizumab and chemotherapy regimen) and the control group (i.e., tislelizumab and chemotherapy regimen) Enrollment will continue during the safety data review without pause. Refer to Section 7.2.3 for details on the SRT.

Figure 11: Study Design Part C (CAPOX regimen)



Abbreviation: BID = twice daily; EOT = end of treatment; q = every
Note: For Cycle 1 only, an additional loading dose of DKN-01 (600 mg, IV) will be administered on Day 15.

Figure 12: Study Design Part C (mFOLFOX6 regimen)



*mFOLFOX6 q 14 days: leucovorin calcium (folinic acid) 400 mg/m2 IV day 1, fluorouracil 400 mg/m2 IV day 1 then 2400mg/ m2 continuous IV over 48 hours day 1 and 2, and oxaliplatin 85 mg/m2 IV day 1

Abbreviation: EOT = end of treatment; q = every.
Note: For Cycle 1 only, an additional loading dose of DKN-01 (400 mg, IV) will be administered on Day 8.

The study consists of a Pre-Screening Period (Part B only; Section 3.1.1.3), a Screening Period (Section 3.1.3), a Treatment Period (Section 3.1.4), and a Follow-up Period. The Follow-up Period includes a follow-up visit approximately 30 days after the last dose of study drug (Section 3.1.6) and provides for additional long-term follow-up for disease progression (if the patient discontinued study drug for a reason unrelated to progressive disease) and for subsequent therapies and survival until death (in all patients) (Section 3.1.7). After treatment discontinuation, patients will enter a long-term follow-up period. The Sponsor has the right to terminate this study at any time.

3.1.2. Pre-Screening (Part B Only)

Patients participating in Part B will agree to and sign a Pre-Screening informed consent to allow tumor biopsy tissue to be tested for DKK1 expression. No screening procedures will be allowed by this consent.

A fresh tumor biopsy sample (preferred) or an archived specimen will be sent to a Sponsor-designated, College of American Pathologists (CAP)-/Clinical Laboratory Improvement Amendments (CLIA)-certified central laboratory for evaluation of DKK1 mRNA in the tumor cells. If the patient's specimen testing result demonstrates elevated DKK1 (H-score ≥35), then the patient will be eligible for Screening in Part B. If the patient's specimen testing demonstrates an H-score <35, then the patient is ineligible for the study.

3.1.3. Screening Period

Patients who agree to participate in this study will sign the informed consent form (ICF) prior to undergoing any screening procedure. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to enrollment (C1D1) may be used for the purposes of screening rather than repeating the standard-of-care tests.

Screening evaluations may be performed within 28 days (35 days for imaging in Part C) prior to first dose of study drug. Hematology, chemistry, pregnancy testing, and ECG must be resulted, and treatment eligibility confirmed prior to dosing on C1D1 (Part B), or treatment eligibility confirmed prior to randomization (Part C).

Patients in the Republic of Korea who are suspected to have concurrent serious respiratory illness or exhibit significant respiratory symptoms unrelated to underlying cancer will also take a pulmonary function test (refer to Appendix 1 for details).

Screening evaluations may be repeated as needed within the Screening period; the Investigator is to assess preliminary patient eligibility according to the latest Screening assessment results.

Part B

The biopsy sample (fresh [preferred] or archival) collected during the Pre-screening period will be used to confirm elevated DKK1 mRNA levels required to meet eligibility criteria for enrollment (H-score ≥35). A fresh biopsy will be collected during the Screening period (+ 14 days) from patients who did not undergo a biopsy during the Pre-screening period for evaluation of DKK1 mRNA levels (unless it is clinically contraindicated per Investigator and after consultation with the Medical Monitor) for a retrospective DKK1 mRNA analysis.

Part C

Once eligibility for entry into the study is confirmed, patients will be randomized to receive either DKN-01 in combination with tislelizumab and chemotherapy regimen (CAPOX or mFOLFOX6) or tislelizumab in combination with chemotherapy regimen (CAPOX or mFOLFOX6) using a central stratified block randomization scheme. The stratification factors will be as follows:

- DKK1 RNAscope TPS (≥20% vs <20%)
- PD-L1 immunohistochemistry CPS (≥5 vs <5).

Randomization may occur up to 3 calendar days prior to C1D1. The EDC (Electronic Data Capture) system will be used to assign patients to either the experimental group or the control group in lieu of a separate IRT (Interactive Response Technology) system. Detailed instructions for assigning treatment will be provided in the eCRF completion guidelines.

3.1.4. Treatment Period

After completion of all Screening activities, treatment eligibility will be reconfirmed by performing safety labs within 3 days prior to dosing on C1D1 (refer to Section 5.2.3). On C1D1, qualified patients will receive study treatment as outlined in Table 8.

Blood sampling for clinical safety laboratory tests will be taken throughout the treatment period according to the schedule detailed in the Study Schedules (Appendix 1). Unscheduled visits (see Section 6.1.2) may occur if the Investigator deems appropriate.

Radiological assessment of tumor-response status will be performed as described in Section 6.4.

Safety will be assessed throughout the study by monitoring AEs/SAEs (toxicity grades assigned per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE, v5.0]) and laboratory results. Vital signs, physical examinations, ECOG performance status change, electrocardiogram (ECG) results, and other examinations will also be used for safety assessment as detailed in the Schedule of Assessments (Appendix 1).

All patients who continue to meet criteria for retreatment (refer to Section 5.2.3) will continue study treatment in the Treatment Period until development of radiographically documented progressive disease, unacceptable toxicity, or another discontinuation criterion is met, as determined by the Investigator or until a patient reaches 2 years of treatment as outlined below (as measured from C1D1).

When a patient reaches 2 years of treatment (as measured from C1D1):

- Patients may continue on study drugs beyond 2 years if the Investigator considers this to be in the best interest of the patient based on an assessment of clinical benefit and potential risks. Continuation of study drugs beyond 2 years must be explicitly approved by the Sponsor and will be contingent on the continued availability of DKN-01 and tislelizumab. The study assessment and procedure schedule will remain the same
- Patients with confirmed CR, PR, or SD may stop treatment after 2 years if the patient wishes. The decision should be based on the Investigator's evaluation, with the patient's clinical benefit and risk taken into consideration. The Investigator

should notify the Sponsor that treatment will be stopped prior to stopping the treatment

Treatment beyond the initial Investigator-assessed, RECIST v1.1 defined disease progression is permitted provided that the patient has Investigator-assessed clinical benefit and is tolerating the study drugs (refer to Section 5.2.3 for further details). Tumor assessment in such patients should continue as planned until study treatment discontinuation.

3.1.5. End of Treatment

The End-of-Treatment Visit (EOT) visit is conducted when the Investigator determines that DKN-01 will no longer be used for Part A and Part B. The End-of-Treatment (EOT) visit is conducted when the patient is no longer deriving clinical benefit from all study treatments and the Investigator determines all treatment should end in Part C. The reason for discontinuation from study treatment will be documented in the electronic case report form (eCRF). If routine laboratory tests (e.g., hematology, serum chemistry) are completed within 7 days before the EOT visit, these tests need not be repeated. Tumor assessment should follow the regular schedule of assessment in Appendix 1. If a patient has known positive ADA (to DKN-01 or tislelizumab) at the EOT visit, he or she should have repeat testing, where feasible, performed in the PD Follow-up Period and/or Survival Follow-up Period until the patient is no longer positive. If a female patient is of childbearing potential, she will be followed monthly with a urine pregnancy test up to 6 months following the last dose of study drug. This testing can occur with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.

3.1.6. Safety Follow-up

Patients who discontinue treatment for any reason will be asked to return to the clinic for the Safety Follow-up Visit (to occur within 30 days [+ 7 days] after the last dose of study drugs, or before the initiation of a new anticancer treatment, whichever occurs first). If the EOT and Safety Follow-up Visits are planned to be conducted within 7 days of one another, the visit procedures from these visits may be combined and completed at the EOT visit, and the Safety Follow-up visit may be conducted instead as a telephone call to document AEs and concomitant medications/procedures.

In addition, telephone contacts with patients should be conducted to assess immune-related AEs and concomitant medications (if appropriate, i.e., associated with an immune-related AE or is a new anticancer therapy) at 60 days and 90 days (± 14 days) after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected immune-related AE at a telephone follow-up contact, the Investigator should arrange an unscheduled visit if further assessment is indicated. Women of childbearing potential will continue to have pregnancy tests monthly for up to 6 months following last dose of study drug. This testing can occur with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.

All AEs, including SAEs, will be collected as described in Section 7.

3.1.7. PD and Survival Follow-up

Patients will be followed for survival and to obtain information on subsequent anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 12 weeks (± 14 days) after the EOT Visit or as directed by the Sponsor until death, withdrawal of consent, loss to follow-up, or end of study.

Patients who do not have PD when they discontinue study treatment will be followed approximately every 12 weeks in the PD Follow-up Period per routine clinical practice until documented disease progression, start of new anti-cancer medicine, death, withdrawal of consent, or study closure. After documentation of PD, all patients will be followed approximately every 12 weeks per routine clinical practice during the Survival Follow-up Period for survival until death, withdrawal of consent, or study closure.

If a patient has known positive ADA (to DKN-01 or tislelizumab) at the EOT visit, he or she should have repeat testing, where feasible, performed in the PD Follow-up Period and/or Survival Follow-up Period until the patient is no longer positive. Women of childbearing potential will continue to have pregnancy tests monthly for up to 6 months following last dose of study drug. This testing can occur with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.

3.2. Discontinuation From the Study Treatment or From the Study

3.2.1. Patient Discontinuation from Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the Investigator has the right to discontinue a patient from the study treatment at any time. Patients who discontinue study treatment for reasons other than disease progression or withdrawal of consent should be followed for assessments of antitumor activity, subsequent anticancer therapy, and survival (Section 3.1.7), if possible. Patients who discontinue study treatment for disease progression should be followed for subsequent anticancer therapy and survival (Section 3.1.7).

The primary reason for discontinuation from the study treatment should be documented on the appropriate eCRF. Patients may discontinue study treatment for reasons which include, but are not limited to, the following:

- Disease progression
- Adverse event
- Use of any concurrent anticancer therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including herbal medicine] for the treatment of cancer)
- Patient noncompliance: Investigative site staff should first counsel patients who are significantly noncompliant (e.g., missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The Investigator may, in consultation with the Medical Monitor, discontinue patients from treatment who are consistently noncompliant.

Patients must be discontinued from study treatment for the following reasons:

- Pregnancy
- Patient decision
- Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety, if he or she were continue the study treatment. (see section 5.2.2.2 and Appendix 7 and 8 for AEs and when discontinuation is required for safety).

3.2.2. Patient Discontinuation from Study

Patients will discontinue study for reasons which include, but are not limited to, the following:

- Patient withdrawal of consent
- Death
- Lost to follow-up

3.3. End of Study

The end of study is defined as the timepoint when, to the Sponsor's knowledge, the final data point is collected from the last patient in the study. This is when the last patient dies, withdraws consent, completes all study assessments, or is lost to follow-up. Alternatively, the end of study is when the Sponsor decides to terminate the study.

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study early may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Overall patient enrollment is unsatisfactory.

The Sponsor will notify each Investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT Visit and Safety Follow-up Visit.

The Investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) of the early termination of the study.

At the end of study, any patients who, in the opinion of the Investigator, continue to benefit from tislelizumab or DKN-01 at study termination, will be offered the option to continue treatment in a company-sponsored clinical study until it is commercially available in the country of the patient's residence.

4. STUDY POPULATION

4.1. Number of Patients

Approximately 232 adult patients will be enrolled to ensure a minimum of 220 evaluable patients. Expected enrollment in each cohort as follows:

- Part A: Approximately 24 patients with treatment-naïve inoperable, locally advanced or metastatic G/GEJ adenocarcinoma will be enrolled to ensure 20 evaluable patients.
- Part B: Approximately 48 patients with previously treated inoperable, locally advanced or metastatic DKK1-high G/GEJ adenocarcinoma will be enrolled to ensure 40 evaluable patients.
- Part C: Approximately 160 patients with treatment-naïve inoperable, locally advanced or metastatic G/GEJ adenocarcinoma will be randomized and enrolled in 2 treatment groups to ensure 80 evaluable patients per treatment group.

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

In Part C, the enrollment assumptions will be monitored during the enrollment period; thus sample size and timeline could be adjusted accordingly.

4.2. Inclusion Criteria

Patients meeting all the following criteria will be considered eligible for study entry:

4.2.1. Part A and C only

1. No previous systemic therapy for inoperable, locally advanced or metastatic G/GEJ adenocarcinoma.

    a. Patients may have received prior neoadjuvant or adjuvant therapy as long as it was completed without disease recurrence for at least 6 months since last treatment.
    b. Patients in Part C may receive one cycle of chemotherapy (CAPOX or mFOLFOX6) during screening to avoid unnecessary delays in patient care, if deemed appropriate by the PI.

4.2.2. Part B only

2. Documented objective radiographic or symptomatic disease progression following first-line therapy with any platinum and/or fluoropyrimidine-based regimen for unresectable or metastatic disease.

    a. Patients may have received prior neoadjuvant or adjuvant therapy. If progression has occurred within 6 months from last dose of neoadjuvant or adjuvant treatment, this regimen will be considered as 1 line of therapy for advanced disease.

    b. Prior trastuzumab (or biosimilar) treatment is acceptable for patients with history of HER2-positive G/GEJ adenocarcinoma.

    c. Prior therapy with an anti-programmed cell death protein 1 (PD-1), anti-PD-L1 in any treatment setting (including adjuvant/neoadjuvant) is acceptable.

3. Documentation of elevated DKK1 mRNA expression in tumor cells from a fresh tumor biopsy (preferred) or archived tumor biopsy specimen. High DKK1 is defined as an H-score ≥35 in mRNA by ISH conducted in a Sponsor-designated central laboratory.

4.2.3. Part C only

4. Documentation of PD-L1 CPS by IHC and DKK1 mRNA expression in tumor cells by ISH from a fresh tumor biopsy (preferred) or archived tumor biopsy specimen conducted in a Sponsor designated central laboratory. If the central lab is unable to result a PD-L1 CPS score, historical CPS data can be used provided it was generated using either the 22C3 pharmDx, 28-8 pharmDx or SP263 assays.

4.2.4. General

5. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments.

6. Age ≥18 years on the day of signing the informed consent (exception: ≥19 years in the Republic of Korea) .

7. Histologically proven gastric adenocarcinoma or Siewert I-III GEJ adenocarcinoma.

8. At least one measurable lesion on radiographic imaging as defined by RECIST v1.1 (Appendix 4).

   a. A lesion in an area subjected to prior loco-regional therapy, including previous radiotherapy, is not considered measurable unless there has been demonstrated progression in the lesion since the therapy as defined by RECIST v1.1
   b. Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation and the previously irradiated lesion is not the only site of disease.

9. Tumor tissue for mandatory pre-treatment evaluation (fresh biopsy [preferred] or archived specimen).

10. ECOG performance status ≤1 within 7 days of first dose of study drug (Appendix 3).

11. Acceptable liver function:

   a. Parts A and B only
      i. Total bilirubin ≤2.0 times upper limit of normal (ULN). Total bilirubin must be <3 × ULN for patients with Gilbert's syndrome
      ii. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 times ULN (if liver metastases are present, then ≤5 × ULN is allowed).
   b. Part C only
      i. Total bilirubin ≤2.0 times upper limit of normal (ULN)
      ii. AST and ALT ≤2.5 times ULN

1. If liver metastases are present, then ≤5 × ULN is allowed (excluding Republic of Korea).

12. Acceptable renal function:

a. Serum creatinine ≤1.5 × ULN or estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration equation (Appendix 9).

13. Acceptable hematologic status (in the Republic of Korea patients must not have required blood transfusion or growth factor support within 14 days before sample collection at Screening for the following):

a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
b. Platelets:
   i. Part A and C only: ≥100 × 10^9/L
   ii. Part B only: ≥75 × 10^9/L
c. Hemoglobin ≥9 g/dL.

14. Acceptable coagulation status:

a. Prothrombin time/activated partial thromboplastin time ≤1.2 × ULN (unless receiving anticoagulation therapy, if receiving anticoagulation therapy, eligibility will be based upon international normalized ratio [INR]) see (b)(i) below
b. INR ≤1.5 (unless receiving anticoagulation therapy)
   i. 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 drugs).

15. Females of childbearing potential must be willing to use a highly effective method of birth control (Appendix 10) for the duration of the study, and for at least 6 months after the last dose of study drugs, and have a negative urine or serum pregnancy test within 7 days before first dose of study drugs.

16. Non-sterile males must be willing to use a highly effective method of birth control (Appendix 10) for the duration of the study and for at least 6 months after the last dose of study drugs

a. A sterile male is defined as one for whom azoospermia has been previously demonstrated in a semen sample examination as definitive evidence of infertility
b. Males with known "low sperm counts" (consistent with "sub-fertility") are not to be considered sterile for purposes of this study.

4.3. Exclusion Criteria

Patients meeting any of the following criteria are not eligible for study entry:

4.3.1. Part A and C only

1. Diagnosis of HER2-positive G/GEJ adenocarcinoma.

2. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, bariatric surgery procedures, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction (for those receiving CAPOX in Part C).

3. Prior therapy with an anti-programmed cell death protein 1 (PD-1) or anti-PD-L1 antibody.

4.3.2. Part B only

4. Systemic anti-cancer therapy (e.g., chemotherapy or immunotherapy) within 21 days prior to first dose of study drug.

4.3.3. General

5. Squamous cell or undifferentiated or other histological type of gastric cancer.

6. Prior therapy with an anti-PD-L2 or any other antibody or drug specifically targeting T-cell co-stimulation or co-inhibitory checkpoint pathways in any treatment setting (including adjuvant/neoadjuvant) or prior therapy with an anti-DKK1 agent. (Part B exception, see entry criterion 2c).

7. Active autoimmune diseases or history of autoimmune diseases that may relapse (refer to Appendix 5).

   a. Note: Patients with the following diseases are not excluded and may proceed to further screening:

      i. Controlled Type I diabetes

      ii. Hypothyroidism (provided it is managed with hormone replacement therapy only)

      iii. Controlled celiac disease

      iv. Skin diseases not requiring systemic treatment (e.g., vitiligo, psoriasis, alopecia)

      v. Any other disease that is not expected to recur in the absence of external triggering factors.

8. Any condition that required treatment with corticosteroids (≥10 mg per day prednisone or equivalent) or other immune suppressive drugs within the 14 days prior to first dose of study drug.

   a. Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded:

      i. Adrenal replacement steroid (dose ≤10 mg daily of prednisone or equivalent)

      ii. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption

      iii. Short course (≤7 days) of corticosteroid prescribed prophylactically (e.g., for contrast dye allergy) or for the treatment of a non-autoimmune condition (e.g.,

delayed-type hypersensitivity reaction caused by contact allergen).

9. Active leptomeningeal disease or uncontrolled brain metastases. Patients with equivocal findings or with confirmed brain metastases are eligible for the study provided that they are asymptomatic and radiologically stable without the need for corticosteroid treatment or seizure prophylaxis for ≥4 weeks before first dose of study drug.

10. Any active malignancy ≤2 years before first dose of study drug, with the exception of the specific cancer under investigation in this study and any locally recurring cancer that has been treated curatively (e.g., resected basal or squamous cell skin cancer, superficial bladder cancer, carcinoma in situ of the cervix or breast).

11. Uncontrolled diabetes or >Grade 1 laboratory test abnormalities in potassium, sodium, or corrected calcium despite standard medical management or ≥Grade 3 hypoalbuminemia within 14 days before first dose of study drug.

12. Uncontrollable pleural effusion, pericardial effusion, or ascites requiring frequent drainage within 7 days prior to first dose of study drug (the cytological confirmation of any effusion is permitted).

13. Clinically significant anorexia (CTCAE ≥Grade 2) within 7 days prior to first dose of study drug.

14. History of interstitial lung disease, non-infectious pneumonitis, pulmonary fibrosis, acute lung disease or uncontrolled systemic diseases.

a. Patients with radiation pneumonitis may be eligible for the study if the radiation pneumonitis has been confirmed as stable (beyond acute phase) without any concerns about recurrence. Patients with severe but stable radiation-induced pneumonitis may be required to undergo routine pulmonary function studies.

15. Severe chronic or active infections requiring systemic antibacterial, antifungal, or antiviral therapy, including tuberculosis infection within 14 days of first dose of study drug.

16. Prior allogeneic stem cell transplantation or organ transplantation.

17. History of severe hypersensitivity reactions to other monoclonal antibodies or any components of study treatment.

18. Known dihydropyrimidine dehydrogenase deficiency.

19. Any of the following cardiovascular risk factors:

a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living within 28 days before first dose of study drug

b. Pulmonary embolism within 28 days before first dose of study drug

c. Any history of acute myocardial infarction within 6 months before first dose of study drug

d. Any history of heart failure meeting New York Heart Association (NYHA) Classification III or IV (Appendix 6) within 6 months before first dose of study drug

e. Any event of ventricular arrhythmia ≥Grade 2 in severity within 6 months before

first dose of study drug

f. Any history of cerebrovascular accident within 6 months before first dose of study drug

g. Uncontrolled hypertension that cannot be managed by standard anti-hypertension medications within 28 days before first dose of study drug

h. Any episode of syncope or seizure within 28 days before first dose of study drug.

20. Fridericia-corrected QT interval >470 msec (female) or >450 (male), or history of congenital long QT syndrome. Any electrocardiogram (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.

21. Known to be human immunodeficiency virus (HIV) positive unless HIV ribonucleic acid (RNA) is undetected; known to have active hepatitis B (acute or chronic infection requiring antiviral treatment; hepatitis B surface antigen-positive) or have hepatitis C antibodies unless hepatitis C virus RNA is undetected/negative.

22. Serious nonmalignant disease or other circumstance that could compromise protocol objectives in the opinion of the Investigator and/or the Sponsor.

23. History of osteonecrosis of the hip or have 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 patients is not required.

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

25. History of gastrointestinal perforation and/or fistulae within 6 months prior to first dose of study drug, clinically significant bleeding from the gastrointestinal tract within 1 month prior to first dose of study drug, or clinically significant bowel obstruction (CTCAE ≥Grade 2).

26. Major surgery within 4 weeks of first dose of study drug.

27. Serious psychiatric or medical conditions that could interfere with treatment.

28. Toxicities (as a result of prior anticancer therapy) that have not recovered to baseline or stabilized, except for AEs not considered a likely safety risk (e.g., alopecia, neuropathy and specific laboratory abnormalities).

29. Administration of a live vaccine within 28 days before first dose of study drug.

a. Note: Seasonal vaccines for influenza or COVID vaccines are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.

30. Underlying medical conditions (including laboratory abnormalities) or alcohol or drug abuse or dependence that will be unfavorable for the administration of study drug, or affect the

explanation of drug toxicity or AEs, or result in insufficient or impaired compliance with study conduct.

31. Women who are pregnant or are breastfeeding.

32. Concurrent participation in another therapeutic clinical study.

    a. Note: Concurrent participation in observational or non-interventional studies is allowed. In addition, patients who have completed active treatment in a clinical study and are in the follow-up period can be enrolled in this study.

33. Treatment with radiation therapy within 14 days prior to first dose of study drug.

5. STUDY TREATMENTS

Study interventions are all pre-specified, investigational and non-investigational medicinal products, medical devices and other interventions (e.g., surgical and behavioral) intended to be administered to the study patients during the study conduct. Only the necessary and least invasive interventions are included.

5.1. Identity of Investigational Products, Packaging, and Handling

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 2ºC – 8ºC.

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

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. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for IV injection in a single-use vial (20R glass, United States Pharmacopeia type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in a single-use glass vial with a rubber stopper and capped by an aluminum flip-off seal cap.

The contents of the label will be in accordance with all applicable local regulatory requirements.

The study drug must be kept at the temperature condition as specified on the label.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the Tislelizumab Investigator's Brochure for other details regarding tislelizumab.

5.1.3. Oxaliplatin (Part A and C Only)

Patients will receive commercially or locally supplied oxaliplatin as part of institutional standard of care.

5.1.4. Capecitabine (Part A and C Only)

Patients will receive commercially or locally supplied capecitabine as part of institutional standard of care.

5.1.5. Leucovorin calcium (Part C Only)

Patients will receive commercially or locally supplied leucovorin calcium (folinic acid), per institutional standard of care.

5.1.6. Fluorouracil (Part C Only)

Patients will receive commercially or locally supplied fluorouracil as part of institutional standard of care.

5.2. Study Drug Administration

5.2.1. Dosing Schedules

The study treatment regimens for Part A and Part B are given in Table 8 (see also Figure 8, Figure 9, and Figure 10). The duration for each cycle is 21 days.

Table 8: Study Treatment Regimens – Part A and B only

Part	DKN-01	Tislelizumab	Oxaliplatin*	Capecitabine*
Part A	300 mg IV D1, D15	200 mg IV D1	130 mg/m^2 IV D1	1000 mg/m^{2}PO BID D1-D15
Part B1	300 mg IV D1, D15	200 mg IV D1	-	-
Part B2	600 mg IV D1, D15	200 mg IV D1	-	-

Abbreviations: BID = twice daily; D = day; IV = intravenously; PO = orally
* Standard regimen as supported by , or per institutional standard of care.

The study treatment regimens for Part C are given in Table 9. The duration for each cycle is 21 days (CAPOX; Figure 11) or 14 days (mFOLFOX6; Figure 12).

Table 9: Study Treatment Regimen – Part C only

The duration for each cycle is based on the chemotherapy regimen: CAPOX is 21 days and mFOLFOX6 is 14 days. The study regimens are as suggested below or per institutional standard practice:

Chemo Regimen	DKN-01	Tislelizumab	Oxaliplatin[1]	Capecitabine[1]	Leucovorin calcium[1, 6]	Fluorouracil[1]
Experimental Group						
CAPOX	600 mg IV D1[2]	200 mg IV D1 q 3 weeks	130 mg/m^2 IV D1	1000 mg/m^2 PO BID; D1-D15[3]	-	-
mFOLFO X6	400 mg IV D1[4]	400 mg IV D1 q 6 weeks[5]	85 mg/m^2 IV D1	-	400 mg/m^2 IV D1	400 mg/m2 IV bolus on D1 then 2400 mg/m2 IV continuous infusion over 48 hours D1 and D2
Control Group						
CAPOX	-	200 mg IV D1 q 3 weeks	130 mg/m^2 IV D1	1000 mg/m^{2}PO BID; D1-D15[3]	-	-
mFOLFO X6	-	400 mg IV D1 q 6 weeks[5]	85 mg/m^2 IV D1	-	400 mg/m^2 IV D1	400 mg/m2 IV bolus on D1 then 2400 mg/m2 IV continuous infusion over 48 hours D1 and D2

Abbreviations: BID = twice daily; D = day; IV = intravenously; PO = orally; q = every
[1] Standard dosing regimen per institutional standard of care.
[2] For **Cycle 1 only**, an additional loading dose of DKN-01 (600 mg, IV) will be administered on Day 15.
[3] A total of 28 doses from Day 1 through Day 15.
[4] For **Cycle 1 only**, an additional loading dose of DKN-01 (400 mg, IV) will be administered on Day 8.
[5] Administered every 6 weeks starting on C1D1 and continuing every third 14-day cycle (e.g., C4D1, C7D1, etc).
[6] If leucovorin is unavailable, 200 mg/m2 levo-leucovorin may be used. Study treatment may be administered without either agent if neither are available or per institutional standard of care.

5.2.1.1. DKN-01

DKN-01 will be administered IV without interruption over a minimum of 30 minutes and up to a maximum of 2 hours as per the Schedule of Assessments. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

5.2.1.2. Tislelizumab

Tislelizumab will be administered as per the Schedule of Assessments through an IV line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter. Specific instructions for product preparation and administration are provided in the Pharmacy Manual.

As a routine precaution, following the first 2 infusions of tislelizumab, patients must be monitored for at least 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, at least a 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The initial infusion (C1D1) will be delivered over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug.

5.2.1.3. Oxaliplatin – Part A and C only

Oxaliplatin will be administered IV as per the Schedule of Assessments according to institutional standard of care. Standard of care premedication for oxaliplatin will be given prior to DKN-01 and tislelizumab for the Part C experimental arm and prior to tislelizumab for the Part C control arm.

5.2.1.4. Capecitabine – Part A and C only

As per the Schedule of Assessments, the patient will administer capecitabine PO twice daily (BID) for a total of 28 doses per cycle according to institutional standard of care. Note: Capecitabine should be taken after food (within 30 minutes of a meal) with water (morning and evening) and at the same time each day (± 60 minutes).

Further, if a Part A or Part C patient is receiving clinical benefit from treatment with capecitabine without evidence of progressive disease and develops a compelling clinical reason after completion of Cycle 2 (e.g., unable to swallow pills) to discontinue the oral medication he/she may be considered for changing to intravenous 5-FU based therapy, after discussion with the Medical Monitor and per institutional standard of care.

Standard of care premedication for capecitabine will be given prior to study drug as necessary.

5.2.1.5. Leucovorin calcium and Fluorouracil – Part C only

Leucovorin calcium and fluorouracil will be administered IV as per the Schedule of Assessments according to institutional standard of care. Standard of care premedication for leucovorin calcium and fluorouracil will be given prior to DKN-01 and tislelizumab for the Part C experimental arm and prior to tislelizumab for the Part C control arm.

5.2.2. Order of Administration

In Part A, the order of IV administration will be DKN-01, tislelizumab, and then oxaliplatin. Capecitabine may be taken at any time on Day 1.

In Part B, DKN-01 will be administered first, followed by tislelizumab.

In Part C, the order of IV administration in the experimental group will be DKN-01, then tislelizumab followed by chemotherapy regimen thereafter.

- For patients receiving CAPOX, the order of IV administration will be DKN-01, tislelizumab, and then oxaliplatin. Capecitabine may be taken at any time on Day 1
- For patients receiving mFOLFOX6, the order of administration will be DKN-01, tislelizumab followed by chemotherapy (oxaliplatin, leucovorin, and fluorouracil will be given per institutional SOC guidelines)

In Part C, the order of IV administration in the control group will be tislelizumab followed by chemotherapy regimen thereafter.

- For patients receiving CAPOX, the order of IV administration will be tislelizumab then oxaliplatin. Capecitabine may be taken at any time on Day 1

- For patients receiving mFOLFOX6, the order of administration will be tislelizumab followed by chemotherapy (oxaliplatin, leucovorin, and fluorouracil will be given per institutional SOC guidelines).

5.2.2.1. Dose Delays

A dose delay is a deviation from prescribed dosing schedule (i.e., the drug is withheld beyond visit window). A dose interruption is an interruption of an infusion.

Every effort should be made to administer the study drug(s) according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines below. Dosing may also be delayed if laboratory parameters shown in Section 5.2.3 are not met. Reasons for dose modifications or delays, the supportive measures taken, and the outcome must be documented in the patient's chart and recorded in the eCRF.

The start of a new cycle may be delayed up to 42 days (for toxicities only; a delay may be more than 42 days for the management of irAEs up to a maximum of 12 weeks after approval from the Medical Monitor) to allow sufficient time for recovery from the previous cycle. Patients who do not recover from toxicity within 42 days (except for management of irAEs, which may require longer than 42 days) may be discontinued from the study and will undergo end of treatment procedures.

Specific treatment modifications to manage treatment-emergent drug reactions for DKN-01 and tislelizumab are described in Appendix 7 and Appendix 8. Specific treatment modifications to manage infusion-related reactions for DKN-01 and tislelizumab are described in Appendix 12 and Appendix 13. Infusion-related or hypersensitivity reactions to capecitabine, oxaliplatin leucovorin calcium, or fluorouracil should be managed per institutional standard of care.

A treatment delay at the start of a cycle (D1) 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 deviation.

For Part A and Part B: If the administration of study drug(s) can resume within ≤10 days, it should be administered in the current cycle. If the study drug needs to be withheld for >10 days, it should be omitted from the current cycle and administration should continue at the start of the next cycle.

5.2.2.1.1. DKN-01 Dose Delays

DKN-01 treatment may be temporarily suspended if the patient experiences a toxicity that is considered related to DKN-01 and requires a dose to be withheld (see Appendix 7). DKN-01-related toxicities must be resolved to baseline or Grade 1 (whichever is more severe) prior to administering the next dose, except for alopecia or ≤Grade 2 fatigue or neuropathy.

5.2.2.1.2. Tislelizumab Dose Delays

Tislelizumab treatment may be temporarily suspended if the patient experiences a toxicity that is considered related to tislelizumab and requires a dose to be withheld. Tislelizumab treatment should resume as soon as possible after the AEs recover to baseline or Grade 1 (whichever is more severe) and within 12 weeks after last dose of tislelizumab. If the patient is not able to

resume tislelizumab ≤12 weeks after the last dose, continued treatment may be allowed if approved by the Medical Monitor.

5.2.2.1.3. Chemotherapy Dose Delays (Part A and Part C only)

Chemotherapy-related toxicities must be resolved to baseline or Grade 1 (whichever is more severe) prior to administering the next dose, except for alopecia or ≤Grade 2 fatigue or neuropathy.

If chemotherapy-related toxicities warrant a dosing delay, chemotherapy administration may restart as soon as is feasible. For example, chemotherapy administration can occur during an unscheduled visit and resynchronize with tislelizumab and DKN-01 at subsequent cycle(s), if possible. Dosing intervals of subsequent cycles of tislelizumab and DKN-01 may be shortened or extended as clinically feasible to allow for resynchronization, but the time between 2 consecutive doses of tislelizumab should be at least 10 days (Parts A, B, and C-CAPOX regimen only) and 28 days (Part C-mFOLFOX6 regimen only) and for DKN-01 should be at least 7 days. If clinically appropriate, the Investigator may delay all treatment components up to a maximum of 7 days to allow synchronized administration of all agents and realigned dosing of treatment cycles according to the original schedule.

5.2.2.2. Dose Adjustments

5.2.2.2.1. DKN-01 Dose Adjustments

Once a patient recovers from DKN-01-related toxicities (see Appendix 7) as described in Section 5.2.2.1.1 and meets guidelines in Section 5.2.3, dosing may resume based on the guidelines in Table 10, Table 11, Table 12, Table 13, Table 14, and Table 15.

Table 10: DKN-01 Dose Adjustments for Parts A and B1

Toxicity Occurrence	DKN-01
First[1]	• Restart at 300 mg after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Second	• Restart at reduced dose of 150 mg after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Third	• Restart at reduced dose of 75 mg after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe). Confer with Medical Monitor.
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 11: DKN-01 Dose Adjustments for Part B2

Toxicity Occurrence	DKN-01
First[1]	• Restart at 600 mg after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Second	• Restart at reduced dose of 300 mg after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Third	• Restart at reduced dose of 150 mg after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe). Confer with Medical Monitor.
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 12: DKN-01 Dose Adjustments for Part C (experimental arm)

Toxicity Occurrence	DKN-01
First[1]	• Restart at 400 mg or 600 mg (depending upon starting dose) after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Second	• Restart at reduced dose of 300 mg after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Third	• Restart at reduced dose of 150 mg after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe). Confer with Medical Monitor.
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.

If, in the opinion of the Investigator, a Part A patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab plus CAPOX but has a compelling clinical reason after completion of Cycle 2 to discontinue oxaliplatin, capecitabine, and/or tislelizumab treatment, the patient will be permitted to continue in the study with DKN-01 monotherapy or any combination of DKN-01 + other study drugs (e.g., oxaliplatin, capecitabine and/or tislelizumab) at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part B patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab but has a compelling clinical reason after completion of Cycle 2 to discontinue tislelizumab treatment, the patient will be permitted to continue in the study with DKN-01 monotherapy at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part C (experimental arm only) patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab plus CAPOX/mFOLFOX6 but has a compelling clinical reason after completion of Cycle 2 to

discontinue one or several of the combination agents, e.g., oxaliplatin, capecitabine, leucovorin calcium, fluorouracil, DKN-01, and/or tislelizumab treatment, the patient will be permitted to continue in the study provided at least one of the agents is continued and no new systemic therapies are added at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part C (control arm only) patient is receiving clinical benefit from treatment with the combination tislelizumab plus CAPOX/mFOLFOX6 but has a compelling clinical reason after completion of Cycle 2 to discontinue one or several of the combination agents, e.g., oxaliplatin, capecitabine, leucovorin calcium, fluorouracil, and/or tislelizumab treatment, the patient will be permitted to continue in the study provided at least one of the agents is continued and no new systemic therapies are added at the discretion of the treating clinician, after discussion with the Medical Monitor.

5.2.2.2.2. Tislelizumab Dose Adjustments

There will be no dose reduction for tislelizumab in this study.

If, in the opinion of the Investigator, a Part A patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab plus chemotherapy regimen (CAPOX) but has a compelling clinical reason after completion of Cycle 2 to discontinue oxaliplatin, capecitabine, and/or tislelizumab treatment, the patient will be permitted to continue in the study with DKN-01 monotherapy or any combination of DKN-01 + other study drugs (e.g., oxaliplatin, capecitabine and/or tislelizumab) at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part B patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab but has a compelling clinical reason after completion of Cycle 2 to discontinue tislelizumab treatment, the patient will be permitted to continue in the study with DKN-01 monotherapy at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part C (experimental arm only) patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab plus CAPOX/mFOLFOX6 but has a compelling clinical reason after completion of Cycle 2 to discontinue one or several of the combination agents, e.g., oxaliplatin, capecitabine, leucovorin calcium, fluorouracil, DKN-01, and/or tislelizumab treatment, the patient will be permitted to continue in the study provided at least one of the agents is continued and no new systemic therapies are added at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part C (control arm only) patient is receiving clinical benefit from treatment with the combination tislelizumab plus CAPOX/mFOLFOX6 but has a compelling clinical reason after completion of Cycle 2 to discontinue one or several of the combination agents, e.g., oxaliplatin, capecitabine, leucovorin calcium, fluorouracil, and/or tislelizumab treatment, the patient will be permitted to continue in the study provided at least one of the agents is continued and no new systemic therapies are added at the discretion of the treating clinician, after discussion with the Medical Monitor.

5.2.2.2.3. Chemotherapy Dose Adjustments (Part A and Part C)

Dose modifications for chemotherapy should be performed per applicable local prescribing information and per local practice according to the Investigator's clinical judgment. Recommended dose modifications for key chemotherapy toxicities are outlined in Table 13 and Table 14. These serve as guidelines and do not replace Investigator judgment and applicable local label recommendations if more stringent. Baseline body weight is used to calculate the required chemotherapy doses. Dose modifications are required if the patient's body weight changes by ≥10% from baseline or according to institutional standards. Chemotherapy doses should not be modified for any body weight change of < 10%.

Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the treatments. If, in the opinion of the Investigator, the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications.

Study drug-related toxicities must be resolved to baseline or Grade 1 (whichever is more severed) prior to administering the next dose, except for alopecia or ≤Grade 2 fatigue or neuropathy.

Table 13: Capecitabine Dose Adjustments (Part A and Part C)[2]

Toxicity Occurrence	Capecitabine
First[1]	• Restart at 1000 mg/m^2 after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Second	• Restart at reduced dose of 750 mg/m^2 after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Third	• Restart at reduced dose of 500 mg/m^2 after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Fourth	• Discontinue

[1]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. [2] dose reductions may be performed per institutional guidelines

Table 14: Oxaliplatin Dose Adjustments (Part A and Part C)[2]

Toxicity Occurrence	Oxaliplatin
First[1]	• Restart at 130 mg/m^2 (CAPOX) or 85 mg/m2 (mFOLFOX6) after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Second	• Restart at reduced dose of 100 mg/m^2 (CAPOX) or 70 mg (mFOLFOX6) after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Third	• Restart at reduced dose of 70 mg/m^2 (CAPOX) or 55 mg (mFOLFOX6) after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).

[1]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. [2] dose reductions may be performed per institutional guidelines

Table 15: Fluorouracil Dose Adjustments (Part C)[2]

Toxicity Occurrence	Fluorouracil
First[1]	• Restart at 1200 mg/m^2/day after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Second	• Restart at reduced dose of 900 mg/m^2/day after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).
Third	• Restart at reduced dose of 750 mg/m^2/day after toxicity resolves to ≤Grade 1 or baseline grade (whichever is more severe).

[1]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 Medical Monitor to consider a one dose reduction level with the first occurrence of toxicity. [2] dose reductions may be performed per institutional guidelines

If, in the opinion of the Investigator, a Part A patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab plus chemotherapy regimen (CAPOX) but has a compelling clinical reason after completion of Cycle 2 to discontinue oxaliplatin, capecitabine, and/or tislelizumab treatment, the patient will be permitted to continue in the study with DKN-01 monotherapy or any combination of DKN-01 + other study drugs (e.g., oxaliplatin, capecitabine and/or tislelizumab) at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part B patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab but has a compelling clinical reason after completion of Cycle 2 to discontinue tislelizumab treatment, the patient will be permitted to continue in the study with DKN-01 monotherapy at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part C (experimental arm only) patient is receiving clinical benefit from treatment with the combination of DKN-01 plus tislelizumab plus CAPOX/ mFOLFOX6 but has a compelling clinical reason after completion of Cycle 2 to discontinue one or several of the combination agents, e.g., oxaliplatin, capecitabine, leucovorin calcium, fluorouracil, DKN-01, and/or tislelizumab treatment, the patient will be permitted to continue in the study provided at least one of the agents is continued and no new systemic therapies are added at the discretion of the treating clinician, after discussion with the Medical Monitor.

If, in the opinion of the Investigator, a Part C (control arm only) patient is receiving clinical benefit from treatment with the combination tislelizumab plus CAPOX/mFOLFOX6 but has a compelling clinical reason after completion of Cycle 2 to discontinue one or several of the combination agents, e.g., oxaliplatin, capecitabine, leucovorin calcium, fluorouracil, and/or tislelizumab treatment, the patient will be permitted to continue in the study provided at least one of the agents is continued and no new systemic therapies are added at the discretion of the treating clinician, after discussion with the Medical Monitor.

Further, if a Part A or C (CAPOX arm) patient is receiving clinical benefit from treatment with capecitabine without evidence of progressive disease and develops a compelling clinical reason after completion of Cycle 2 (e.g., unable to swallow pills) to discontinue the oral medication he/she may be considered for changing to intravenous 5-FU based therapy, after discussion with the Medical Monitor and per institutional standard of care.

5.2.3. Criteria for Retreatment

5.2.3.1. Criteria for Initiation of a New Treatment Cycle

Prior to initiating a new cycle including Cycle 1, patients must meet the following criteria:

- ANC resolved to baseline grade or ≤Grade 1 (≥1.5 × 10^9/L)
- Part A: Platelet count ≥100 × 109/L
- Part B: Platelet count ≥75 × 109/L
- Part C:
    - Patients receiving chemotherapy during screening are permitted to dose on Cycle 1 Day 1 and subsequent cycles (CxD1) with a platelet count of ≥75 × 10^9/L
    - Patients not receiving chemotherapy during screening are permitted to dose at Cycle 1 Day 1 with a platelet count of ≥100 × 10^9/L. Retreatment is permitted in subsequent cycles (CxD1) with a platelet count of ≥75 × 10^9/L
- Creatinine clearance >30 ml/min
- Liver-associated biochemical abnormalities resolved to ≤Grade 1 or baseline grade
- Any other drug-related AEs that may have occurred resolved to ≤Grade 1 severity or baseline grade except for alopecia or ≤Grade 2 fatigue or neuropathy.

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.

5.2.3.2. Criteria for DKN-01 Treatment on Day 8 or Day 15 of a Treatment Cycle

Treatment may be administered on D8 or D15 for patients meeting the following criteria:

- ANC ≥1.0 × 10^9/L
- Platelet count ≥75 × 10^9/L
- Liver-associated biochemical abnormalities resolved to ≤Grade 1 or baseline grade
- Any other drug-related AEs that may have occurred resolved to ≤Grade 1 severity or baseline grade except for alopecia or ≤Grade 2 fatigue or neuropathy.

5.3. Prior and Concomitant Therapy

Most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the Investigator for supportive care (e.g., antiemetics, antidiarrheals, blood components, bisphosphonates, growth factor support) and in a patient's interest are allowed. Opiates and other medication required for palliative management of patients are allowed. Patients must notify the Investigator of all concurrent medications used during the study.

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.

5.3.1. Systemic Corticosteroids

Systemic corticosteroids given for the control of irAEs must be tapered gradually (see Appendix 8) and be at non-immunosuppressive doses (≤10 mg/day of prednisone or equivalent) before the next tislelizumab administration. The short-term use of steroids as prophylactic treatments (e.g., patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

5.3.2. Radiation Therapy

Palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline provided the following criteria are met:

- Repeat imaging demonstrates no new sites of bone metastases
- The lesion being considered for palliative radiation is not a target lesion for RECIST v1.1
- The case is discussed with the Medical Monitor, and the Medical Monitor agrees that the conditions required to receive palliative radiation are met.

Additionally, palliative radiation or other focally ablative therapy for other non-target sites of the disease is permitted if clinically indicated per Investigators' discretion. The Medical Monitor should be informed of the on-study radiotherapy. These patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease.

Administration of palliative radiation therapy will be considered progression for the purposes of determining PFS.

It is not required to withhold study drugs tislelizumab or DKN-01 treatment during palliative radiotherapy.

5.3.3. Prohibited Concomitant Medications/Procedures

Live vaccines within 28 days before first dose of study drug and within 60 days after the last dose of study drug(s) are prohibited.

The following medications are prohibited during Screening and through the End-of-Treatment visit:

- Any concurrent anticancer therapy, including chemotherapy (except Part C 1 cycle allowed during screening), hormonal therapy, immunotherapy, standard anticancer agents, or investigational anticancer agents
- Herbal remedies for the treatment of cancer or patent medicines with approval from the local health authority for use as anticancer treatment (regardless of cancer type)
- Herbal remedies with immune-stimulating properties (e.g., mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (e.g., hypericin).

There are medications prohibited depending on the chemotherapy regimen that is dosed (Part A and C only). Please refer to the package insert for each approved chemotherapy agent used for these guidelines.

Patients must notify the Investigator of all herbal remedies used during the study.

5.3.4. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE)
- Systemic corticosteroids >10 mg daily (prednisone or equivalent), except to treat or control a drug related AE (per protocol) or for short-term use as prophylactic treatment
- Abuse of alcohol or other drugs during the study
- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored
- Radiation therapy, except for palliative radiation therapy described in Section 5.3.2.

There are medications prohibited depending on the chemotherapy regimen that is dosed (Part A and C only). Please refer to the package insert for each approved chemotherapy agent used for these guidelines.

5.4. Blinding

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

5.5. Randomization

For Part C of the study, patients will be assigned to receive either DKN-01 in combination with tislelizumab and chemotherapy regimen (CAPOX or mFOLFOX6) or tislelizumab in combination with chemotherapy regimen (CAPOX or mFOLFOX6) using a central stratified block randomization scheme, with the following stratification factors:

- DKK1 RNAscope TPS (≥20% vs <20%)
- PD-L1 immunohistochemistry CPS (≥5 vs <5).

Randomization may occur up to 3 calendar days prior to C1D1. The EDC (Electronic Data Capture) system will be used to assign patients to either the experimental group or the control group in lieu of a separate IRT (Interactive Response Technology) system. Detailed instructions for assigning treatment will be provided in the eCRF completion guidelines. The randomization block size will be defined in the EDC system.

5.6. Assessment of Treatment Compliance

All study drug (except capecitabine; Part A and Part C) 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.

5.6.1. Study Treatment Diary

The patient will be requested to maintain a dosing diary of each dose of capecitabine (Part A and Part C only). The dosing diary will be returned and reviewed by the site staff at each clinic visit.

6. STUDY ASSESSMENTS AND PROCEDURES

A table of scheduled study assessments is provided in Appendix 1. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented in the medical record for each patient.

Dosing will occur only if the clinical assessment and local laboratory test values (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines (Section 5.2.3).

6.1. General Considerations

Study procedures and their timing are summarized in the Schedule of Activities (Appendix 1). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

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. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to enrollment (C1D1) may be used for the purposes of screening rather than repeating the standard-of-care tests.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities (Appendix 1).

Only necessary and the least invasive assessments are included. Where applicable, patients must be warned that they may experience pain or discomfort.

6.1.1. Visit Windows

All visits must occur within ± 3 calendar days from the scheduled date, unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment infusion/dose unless otherwise noted. Laboratory results are required to be reviewed prior to dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other justifiable event, the visit should be scheduled on the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule from the preceding cycle. Note: tumor imaging should be conducted every 6 weeks based on the

date of C1D1 until week 24 where imaging is then conducted every 9 weeks on the same schedule.

6.1.2. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the Investigator's request and may include vital signs/focused physical examination; ECG; ECOG performance status; AE review; concomitant medications and procedures review; radiographic assessments; disease related constitutional symptoms; and laboratory and biomarker assessments (see Appendix 1). The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on the Investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

6.2. Screening and Eligibility

6.2.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures. Informed consent forms for all patients, including those who fail screening, will be maintained at the study site. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to enrollment (C1D1) may be used for the purposes of screening rather than repeating the standard-of-care tests.

Note: To avoid unnecessary delays which could impact patient care, during the Screening Period patients who in the opinion of the Investigator are unable to wait more than 2 weeks to start treatment, may receive one cycle of chemotherapy (CAPOX or mFOLFOX6) prior to randomization while awaiting biomarker results. Patients meeting these requirements should be discussed with the Medical Monitor.

Once DKK1 and PD-L1 results from the central lab are received and the patient has been confirmed to meet all other eligibility requirements, the patient will be randomized to receive either DKN-01 in combination with tislelizumab and chemotherapy (CAPOX or mFOLFOX6) or tislelizumab in combination with chemotherapy (CAPOX or mFOLFOX6). The chemotherapy regimen administered during Screening must be equivalent to that following randomization.

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 treatment eligibility. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.2.2. Demographics, Medical History, 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 sex, race/ethnic origin, and year of birth. Information on significant medical and surgical history

including dates, outcome, and if these are 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 (including paracenteses), 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 30 days of the initial Screening visit will be recorded.

Any clinically significant findings on screening assessments (physical examination, vital signs, ECG) prior to first dose of study treatment will be recorded in medical history.

The medical history will be reviewed prior to dosing on C1D1 to assess continued treatment 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 if any changes have occurred since the previous study visit.

6.2.3. Prior and 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.

6.3. Safety Assessments

Refer to Section 7 for additional details on safety monitoring, including AE reporting.

6.3.1. Physical Examination

A complete physical examination (general appearance, head/ears/eyes/nose/throat, lungs/chest, heart, abdomen, lymph nodes, musculoskeletal, extremities, and neurological examination) will be conducted at the time points designated in Appendix 1. 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 Appendix 1 to address any complaints or concerns verbalized by the patient at all other study visits.

Any clinically significant abnormalities following the first dose of study treatment should be documented as AEs.

6.3.2. Vital Signs and Weight

Vital signs are to be measured at the time points designated in Appendix 1. Vital signs to be measured include systolic and diastolic blood pressure (mmHg; measured in the same arm), temperature (°C), pulse (bpm), and respiration rate (breaths/minute).

Weight will be measured at Screening, on Day 1 of each treatment cycle, and at the end-of-treatment 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.

Any clinically significant abnormalities following the first dose of study treatment should be documented as AEs.

6.3.3. Electrocardiograms

A 12-lead ECG will be obtained at the time points designated in Appendix 1. 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 the patient signs the informed consent, 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.

Any clinically significant abnormalities following the first dose of study treatment should be documented as AEs.

6.3.4. Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group Performance Status (Oken, Creech et al. 1982) will be determined at the time points designated in Appendix 1.

6.3.5. Safety Laboratory Evaluations

Routine clinical laboratory evaluations will be performed locally by a certified laboratory selected for the study (see Appendix 2). 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 5.2.3 for laboratory criteria required to initiate a new treatment cycle and for subsequent study drug doses within a cycle.

Clinical laboratory evaluations are to be performed at the time points designated in Appendix 1. Final clinical laboratories are to be performed at the safety follow-up 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. Any clinically significant abnormalities should be documented as AEs.

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.

6.3.6. Ophthalmic Examinations (Korea only)

Eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) will be assessed for patients enrolled in the Republic of Korea at the timepoints specified in Appendix 1.

6.3.7. Pulmonary Function Tests (Korea only)

For those patients with radiation pneumonitis enrolled in the Republic of Korea, pulmonary function tests are to be performed at the timepoints specified in Appendix 1.

6.3.8. Thyroid and Pancreatic Tests (Korea only)

Free (FT3) triiodothyronine, free (FT4) thyroxine, amylase and lipase tests will be assessed for patients enrolled in the Republic of Korea at the timepoints specified in Appendix 1.

6.4. Tumor Response Evaluations

Tumor imaging will be performed within 28 days (35 days for Part C) before the first dose of study drug. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to first dose may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 6 weeks (± 7 days) from C1D1 for the first 24 weeks, and then every 9 weeks (± 7 days) after 24 weeks based on RECIST v1.1 (Appendix 4). If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted on the planned schedule.

Screening assessments and each subsequent assessment of the tumor must include computed tomography (CT) scans of chest, abdomen, and pelvis with oral/IV contrast, unless contraindicated. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc.). See below if patient has contraindication to CT contrast media.

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at Screening is required to be used throughout the study (e.g., the same contrast protocol for CT scans).

- Imaging of the brain (preferably MRI) at baseline is required for all screened patients. Screening evaluations will be performed within 28 days (35 days for Part C) prior to first dose
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast enhanced MRI (if possible) of abdomen and pelvis should be performed
- If a CT scan for tumor assessment is performed on a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan
- Bone scans (Technetium-99m [Tc-99m]) or PET should be performed at Screening if clinically indicated. If bone metastases are present at Screening and cannot be seen

on CT or MRI scans, Tc-99m or PET bone scans should be repeated when a CR is suspected in target lesion or when progression in bone is suspected

- CT scans of the neck or extremities should be performed at Screening only if clinically indicated and should be followed throughout the study if there is evidence of metastatic disease in these regions at Screening
- At the Investigator's discretion, other methods of assessment of target lesion and nontarget lesions per RECIST v1.1 may be used.

After first documentation of response (CR or PR), confirmation of tumor response should occur at a minimum of 4 weeks after the first response or at the next scheduled assessment time point. Radiological images will be read locally and then sent to a central imaging vendor (Part C only). The Sponsor may have a central imaging vendor perform an independent evaluation of some or all of the radiological images in Part C. More information can be found in the Imaging Manual.

For immune therapies such as tislelizumab, pseudo progression may occur due to immune cell infiltration and other mechanisms leading to an apparent increase of existing tumor masses or appearance of new tumor lesions. Also, some patients may benefit from additional immune therapies despite evidence of disease progression. The following criteria must be met in order to treat patients with suspected pseudo progression or confirmed evidence of disease progression:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values)
- Stable ECOG performance status ≤1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer. Patients must be informed that they may be forgoing treatment that has shown benefit by continuing treatment beyond progression
- The decision to continue study drug(s) beyond initial Investigator-assessed progression must be agreed with the Sponsor Medical Monitor and documented in the study records.

Tumor assessment should continue as planned in patients receiving study drug(s) beyond initial Investigator-assessed progression. Tumor assessment in such patients should continue until study treatment discontinuation.

Patients who discontinue study treatment early for reasons other than disease progression (e.g., toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer treatment, experiences disease progression, withdraws consent, is lost to follow-up, dies, or until the study terminates, whichever occurs first.

Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held. That is, they should not be adjusted for delays in cycles.

Tumor response and progression will also be assessed using the Immune-related Response Criteria, 2017 (iRECIST) for any patients continuing treatment after the initial assessment of progressive disease using RECIST 1.1(Seymour, Bogaerts et al. 2017).

Patients should have the same radiographic imaging modality used throughout the study (at baseline and at subsequent assessments) in order to provide uniformity to radiographic assessments.

6.5. 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 Period until radiographically documented PD. During this PD Follow-up Period, efficacy assessments for disease response and PD per RECIST v1.1 will be performed every 12 weeks (± 14 days) (see Appendix 1). After discontinuation of treatment and documentation of PD, all patients will be followed in the Survival Follow-up Period 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 3 months [± 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 anticancer therapies. If a female patient is of childbearing potential, she will be followed monthly with a urine pregnancy test up to 6 months following the last dose of study drug. This testing can occur at with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.

6.6. Pharmacokinetics, Pharmacodynamics, and Biomarker Analyses

Blood samples are to be collected for PK, pharmacodynamics, and scientific analyses, as indicated in the following subsections and at the time points designated in Appendix 1. After processing of the samples for the protocol-specified assays, any remaining biological material (whole blood, serum, plasma) is to be stored for future scientific analyses, as deemed appropriate.

Details of sample collection and processing can be found in the Laboratory Manual.

6.6.1. Blood Sample Collection for Biomarker (Proteome) Analysis

Serum and plasma blood samples will be collected for a scientific biomarker (proteome) analysis at the time points designated in Appendix 1.

6.6.2. 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 Appendix 1. Free serum DKK1 levels may be estimated.

Serum levels of DKK1 will be measured using a validated enzyme-linked immunosorbent assay, designed to perform in the presence of DKN-01.

6.6.3. Circulating Tumor DNA

Blood samples for circulating tumor DNA (ctDNA) analysis will be collected pre-dose at baseline and at time of relapse (see Appendix 1). Change from baseline in ctDNA post-treatment may be determined.

6.6.4. Pharmacokinetic Samples

Blood samples will be collected for the assessment of serum DKN-01 and tislelizumab concentrations at the time points designated in Appendix 1. 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.

Serum samples will be assayed for tislelizumab concentration with use of a validated immunoassay.

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 15 years following study closure.

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

6.6.5. Antidrug Antibodies

DKN-01 or tislelizumab may elicit an immune response. Patients with signs of any potential immune response to DKN-01 or tislelizumab will be closely monitored. Validated screening and confirmatory assays will be employed to detect ADAs at multiple time points throughout the study (see Appendix 1). The immunogenicity evaluation will utilize a risk-based immunogenicity strategy (Rosenberg and Worobec 2004, Worobec and Rosenberg 2004, Koren, Smith et al. 2008) to characterize ADA responses to DKN-01 or tislelizumab in support of the clinical development program. This tiered strategy will include an assessment of whether ADA responses correlate with relevant clinical endpoints. Implementation of ADA characterization assays will depend on the safety profile and clinical immunogenicity data.

The following assessment will be performed at a central laboratory:

- ADA assays: serum samples will be tested for the presence of ADAs to DKN-01 or tislelizumab using a validated immunoassay.

Shipping, storage, and handling of samples for the assessment of DKN-01 or tislelizumab ADA assays will be managed through a central laboratory. Instruction manuals and supply kits will be provided for all central laboratory assessments.

For patients who experience an infusion-related reaction to DKN-01 (see Appendix 12), 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 pharmacodynamic markers.

If a patient has known positive ADA (to DKN-01 or tislelizumab) at the EOT visit, he or she should have repeat testing, where feasible, performed in the PD Follow-up Period and/or Survival Follow-up Period until the patient is no longer positive.

6.6.6. Tumor Biopsy Samples

A tumor sample (fresh biopsy [preferred] or archived specimen) will be obtained from all patients during Pre-screening (Part B only) and Screening and will be sent to the Sponsor-designated central laboratory.

For Part B, the biopsy sample (fresh biopsy [preferred] or archival) collected during the Pre-Screening period will be used to confirm elevated DKK1 mRNA levels required to meet eligibility criteria for enrollment. A fresh biopsy will be collected during the Screening period from patients who did not undergo a biopsy during the Pre-screening period for evaluation of DKK1 mRNA levels (unless it is clinically contraindicated per Investigator and after consultation with the Medical Monitor) for a retrospective DKK1 mRNA analysis.

For all Part A patients and Part B patients with fresh biopsies, the patient's biopsy sample obtained during the Screening Period will be sent to the Sponsor-designated central laboratory for retrospective evaluation of DKK1 expression.

All DKK1 testing will be conducted with a proprietary CISH assay using RNAscope technology at Flagship Biosciences, Inc. Westminster, CO, a CAP-accredited and Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. For Part C, PD-L1 expression will also be conducted by Flagship Biosciences. If the central lab is unable to result a PD-L1 CPS score, historical CPS data can be used provided it was generated using either the 22C3 pharmDx, 28-8 pharmDx or SP263 assays.

For both Parts A and B, PD-L1 expression will be retrospectively assessed and if sufficient tumor biopsy tissue is available. In Part A, B, and C, scientific analysis, including microsatellite status (e.g., microsatellite stable MSS, microsatellite instability-low [MSI-L] or microsatellite instability-high [MSI-H]), genomic profiling, RNA profiling (e.g., RNA-Seq), immunohistology, Epstein Barr virus (EBV), infiltrating immune cells by IHC, and additional IHC analyses may be performed.

For Part C patients, DKK1 testing and PD-L1 expression will be prospectively analyzed to permit stratification prior to randomization. DKK1 expression will be assessed using a Tumor Percentage Score (TPS). TPS has demonstrated significant correlation with H-score in retrospective analysis.

For Part C patients, an on-treatment biopsy is required if clinically feasible at Day 21 (+ 7 days). If possible, this should come from the same lesion used for the screening analysis. If the original lesion is no longer measurable, then a biopsy from another lesion is acceptable. Additional tumor tissue collected at any time during the study per standard of care may be submitted to the central laboratory for evaluation. Any on-treatment biopsy tissue will be sent to the Sponsor-designated central laboratory for evaluation of DKK1 expression and other biomarkers of interest.

An additional biopsy to evaluate the effects of treatment on the tumor tissue may be collected at any time during the study if a repeat biopsy is required clinically and the patient consents to the biopsy.

Shipping, storage, and handling of archival tumor, fresh tumor, and leftover tumor tissue for the assessment of tumor biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling.

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.

6.6.7. Biomarkers

Blood samples for scientific analysis relevant to DKN-01 and/or the study indication will be collected at the time points specified in Appendix 1.

Samples may be stored for a maximum of 15 years following last patient visit for the study at a facility selected by the Sponsor.

Shipping, storage, and handling of blood samples for the assessment of biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling.

7. SAFETY MONITORING AND REPORTING

The Investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

7.1. Risks Associated with Study Drug

7.1.1. Risks Associated with Tislelizumab

Tislelizumab is an investigational agent that is currently in clinical development. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and published data on other molecules within the same biologic class.

The PD-L1/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of irAEs, specifically the induction or enhancement of autoimmune conditions.

Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested evaluation and management guidelines for suspected irAEs are provided in Appendix 8.

7.1.2. Risks Associated with DKN-01

DKN-01 is a potent, humanized monoclonal antibody that is currently in clinical development. The following recommendation is based on results from nonclinical and clinical studies with DKN-01 and published data on other molecules within the same biologic class.

Specific treatment modifications to manage treatment-emergent drug reactions for DKN-01 and tislelizumab are described in Appendix 7 and Appendix 8. Specific treatment modifications to manage infusion-related reactions for DKN-01 and tislelizumab are described in Appendix 12 and Appendix 13.

Refer to Section 1.6 for a benefit-risk assessment.

7.2. General Plan to Manage Safety Concerns

7.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with tislelizumab, as well as the nonclinical/clinical data from other PD-L1/PD-1 inhibitors, were considered. Specifically, patients at risk for study-emergent active autoimmune diseases or with a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live vaccine within 28 days before first dose of study drug are excluded from the study. Patients with contraindications for DKN-01, capecitabine, oxaliplatin, or fluorouracil treatment are also excluded from the study (see Section 4 for the full list of exclusion criteria).

7.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE v5.0. Patients will be evaluated clinically and with standard laboratory tests at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs (see Table 16), physical examinations, laboratory measurements (hematology, chemistry, etc.), and other assessments including those listed in Section 6.3. In addition, patients will be closely monitored for the development of any signs or symptoms of infections or autoimmune conditions.

At the start of each cycle, study drug(s) will only be administered after clinical laboratory results have been reviewed. Administration of study drug(s) will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (see Section 5.2).

Serum samples will be drawn for determination of ADA to tislelizumab and DKN-01.

Investigators are instructed to report all AEs (including pregnancy-related AEs).

7.2.3. Safety Review Team

A safety review team (SRT) will be formed to monitor the safety of patients throughout the study on an ongoing basis and to determine whether to continue dosing and enrollment or to suggest modifications to the study design to ensure the welfare of patients.

The SRT will meet after the first 5 patients in Part A as well as after the first 5 patients in Part B1 and the first 5 patients in Part B2 have completed the first cycle of study treatment, regularly, and on an ad hoc basis to discuss any emergent study-related safety issues. For Part C, a review by the SRT will occur after the first 5 patients on each chemotherapy regimen (CAPOX and mFOLFOX6) have completed Cycle 1 from both the experimental group (i.e., DKN-01 in combination of tislelizumab and chemotherapy regimen) and the control group (i.e., tislelizumab and chemotherapy regimen). Enrollment will continue during the safety data review without pause.

7.3. Adverse Events

7.3.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of AEs include:

- Worsening of a chronic or intermittent preexisting condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- Detection or diagnosis of a new condition after study drug administration, even though the condition may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE).

When an AE or SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The Investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the Sponsor.

7.3.2. Assessment of Severity

The Investigator will assess the severity of each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v5.0.

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting selfcare ADL
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE.

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (e.g., grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities as described in Section 7.6.2.

7.3.3. Assessment of Causality

The Investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The Investigator should consult the DKN-01 Investigator’s Brochure or Tislelizumab Investigator’s Brochure in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the Investigator has only limited information to include in the initial report to the Sponsor. However, it is very important that the Investigator always assesses causality for every SAE prior to transmission of the SAE report to the Sponsor, because the causality assessment is one of the criteria used when determining

regulatory reporting requirements. The Investigator may subsequently change his/her opinion of causality considering follow-up information and may amend the SAE report accordingly.

The causality of each AE should be assessed and classified by the Investigator as "related" or "not related" based on all information available at the time of reporting. An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (i.e., there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility
- An AE should be considered "related" to study drug if any of the following criteria are met, otherwise the event should be assessed as "not related":
    - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
    - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
    - There is some evidence to suggest a causal relationship (e.g., the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (e.g., the patient's clinical condition or other concomitant AEs).

7.3.4. Follow-up of Adverse Events

After the initial AE or SAE report, the Investigator is required to proactively follow each patient and provide further information to the Sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The Sponsor may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The Investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the Sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the Sponsor according to the SAE instructions provided by the Sponsor within the time frames outlined in Section 7.6.2. The Sponsor will consider the impact of new or updated information on the benefit-risk balance.

7.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (e.g., clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (e.g., ECGs, X-rays, or vital signs) that are judged by the Investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the Investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- Are associated with clinical signs or symptoms, or
- Require active medical intervention, or
- Lead to dose interruption or discontinuation, or
- Require close observation, more frequent follow-up assessments, or further diagnostic investigation.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

7.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
  Note: The term “life-threatening” in the definition of “serious” refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization
  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting.
- Results in disability/incapacity
  Note: The term “disability” means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea,

vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the Investigator based on medical judgement (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The following are NOT considered to be SAEs:

- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience.

7.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (i.e., not present in the product's Reference Safety Information and meets the definition of a serious adverse drug reaction), the specificity or severity of which is not consistent with those noted in the DKN-01 Investigator's Brochure or Tislelizumab Investigator's Brochure.

7.6. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

7.6.1. Adverse Event Recording Period

A safety event that occurs during the Pre-screening (Part B Only) period (i.e., after the patient has signed the informed consent form for Pre-screening but prior to consent for the main study), will be reported as an SAE only if the event is related to a protocol -mandated procedure. In all study parts, after the patient signs informed consent form for the main study, all safety events that meet the serious criteria will be reported as SAEs. AE collection will begin after the administration of study drugs(s).

Note: An SAE narrative will not be required for SAEs that occur prior to study drug administration unless the event was related to a protocol mandated procedure.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after last dose of study drug(s) (including comparator drug/other IMP) or initiation of new anticancer therapy, whichever occurs first. Reporting will also discontinue if the patient withdraws consent. Immune-related AEs (serious or non-serious) should be reported until 90 days after the last dose of DKN-01 and tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the Investigator should be reported regardless of time since the last dose of treatment.

AEs and SAEs should be recorded according to the details in Table 16. For the follow-up period for AEs, see Section 7.3.4.

Table 16: Guidance for Duration of Recording New or Worsening Adverse Events in All Treatment Arms

Event type	Record new or worsening events that occur during this period	
	Begin	End
SAEs[a]	Signing of informed consent[b]	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Nonserious AEs and SAEs due to PD	Do not record (see Section 7.6.4)	
All nonserious AEs, except those due to PD	First dose of study drug	Up to 30 days after last dose, initiation of new anticancer therapy, death, withdrawal of consent, or loss to follow-up, whichever occurs first
Immune-related AEs (serious or nonserious)		Up to 90 days after last dose (regardless of initiation of new anticancer therapy), death, withdrawal of consent, or loss to follow-up, whichever occurs first

Abbreviations: AE = adverse event; PD = progressive disease; SAE = serious adverse event.
[a] All SAEs considered related to the study drug(s) that are brought to the attention of the Investigator should be reported regardless of time since the last dose of treatment.
[b] See Section 7.6.1 for SAEs occurring after pre-consent prior to main consent (Part B only)

7.6.2. Reporting Serious Adverse Events

7.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the Investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the Sponsor or designee as described in Table 17.

Table 17: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Sending Initial Report	Documentation Method	Timeframe for Sending Follow-up Report	Documentation Method	Reporting Method
All SAEs with exception of PD	Within 24 hours of first knowledge of the SAE	SAE Report	As expeditiously as possible	SAE Report	Email or fax SAE Report form

Abbreviations: PD = progressive disease; SAE = serious adverse event.

7.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an Investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the Sponsor within 24 hours as outlined above in Section 7.6.2.1. The SAE Report will always be completed as thoroughly as possible with all available details of the event and forwarded to the Sponsor or designee within the designated time frames.

If the Investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the Sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The Investigator must always provide an assessment of causality for each SAE prior to transmission of the SAE report to the Sponsor, as described in Section 7.3.3.

The Sponsor will provide contact information for SAE reporting.

7.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The Investigator will report all SAEs to the Sponsor in accordance with the procedures detailed in Section 7.6.2.1. The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The Investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All suspected unexpected serious adverse reactions (as defined in Section 7.5), will be submitted to all applicable regulatory authorities and Investigators for tislelizumab studies. Where applicable, the Sponsor will report all unexpected events which affect the benefit-risk balance of the clinical trial (which are not suspected unexpected serious adverse reactions) no later than 15 days of becoming aware.

When a study center receives an initial or follow-up safety report or other safety information (e.g., revised Investigator's Brochure[s]) from the Sponsor, the Investigator or designated responsible person is required to promptly notify his/her IRB or IEC per institutional SOPs. The Investigator should place copies of Safety Reports from the Sponsor in the Investigator Site File.

Where applicable, serious adverse reactions occurring after the end of the study should be reported without undue delay.

7.6.3. Eliciting Adverse Events

The Investigator or designee will ask patients about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

7.6.4. Disease Progression

Disease progression, which is expected in this study population and measured as an efficacy endpoint, should not be recorded as an AE term. Similarly, nonserious AEs that are clearly consistent with the pattern of progression of the underlying disease and are considered unequivocally due to disease progression should not be recorded. However, if there is any uncertainty as to whether a nonserious AE is due to disease progression, it should be recorded as an AE. Serious adverse events due to disease progression, including death, should not be reported unless the Investigator deems them to be possibly related to the study drug (see Section 7.6.2). Disease progression and clinical progression are captured in the clinical database (i.e., tumor assessment, EOT, and EOS eCRFs). Death related to clinical/RECIST disease progression are captured on the Death and EOS eCRFs.

7.6.5. Deaths

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an AE, e.g., "death," "death of unknown cause," or "death unexplained."

7.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 180 days after the last dose of DKN-01 or tislelizumab a pregnancy report form is required to be completed and expeditiously submitted to the Sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

7.6.7. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The Sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, Investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the Sponsor will assess the expectedness of the SAEs using the following reference safety information documents:

- Tislelizumab Investigator's Brochure
- DKN-01 Investigator's Brochure

7.6.8. Assessing and Recording Immune-Related Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the Investigator to be immune-related (see Appendix 8) should be classified as irAEs and identified as such in the eCRF AE page. Not all tislelizumab studies include a section on the eCRF AE page where irAEs are clearly identified. Therefore, all studies will rely on the company list of potential irAE preferred terms to identify all cases in each study to be further assessed as immune-related AEs by the Sponsor, in addition to those irAEs reported by the Investigator via the AE CRF page.

Investigators should consult the guidance on diagnostic evaluation and management of irAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 8.

All conditions similar to those listed should be evaluated to determine whether they are irAEs, based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 8.

7.6.9. Recording Infusion-Related Reactions

The symptoms of infusion-related reactions may include, but are not limited to, fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions (see CTCAE v5.0, page 67 under the Injury, Poisoning and Procedural Complications SOC, Appendix 12, and Appendix 13) may include acute respiratory distress syndrome, syncope, myocardial infarction, ventricular fibrillation, or cardiogenic shock.

7.6.10. Medication Errors

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.

Any medication errors with DKN-01, tislelizumab, or capecitabine/oxaliplatin/fluorouracil chemotherapy should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration must be reported within 24 hours of awareness via the SAE reporting process described in Section 7.6.2. Supportive care measures should be administered as appropriate.

7.6.11. Overdose

DKN-01, tislelizumab, oxaliplatin, leucovorin calcium, and fluorouracil to be used in this protocol will be administered by the study team. Patients will not self-administer these study medications.

Patients will self-administer capecitabine twice daily on Days 1 through 15 of each cycle for a total of 28 doses.

7.6.11.1. DKN-01

There have been no instances of medication error or overdose of DKN-01 during clinical studies.

Any overdose or incorrect administration of DKN-01 should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an incorrect administration of DKN-01 will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration must be reported within 24 hours of awareness via the SAE reporting process described in Section 7.6.2. Supportive care measures should be administered as appropriate.

7.6.11.2. Tislelizumab

Any overdose of tislelizumab (defined as ≥600 mg in a 24-hour period) should be noted in the patient's chart and on the appropriate eCRF. AEs associated with an overdose of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose must be reported within 24 hours of awareness via the SAE reporting process described in Section 7.6.2. Supportive care measures should be administered as appropriate.

7.6.11.3. Oxaliplatin

There is no known antidote for oxaliplatin overdose (Eloxatin 2015). In addition to thrombocytopenia, the anticipated complications of an oxaliplatin overdose include hypersensitivity reaction, myelosuppression, nausea, vomiting, diarrhea and neurotoxicity. Several cases of overdoses have been reported with oxaliplatin. Adverse reactions observed were Grade 4 thrombocytopenia (<25,000/mm^3) without any bleeding, anemia, sensory neuropathy such as paresthesia, dysesthesia, laryngospasm and facial muscle spasms, gastrointestinal disorders such as nausea, vomiting, stomatitis, flatulence, abdomen enlarged and Grade 4 intestinal obstruction, Grade 4 dehydration, dyspnea, wheezing, chest pain, respiratory failure, severe bradycardia and death. Patients suspected of receiving an overdose should be monitored, and supportive treatment should be administered. The maximum dose of oxaliplatin that has been administered in a single infusion is 825 mg.

7.6.11.4. Capecitabine

The manifestations of acute overdose would include nausea, vomiting, diarrhea, gastrointestinal irritation and bleeding, and bone marrow depression (Xeloda 2015). Medical management of overdose should include customary supportive medical interventions aimed at correcting the presenting clinical manifestations. Although no clinical experience using dialysis as a treatment for capecitabine overdose has been reported, dialysis may be of benefit in reducing circulating concentrations of 5'-DFUR, a low–molecular-weight metabolite of the parent compound.

Single doses of capecitabine were not lethal to mice, rats, and monkeys at doses up to 2000 mg/kg (2.4, 4.8, and 9.6 times the recommended human daily dose on an mg/m^2 basis).

7.6.11.5. Leucovorin calcium

Excessive amounts of leucovorin calcium may nullify the chemotherapeutic effect of folic acid antagonists (Leucovorin calcium 2012).

7.6.11.6. Fluorouracil

Administer uridine triacetate within 96 hours following the end of fluorouracil infusion for management of fluorouracil overdose. (Fluorouracil 2016).

8. STATISTICAL CONSIDERATIONS

8.1. Part A and Part B

8.1.1. Sample Size Determination

The sample size for Part A and B of this Phase 2 study is not based on formal statistical calculations as this is a pilot study designed primarily to seek information on the safety, efficacy, and pharmacokinetics/pharmacodynamics of DKN-01 in combination with tislelizumab ± CAPOX. Data collected from previous clinical studies indicates that DKN-01 is well tolerated. It was therefore determined that 20 patients would be sufficient to assess the safety and tolerability of DKN-01 in combination with tislelizumab ± CAPOX in a pilot study.

Approximately 24 patients (first-line treatment) will be enrolled in Part A to ensure 20 evaluable patients. Approximately 48 patients (DKK1-high G/GEJ adenocarcinoma, second-line treatment) will be enrolled in Part B to ensure 40 evaluable patients. With a sample size of 20 evaluable patients in Part A, observed ORR rates of 69%, 77%, or 80% would be statistically greater than the 50% expected success rate at a 0.05 one-sided significance level with at least 50%, 80%, or 90% power, respectively(Klempner, Bendell et al. 2020). With a sample size of 40 evaluable patients in Part B, observed ORR rates of 42%, 49%, or 53% would be statistically greater than the ≥30% expected success rate at a 0.05 one-sided significance level with at least 50%, 80%, or 90% power, respectively.

It is estimated that approximately 180 patients will be screened to achieve the target of 24 patients enrolled in Part A and 48 patients in Part B.

8.2. Part C

8.2.1. Statistical Hypothesis

The primary efficacy endpoint is PFS, and the study is designed to test the superiority of DKN-01 plus tislelizumab and chemotherapy (CAPOX or mFOLFOX6), the experimental treatment, over tislelizumab and chemotherapy (CAPOX or mFOLFOX6), the control treatment, for DKK1-high and in all patients. The primary analysis will test the following hypotheses:

- Null Hypothesis: The hazard ratio for PFS between experimental and control treatment is equal to one.
- Alternative Hypothesis: The hazard ratio for PFS between experimental and control treatment is less than one.

8.2.2. Sample Size Determination

The sample size for Part C of this Phase 2 study is based on formal statistical calculations as this part of the study is designed primarily to seek information on the efficacy of DKN-01 in combination with tislelizumab and chemotherapy regimen (CAPOX or mFOLFOX6) as compared to the combination of tislelizumab and chemotherapy regimen (CAPOX or mFOLFOX6) alone in DKK1-high patients and in patients regardless of their DKK1 status (all-comers). It is determined that a total of approximately160 patients (80 patients in each treatment

group) would be sufficient to assess the efficacy of DKN-01 in combination with tislelizumab and chemotherapy for DKK1-high patients and in patients regardless of their DKK1 status.

With a power of 83% and a one-sided Type I error of 10%, a total of 137 PFS events of all-comers are required to detect a treatment effect hazard ratio of 0.681 (median PFS for all-comers is 7.7 months in the control arm and 11.3 months in the experimental arm). With a power of 80% and a one-sided Type I error of 10%, a total of 49 PFS events of DKK1-high patients are required to detect a treatment effect hazard ratio of 0.546 (median PFS for DKK1-high patients is 6.5 months in the control arm and 11.9 months in the experimental arm) in DKK1-high patients.

The sample size and power calculations are based on the following assumptions: Assuming a recruitment period of 12 months, a 10% probability of dropping out during the course of the study, a minimum follow-up of 24 months, and approximately 50% patients will be DKK1-high. If the proportion of DKK1 high patients is not 50%, the power of PFS in DKK1-high patients will vary and may require further evaluation.

Both sample size calculations have been performed using the STT2 module (Two Sample Log-Rank Test of Exponential Survival with Exponential Dropout) of nQuery Version 9.2.1.0 from Statistical Solutions Ltd.

8.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

	Description
Enrolled	All patients who signed the main study informed consent form (ICF).
Safety Population	For Part A and B: All patients who signed the ICF and received at least 1 dose of DKN-01. This is the primary population for the Safety Analysis. For Part C: The safety population is defined as all patients who are randomized and receive at least one dose of study treatment.
Efficacy	
Intent-to-Treat (ITT) Population	For Part A and B: The intent-to-treat population (full analysis set) is defined to be all patients who enrolled and received at least one dose of DKN-01. For Part C: The Intent-to-treat population is defined to be all patients randomized to treatment. Patients will be included in the treatment group assigned at randomization regardless of the actual treatment received.
Modified Intent-to-Treat (mITT) Population	For Part A and B: All patients who received more than one dose of DKN-01. This is the primary population for the efficacy analyses including PFS and OS. For Part C: All randomized patients who receive at least one cycle of study treatment.
Response Evaluable Population	Part A: All patients who received any amount of DKN-01 + tislelizumab + oxaliplatin + capecitabine and have measurable baseline and at least 1 evaluable post-baseline RECIST tumor response assessment. Part B1 and B2: All patients who received any amount of DKN-01 + tislelizumab and have a measurable baseline and at least 1 evaluable post baseline RECIST tumor response assessment. Part C: All patients who received any amount of tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) ± DKN-01 and have measurable baseline and at least 1 evaluable post-baseline RECIST tumor response assessment.
Per-Protocol (PP) Population	Part A and B: All enrolled patients without important protocol deviations that necessitates exclusion from this population or compliance issues, as applicable. Part C: All patients who are randomized and received the study treatment (Tislelizumab + chemotherapy (CAPOX or mFOLFOX6) ± DKN-01) as planned and have no important protocol deviations. The PP population will be used for sensitivity analyses of the primary and secondary objectives.
Pharmacokinetics Population DKN-01	All enrolled patients with available serum-time concentration data from patients dosed with DKN-01.
Pharmacokinetics Population tislelizumab	All enrolled patients with available serum-time concentration data from patients dosed with tislelizumab

Biomarker population	There is one biomarker population for each of the following biomarkers: - DKK1 tumor expression in messenger RNA (mRNA) by chromogenic in situ hybridization (CISH). - Programmed cell death protein ligand-1 (PD-L1) expression by IHC

Abbreviations: DKK1 = Dickkopf-1; ICF = informed consent form; PD-L1 = programmed cell death protein ligand 1.

8.4. Statistical Analyses

This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

Data analyses in general will be primarily descriptive and presented by study part and overall; full details will be provided in the Statistical Analysis Plan. For continuous safety and efficacy variables, descriptive statistics (n-number of patients with data, mean, standard deviation, median, minimum, and maximum) will be presented. For categorical variables, frequency distributions (counts and associated percentages) will be presented.

The statistical analysis plan will be developed and finalized before final database lock and will describe the patient populations to be included in the analyses, and the procedures for accounting for missing, unused, and spurious data.

8.4.1. Efficacy Analyses

8.4.1.1. Part A and B

For Study Parts A and B, the modified intent-to-treat population is the primary efficacy population. Additional summaries may be created for the response evaluable population, the per-protocol population, and the safety population. Efficacy endpoints will also be assessed for subgroups of interest. Any statistical results will be interpreted in the perspective of the exploratory nature of the study.

The best overall response (BOR) will be determined in accordance with RECIST v1.1. The following response rates will be presented by study part: ORR, DCB, and DCR. The time to event endpoints (DOR, PFS, and OS) will be assessed by the Kaplan-Meier method. Estimated median, 25^{th} and 75^{th} percentiles, and standard errors from Kaplan-Meier summaries will be presented for the time-to-event data.

8.4.1.2. Part C

Analysis of the primary efficacy endpoint

The primary endpoint is PFS, which is measured from the date of randomization to the date of documented disease progression, based on Investigator assessed radiologic review using RECIST v1.1, or death due to any cause, whichever occurs first. If the patient has not died, but there is no radiographic post-baseline tumor assessment, PFS will be censored at the date of randomization. If there are radiographic post-baseline tumor assessments, PFS will be censored at the most recent tumor assessment before the data cutoff or study withdrawal, whichever occurs first.

The primary analysis will be the comparison of PFS for DKK1-high and in all patients between the two treatment arms in the ITT population, using the one-sided stratified log-rank test, with stratification factors as used in the randomization. Data will be summarized in Kaplan-Meier curves together with medians and 95% confidence intervals for those medians. The Cox Proportional Hazards model, stratified for the randomization factors, will be used to obtain a hazard ratio together with its 95% confidence interval.

No multiplicity adjustment is planned for the treatment comparisons of the primary endpoint as this is a Phase 2 study for exploratory and for signal finding purpose. All other efficacy analyses will be considered exploratory.

Analysis of secondary endpoints

ORR is defined as the proportion of patients who achieve objective tumor response (CR or PR) per RECIST 1.1, assessed by the Investigator. The comparison of ORR between the two treatment arms will be based on the Cochran-Mantel-Haenzel test, with stratification factors as for the analysis of PFS. Results will be reported in terms of an odds ratio and the associated 95% confidence interval using the Clopper-Pearson method (Clopper 1934). Results will also be summarized by treatment arms and appropriate subgroups.

For DOR, PFS, and OS, the time to event curves between the two treatment arms will be compared with a log-rank test along with the corresponding hazard ratio.

In general, confidence intervals (95%, unless otherwise stated) will be presented for select efficacy variables. Standard figures for summarizing the response to treatment overall and within subgroups, will be provided.

Overall Survival (OS) is defined as the time from the date of randomization to death due to any cause. For a patient who is not known to have died by the end of study follow-up, observation of OS is censored on the date the patient was last known to be alive (i.e., date of last contact). Patients lacking data beyond the day of randomization will have their survival time censored on the date of randomization (i.e., OS duration of 1 day).

Other Aspects of the Efficacy Analysis

All primary and secondary efficacy analyses may be repeated in the PP population.

The concordance between Investigator assessment and central imaging assessment will be evaluated.

Subgroup Analyses

Hazard ratios and 95% confidence intervals will be calculated for PFS within subgroups using the unadjusted Cox proportional hazards model in order to evaluate the consistency of treatment effect. These subgroups will include those defined by the stratification factors. Other subgroups may also be considered, with a full list being identified in the SAP.

8.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population. Analyses will be described in detail in the statistical analysis plan and will include summaries of adverse events, laboratory events, vital signs, ECGs, physical examination, ECOG findings, drug exposure and dose modifications, including dose interruptions.

AEs that occur after signing informed consent and prior to administration of study treatment will not be considered as treatment emergent but will be collected and listed. Adverse event summaries will be based on treatment-emergent adverse events (TEAEs), defined as any AE that occurs during or after administration of the first dose of treatment through 30 days after the last dose, or any event that is present at baseline but worsens in intensity.

8.4.3. Other Analyses

The DKN-01 concentration data are sparse in nature, and therefore no formal PK analyses are planned for this study. Concentration data for both DKN-01 and DKK1 will be collected and summarized by nominal collection time. Mean concentration-time graphs by dose group may be prepared. In addition, the concentration data will be characterized by dose level and drug administration. At each nominal collection time, values for the mean, standard deviation, median, minimum and maximum will be reported as applicable.

Univariate and multivariate models will be used to evaluate biomarker endpoints in relation to efficacy outcomes. Multivariate analysis will be conducted to determine if DKK1 expression is associated with clinical benefit independently of known predictors to checkpoint inhibitor therapies (e.g., PD-L1, microsatellite stability status and TMB).

9. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator must maintain adequate and accurate records to ensure that the conduct of the study may be fully documented. Such records include, but are not limited to, the protocol, protocol modifications (hereafter referred to as amendments), ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the Investigator will receive patient data, which will include an audit trail containing a complete record of all changes to such data.

9.1. Access to Information for Monitoring

In accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

Off-site monitoring may be performed. Any off-site monitoring will be performed in accordance with local regulations, where applicable.

9.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene or Leap may conduct inspections or audits any time during or after completion of this clinical study. If the Investigator is notified of an inspection by a regulatory authority, the Investigator agrees to notify the Sponsor or its designee immediately. The Investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

10. QUALITY ASSURANCE AND QUALITY CONTROL

10.1. Regulatory Authority Approval

The Sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country specific regulatory requirements or file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country.

10.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

10.3. Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be performed periodically by the Sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

Site visits will be conducted by the Sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The Investigator is to permit national and local health authorities; Sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

10.4. Drug Accountability

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records, and returned or destroyed study product. Dispensation records will document quantities received from BeiGene's or Leap's designated depot or its designee and quantities dispensed to patients, including batch/lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene and Leap requirements specified in the Pharmacy Manual. At appropriate times during the conduct of the study or at the end of the study following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet BeiGene's or Leap's requirements specified in the Pharmacy Manual for disposal, arrangements will be made between the site and BeiGene or Leap or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

11. ETHICS/PROTECTION OF HUMAN PATIENTS

11.1. Ethical Standard

This study will be conducted by the Principal Investigator and the study center in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the patient. The study will also comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

11.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted, reviewed, and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. Copies of the IEC/IRB correspondence and approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the Sponsor promptly.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the Sponsor, Investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written investigational new drug (IND) safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

11.3. Protocol Amendments

Any protocol amendments will be prepared by the Sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the Sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign each revised ICF confirming their willingness to remain in the study.

11.4. Informed Consent

The Sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/IEC-approved ICFs must be provided to the Sponsor for health authority submission purposes according to local requirements.

Patients must be informed that their participation is voluntary. Patients or their healthcare proxy will be required to sign a statement of informed consent that meets the requirements, where applicable, of 21 CFR 50, ICH guidelines, Health Insurance Portability and Accountability Act requirements, EU CTR 536/2014, local regulations, and the IRB/EC or study center.

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB-/IEC-approved consent forms must be provided to the Sponsor for health authority submission purposes.

Patients must be reconsented to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

11.5. Patient and Data Confidentiality

The principal Investigator and Sponsor will maintain confidentiality and privacy standards by following applicable data privacy laws covering the collection, storage, transmission, and processing of patients' personal and medical information.

The principal Investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' names are not included in any dataset transmitted to any Sponsor location.

Patient medical information obtained during this study is confidential and may be disclosed only to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In the event of a breach of the confidentiality of a patient's personal and medical information, the principal Investigator and Sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable data privacy laws.

If a serious breach of the EU CTR 536/2014 or of the protocol occurs that is likely to affect the safety, rights of study patients and/or data reliability and robustness to a significant degree, this must be reported by the Sponsor in the EU Clinical Trials Information System within 7 days. The Sponsor's (or designee's) process will be in place to support this. Any serious breaches will be reported in the clinical study report.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated during this study must be available for inspection upon request by representatives of the US Food and Drug Administration and all other national and local health authorities; by Sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The Investigator must ensure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The Investigator agrees that all information received from the Sponsor, including but not limited to, the Investigator's Brochure[s], this protocol, eCRFs, the IND, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study is executed, and that contract includes confidentiality provisions inconsistent with this section, that contract's provisions shall apply to the extent they are inconsistent with this section.

11.6. Financial Disclosure

Investigators are required to provide the Sponsor with sufficient accurate financial information in accordance with regulations to allow the Sponsor to submit complete disclosure or certification to the absence of certain financial interest of the Investigators, and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of the Investigators with Leap Therapeutics and BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the Sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (i.e., last patient, last visit).

11.7. Data Handling and Record Keeping

11.7.1. Data Collection and Management Responsibilities

11.7.1.1. Data Entry in the Electronic Case Report Form

All study-related data collected or received by the Investigator or study team shall be promptly entered into the eCRFs. In no event should the entry of the study data into the eCRF be later than what is stipulated in the site contract after the data is collected or received by the Investigator or study team without prior communication with and approval by the Sponsor.

11.7.1.2. Data Collection

Data required by the protocol will be entered into an electronic data capture (EDC) system.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The Investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The e-signature of the Investigator or designee must be provided in the EDC system to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of Leap Therapeutics and BeiGene and should not be made available in any form to third parties without written permission from Leap Therapeutics and BeiGene, except for authorized representatives of Leap Therapeutics and BeiGene or appropriate regulatory authorities.

11.7.1.3. Data Management/Coding

All final patient data, both eCRF and external data (e.g., laboratory data), collected according to the protocol will be stored by Leap Therapeutics and BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file that includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out with due consideration given to data protection and medical confidentiality.

The AE verbatim descriptions (the Investigator's description from the eCRF) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to MedDRA by lower-level term, preferred term, and primary system organ class. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

11.8. Data Integrity and In-house Blinding

Functions/persons with access to the EDC system shall be prohibited from using the EDC system to generate unnecessary listings/summaries that may introduce unwanted bias or to share such outputs from the EDC system with other functions/persons who do not have access to the EDC.

11.9. Study Records Retention

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should

be classified into at least 1 of the following 2 categories: 1) Investigator's study file, and/or 2) patient clinical source documents.

The Investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent forms, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include documents such as (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment logs, etc.

Following closure of the study, the Investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed (e.g., audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must ensure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

The Sponsor will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements, local laws or regulations, or the Sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The Investigator must notify the Sponsor of any changes in the archival arrangements, including but not limited to the following: archival at an off-site facility, or transfer of ownership of or responsibility for the records in the event the Investigator leaves the study center.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and Leap Therapeutics and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the CRO managing the biological samples, for the shorter of, a period of up to 15 years or as allowed by your IRB/IEC.

11.10. Protocol Deviations

The Investigator is responsible for ensuring that the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to the Sponsor.

The Investigator is to document and explain any deviations from the approved protocol. The Investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the Sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

11.11. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene and Leap Therapeutics will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance and the need to protect the intellectual property of the Sponsor, regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the Sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (ICMJE 2019).

Both positive and negative study results will be disclosed. In general, the results of research will be submitted for publication to peer-reviewed scientific journals. These journals often do not consider negative results for publication. However, results will be otherwise disclosed on www.clinicaltrials.gov and other public regulatory websites per regulatory requirement.

Each Investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the Sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the Sponsor to protect proprietary information, provide comments based on information from other studies that may not yet be available to the Investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be presented in the Investigator's clinical study agreement. Each Investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the Sponsor to allow for patent filings in advance of the publication/presentation.

11.12. Study Continuation Plan

Alternative study assessments and/or procedures may be implemented after review and approval by the Sponsor under extraordinary circumstances (e.g., pandemic, weather emergency, local/national declaration of emergency) to protect patient safety and data quality.

11.13. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator or study center personnel, as appropriate:

- Return of all study data to the Sponsor
- Resolution and closure of all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Collection of all study documents for the trial master file filing according to GCP and local regulation
- Shipment of samples (including, but not limited to, those for PK, ADA, and biomarkers) to the assay lab for central lab analysis according to protocol and lab manual requirements.

In addition, the Sponsor reserves the right to suspend the enrollment or prematurely discontinue this study either at a single study center or at all study centers at any time for any reason. Potential reasons for suspension or discontinuation include but are not limited to: safety or ethical issues or noncompliance with this protocol, GCP, the Sponsor's written instructions, the clinical study agreement, or applicable laws and regulations. If the Sponsor determines such action is needed, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, the Sponsor will provide advance notification to the Investigator of the impending action before it takes effect.

The Sponsor will promptly inform all other Investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons. The Sponsor will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the Investigator must inform the IRB/IEC promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the Sponsor. In addition, arrangements will be made for the return of all unused study drug(s) in accordance with the applicable Sponsor procedures for the study.

Financial compensation to the Investigators and/or institutions will be in accordance with the clinical study agreement established between the Investigator and/or institutions and the Sponsor.

11.14. Information Disclosure and Inventions

All rights, title, and interests in any inventions, know-how, or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the Sponsor and are hereby assigned to the Sponsor.

If a written contract for the conduct of the study, which includes ownership provisions inconsistent with this statement, is executed between the Sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the Sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the Sponsor and will be kept confidential by the Investigator and other study center personnel.

This information and data will not be used by the Investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the Sponsor.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the Investigator or study center personnel
- Information that is necessary to disclose in confidence to an IRB/IEC solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 11.11.

If a written contract for the conduct of the study, which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

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APPENDIX 1. SCHEDULE OF ASSESSMENTS

Schedule of Activities – Part A

Procedure	Screening[1]	Treatment Period: Cycle 1 C1D1	Treatment Period: Cycle 1 C1D15	Treatment Period: at or after Cycle 2 D1	Treatment Period: at or after Cycle 2 D15	End-of-Treatment[22]	Safety Follow-Up[22]	PD Follow-up[2]	Survival Follow-up[3]	Unscheduled Visits[4]
	Days -28 to 0		± 3D	+3D	±3D		+7D	± 14D	± 14D	
Screening 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]									X[7]
Height	X									
Weight	X	X		X		X	X			
Body surface area		X		X						
Vital signs[26]	X	X		X		X	X			X
Electrocardiogram[26]	X	X[9]		X		X	X			X
ECOG performance status	X	X		X		X	X			X
Physical examination	X	X[25]				X	X			
Abbreviated physical examination			X	X	X					X
Laboratory sample collection: [8]										
Hematology[8]	X	X[9, 25]	X	X	X	X	X			X
Coagulation	X	X[25]				X	X			X
Clinical chemistries[8]	X	X[9, 25]	X	X	X	X	X			X
TSH	X	X[25]		X		X	X			X
Urinalysis[8]	X	X[25]		X		X	X			X
Pregnancy testing[10]	X	X[9]		X		X	X	X	X	X

Procedure	Screening[1]	Treatment Period: Cycle 1 C1D1	Treatment Period: Cycle 1 C1D15	Treatment Period: at or after Cycle 2 D1	Treatment Period: at or after Cycle 2 D15	End-of-Treatment[22]	Safety Follow-Up[22]	PD Follow-up[2]	Survival Follow-up[3]	Unscheduled Visits[4]
	Days -28 to 0		± 3D	+3D	±3D		+7D	± 14D	± 14D	
Serum DKK1[24]		pre-dose, EOI, 3-12h post-dose	pre-dose, EOI, 3-12h post-dose	pre-dose, EOI	pre-dose, EOI		X			X
Serum DKN-01 PK[24]		pre-dose, EOI, 3-12h post-dose	pre-dose, EOI, 3-12h post-dose	pre-dose, EOI	pre-dose, EOI		X			
Serum tislelizumab PK		pre-dose EOI[11]		pre-dose EOI[11]			X[11]			
DKN-01 ADA[24]		pre-dose		pre-dose (every ODD cycle)[23]			X	X[12]	X[12]	
Tislelizumab ADA		pre-dose[13]		pre-dose[13]			X[13]	X[12]	X[12]	
ctDNA		pre-dose				X[14]		X[14]		
Study drug administration[15]:										
DKN-01[16]		X	X	X	X					
Tiselelizumab[16]		X		X						
Oxaliplatin[16]		X		X						
Capecitabine[16]		X	X	X	X					
Baseline head imaging (MRI preferred)	X									
Tumor imaging[17]	X			X		X		X		X
Dispense capecitabine		X		X						
Compliance diary-train/distribute		X	X	X	X					
Compliance diary-collect/monitor			X		X	X				
RECIST disease response assessment[18]				X		X		X		
iRECIST assessment[19]				X		X		X		

Procedure	Screening[1]	Treatment Period: Cycle 1 C1D1	Treatment Period: Cycle 1 C1D15	Treatment Period: at or after Cycle 2 D1	Treatment Period: at or after Cycle 2 D15	End-of-Treatment[22]	Safety Follow-Up[22]	PD Follow-up[2]	Survival Follow-up[3]	Unscheduled Visits[4]
	Days -28 to 0		± 3D	+3D	±3D		+7D	± 14D	± 14D	
AEs, including infusion-related reactions and irAEs[20]	X	X	X	X	X	X	X			X
Concomitant medications and procedures[21]	X	X	X	X	X	X	X			X
Survival and subsequent therapies						X		X	X	

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; BID = twice daily; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; DKK1 = Dickkopf-1; ECOG = Eastern Cooperative Oncology Group; EBV = Epstein Barr virus; EOI = end of infusion; EOT = end of treatment; IEC = independent ethics committee; IHC = immunohistochemistry; irAE = immune-related adverse event; IRB = institutional review board; iRECIST = Immune-related Response Evaluation Criteria in Solid Tumors; IV = intravenous; MRI = magnetic resonance imaging; MSI-H/MSI-L = microsatellite instability-high/low; MSS = microsatellite stable; PD = progressive disease; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; PI = Principal Investigator; PO = oral; Q12 weeks = once every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid-stimulating hormone.

Table footnotes:

1. Screening consent must be obtained prior to undergoing any Screening procedures. All Screening assessments must be performed within 28 days before C1D1. The results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to enrollment(C1D1) may be used for the purposes of Screening rather than repeating the standard-of-care tests. After completion of all Screening activities, eligibility will be reconfirmed including review of inclusion/exclusion criteria and medical history prior to dosing on C1D1.
2. PD Follow-up Period applies only to patients who discontinue study treatment without documented PD. Follow-up assessments will be every 12 weeks (±14 days).
3. All patients will be followed in the Survival Follow-up Period 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 EOT visit or PD Follow-up Period discontinuation visit, as applicable. If a female patient is of childbearing potential, she will be followed monthly with a urine pregnancy test up to 6 months following last dose of study drug. This testing can occur at with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.
4. Unscheduled visits may be performed at any time during the study whenever necessary to assess or follow-up on AEs as deemed necessary by the PI or designee. The PI or designee may perform assessments outside of the study schedule (unscheduled visits) for safety purposes based on his/her clinical judgment. Only assessments deemed necessary by PI will be performed. The date and reason for the Unscheduled visit should be recorded in the source documentation, including recording of AEs and concomitant medications.
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. Tumor tissue is mandatory. Fresh biopsy is preferred; archived specimen may be acceptable. The tumor tissue will be tested for DKK1 mRNA expression and PD-L1. In addition, should sufficient tumor sample be available, the biopsy may be tested for MSS assessment, genomic profiling, RNA profiling (e.g., RNA-Seq), immunohistology, EBV, infiltrating immune cells, and additional IHC analysis as applicable.

7. An additional biopsy to evaluate the effects of treatment on the tumor tissue may be collected at any time during the study if a repeat biopsy is required clinically and the patient consents to the biopsy. Patients will be allowed to continue on treatment until they require discontinuation for any reason (i.e., progression, AE) or until a patient reaches 2 years of treatment (as measured from C1D1).
8. Refer to Appendix 2. After two years on treatment, safety labs will only be required on Day 1 of each new treatment cycle unless clinically indicated.
9. Hematology, chemistry, pregnancy testing, and ECG must be resulted, and eligibility confirmed prior to dosing.
10. 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. If a female patient is of childbearing potential, she will be followed monthly with a urine pregnancy test up to 6 months following last dose of study drug. This testing can occur at with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.
11. Sampling, handling, and processing procedures are outlined in the Laboratory Manual. Predose (within 60 min before start infusion) samples are required to be collected at Day 1 of C1, C2, C5, C9 and C17; post-dose/end of infusion (EOI) (within 30 minutes after completing tislelizumab infusion) samples are required to be collected at Day 1 of C1 and C5. An additional PK sample is required to be collected at the Safety Follow-Up Visit. If a patient presents with any immune-related adverse event, additional blood PK samples may be taken to determine the concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/IECs.
12. If a patient has known positive ADA (to DKN-01 or tislelizumab) at the EOT visit, he or she should have repeat testing, where feasible, performed in the PD Follow-up Period and/or Survival Follow-up Period until the patient is no longer positive.
13. Blood used to test for anti-tislelizumab antibodies should be collected within 60 minutes before beginning the Day 1 infusion of C1, C2, C5, C9, and C17 and at the mandatory Safety Follow-Up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs.
14. ctDNA is to be obtained upon PD (at EOT if discontinuing due to PD, or otherwise in PD follow-up).
15. Study drug is to be administered in the following order: premedications → DKN-01 → tislelizumab → oxaliplatin → capecitabine (see Section 5.2.2).
16. DKN-01 will be administered IV over a minimum of 30 minutes and up to a maximum of 2 hours on Days 1 and 15 of each cycle without interruption. Tislelizumab will be administered IV over 60 minutes on C1D1 and then over 30 minutes on D1 of each cycle if well tolerated (note: tislelizumab must not be concurrently administered with any other drug). Oxaliplatin will be administered IV according to institutional standard of care on Day 1 of each cycle. On Days 1 through 15, the patient will administer capecitabine PO twice daily (BID) for a total of 28 doses per cycle. Note: Capecitabine should be taken after food (within 30 minutes of a meal) with water (morning and evening) and at the same time each day (±60 minutes).
17. Baseline imaging studies will be performed within 28 days before C1D1. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to enrollment may be used for the purposes of Screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 6 weeks (± 7 days), from Cycle 1 Day 1, for the first 24 weeks, then every 9 weeks (± 7 days) after 24 weeks. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted on the planned schedule. Screening assessments and each subsequent assessment of the tumor must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc.). All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at Screening is required to be used throughout the study (e.g., the same contrast protocol for CT scans).
18. Disease response is to be assessed every 6 weeks (± 7 days), from Cycle 1 Day 1, for the first 24 weeks, then every 9 weeks (± 7 days) after 24 weeks based on RECIST v1.1. After first documentation of response (CR or PR), confirmation of tumor response should occur at a minimum of 4 weeks after the first response or at the next scheduled assessment time point.
19. Tumor response and progression will be assessed by the Investigator using iRECIST, 2017. RECIST v1.1 will be used to determine treatment decisions.
20. After the patient signs informed consent form for the main study, all safety events that meet the serious criteria will be reported as SAEs. AE collection will begin after the administration of study drugs(s). (Note: An SAE narrative will not be required for SAEs that occur prior to study drug administration unless the event was related to a protocol mandated procedure). After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after last dose of study drug(s) (including comparator drug/other IMP) or initiation of new anticancer therapy, whichever occurs first. Reporting will also discontinue if the patient withdraws consent. Immune-related AEs (serious or non-serious) should be reported until 90 days after the last dose of DKN-01 and tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the Investigator should be reported regardless of time since the last dose of treatment
21. At the Screening visit, collect concomitant medications and procedures taken during the last 30 days.

22. If the EOT and Safety Follow-up Visits are planned to be conducted within 7 days of one another, the visit procedures from the visits may be combined and completed at the EOT visit, and the Safety Follow-up visit may be conducted instead as a telephone call to document AEs and concomitant medications/procedures. Telephone contacts with patients also should be conducted to assess immune-related AEs and concomitant medications (if appropriate, i.e., associated with an immune-related AE or is a new anticancer therapy) at 60 days and 90 days (± 14 days) after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected immune related AE at a telephone follow-up contact, the Investigator should arrange an unscheduled visit if further assessment is indicated.
23. DKN-01 ADA blood will be collected on C1D1 pre-dose and on all ODD cycles (C3D1pre-dose, C5D1 pre-dose, C7D1 pre-dose, etc). After two years on treatment, DKN-01 ADA samples will not be collected during routine visits except for at the safety follow visit unless the subject had a known positive ADA at the EOT visit, then they should have repeat testing, where feasible, performed in the PD Follow Up and/or Survival Follow Up period until it is no longer positive.
24. Sample collection windows: Pre-Dose: Samples should be drawn within 60 minutes of the start of the DKN-01 infusion. End of Infusion (EOI): samples should be collected ± 5 minutes after the end of DKN-01 infusion. 3-12 hr Post-Dose: Samples should be drawn a minimum of 3 hours after the DKN-01 infusion is completed. The sample can be drawn up to 12 hours after the DKN-01 sample is complete. After two years on treatment, DKK1 PK and serum samples will only be required at the safety follow up visit.
25. May be collected and resulted up to day 2 days prior to C1D1 to confirm eligibility and permit dosing on C1D1
26. Vital signs and ECG should be performed prior to the collection of laboratory (blood) samples at all visits.

NOTE: All assessments should be performed prior to administration of study drugs (within -2 days) unless stated otherwise.

Schedule of Activities – Part B

Procedure	Pre-Screening[1]	Screening[2]	Treatment Period				End-of-Treatment[24]	Safety Follow-up[24]	PD Follow-up[3]	Survival Follow-up[4]	Unscheduled Visits[5]
			Cycle 1		≥Cycle 2						
			C1D1	C1D15	D1	D15		30 Days Post EOT	Q12 Weeks from EOT	Q12 Weeks from EOT	
		Days -28 to 0		± 3D	+ 3D	± 3D		+7D	± 14D	± 14D	
Pre-Screening informed consent	X										
Screening informed consent		X									
Medical history		X									
Cancer history, including treatment history[6] and, if available, genomics		X									
Demographics		X									
DKK1 tumor mRNA expression[7]	X[7]										
Tumor tissue collection/biopsy	X[8]	X[32]									X[9]
Height		X									
Weight		X	X		X		X	X			
Body surface area			X		X						
Vital signs[31]		X	X		X		X	X			X
Electrocardiogram[31]		X	X[11]		X		X	X			X
ECOG performance status		X	X		X		X	X			X
Physical examination	X	X	X[27]				X	X			
Abbreviated physical examination				X	X	X					X
Laboratory sample collection: [10]											
Hematology[10]		X	X[11, 27]	X	X	X	X	X			X
Coagulation		X	X[27]				X	X			X
Clinical chemistries[10]		X	X[11, 27]	X	X	X	X	X			X

Procedure	Pre-Screening[1]	Screening[2]	Treatment Period				End-of-Treatment[24]	Safety Follow-up[24]	PD Follow-up[3]	Survival Follow-up[4]	Unscheduled Visits[5]
			Cycle 1		≥Cycle 2						
			C1D1	C1D15	D1	D15		30 Days Post EOT	Q12 Weeks from EOT	Q12 Weeks from EOT	
		Days -28 to 0		± 3D	+ 3D	± 3D		+7D	± 14D	± 14D	
TSH (Patients in Korea, FT3 and FT4 will also be assessed)		X	X[27]		X		X	X			X
Urinalysis[10]		X	X[27]		X		X	X			X
Pregnancy testing[12]		X	X[11]		X		X	X			X
Serum DKK1[26]			pre-dose, EOI, 3-12h post-dose	pre-dose, EOI, 3-12h post-dose	pre-dose, EOI	pre-dose, EOI		X			X
Serum DKN-01 PK[26]			pre-dose, EOI, 3-12h post-dose	pre-dose, EOI, 3-12h post-dose	pre-dose, EOI	pre-dose, EOI		X			
Serum tislelizumab PK			pre-dose and EOI[13]		pre-dose EOI[13]			X[13]			
DKN-01 ADA[26]			pre-dose		pre-dose (every ODD cycle)[25]			X	X[14]	X[14]	
Tislelizumab ADA			pre-dose[15]		pre-dose[15]			X[15]	X[14]	X[14]	
ctDNA			pre-dose				X[16]		X[16]		
Study drug administration[17]:											
DKN-01[18]			X	X	X	X					

Procedure	Pre-Screening[1]	Screening[2]	Treatment Period				End-of-Treatment[24]	Safety Follow-up[24]	PD Follow-up[3]	Survival Follow-up[4]	Unscheduled Visits[5]
			Cycle 1		≥Cycle 2						
			C1D1	C1D15	D1	D15		30 Days Post EOT	Q12 Weeks from EOT	Q12 Weeks from EOT	
		Days -28 to 0		± 3D	+ 3D	± 3D		+7D	± 14D	± 14D	
tiselelizumab[18]			X		X						
Baseline head imaging (MRI preferred)		X									X
Tumor imaging[19]		X			X		X		X		X
RECIST disease response assessment[20]					X		X		X		
iRECIST assessment[21]					X		X		X		
AEs, including infusion-related reactions and irAEs[22]	X	X	X	X	X	X	X	X			X
Concomitant medications and procedures[23]		X	X	X	X	X	X	X			X
Survival and subsequent therapies							X		X	X	
Pulmonary Function Tests (Korea only)			X[28]		X[28]		X[28]	X[28]			
FT3 and FT4 (Korea only)		X[30]	X[30]		X[30]		X[30]	X[30]			
Ophthalmic Examination (Korea only)		X[29]			X[29]		X[29]	X[29]			
Amylase and Lipase (Korea only)		X[30]	X[30]		X[30]		X[30]	X[30]			

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; DKK1 = Dickkopf-1; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EOT = end of treatment; IEC = independent ethics committee; IHC = immunohistochemistry; irAE = immune-related adverse event; IRB = institutional review board; iRECIST = Immune-related Response Evaluation Criteria in Solid Tumors; IV = intravenous; MRI = magnetic resonance imaging; MSI-H/MSI-L = microsatellite instability-high/low; MSS = microsatellite stable; PD = progressive disease; PD-L1 = programmed cell death ligand 1; PI = Principal Investigator; PK = pharmacokinetics; Q12 weeks = once every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid-stimulating hormone.

Table footnotes:

1. Pre-Screening consent must be obtained prior to undergoing DKK1 testing (see footnote 7).
2. To be eligible to proceed with Screening consent, patients must be DKK1-high (see footnote 7). Screening consent must be obtained prior to undergoing any Screening procedures. All Screening assessments must be performed within 28 days before C1D1. The results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to enrollment (C1D1) may be used for the purposes of screening rather than repeating the standard-of-care tests. After completion of all Screening activities, eligibility will be reconfirmed including review of inclusion/exclusion criteria and medical history prior to dosing on C1D1.
3. PD Follow-up Period applies only to patients who discontinue study treatment without documented PD. Follow-up assessments will be every 12 weeks (±14 days).
4. All patients will be followed in the Survival Follow-up Period 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 Period discontinuation visit, as applicable. If a female patient is of childbearing potential, she will be followed monthly with a urine pregnancy test up to 6 months following last dose of study drug. This testing can occur at with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.
5. Unscheduled visits may be performed at any time during the study whenever necessary to assess or follow-up on AEs as deemed necessary by the PI or designee. The PI or designee may perform assessments outside of the study schedule (unscheduled visits) for safety purposes based on his/her clinical judgment. Only assessments deemed necessary by PI will be performed. The date and reason for the Unscheduled visit should be recorded in the source documentation, including recording of AEs and concomitant medications.
6. Cancer treatment history is to include documentation of prior cancer therapies, radiation therapy, surgery, and use of blood products, including red cell and platelet transfusions and growth factors within the previous 3 months.
7. Patients must be DKK1-high as determined by elevated DKK1 mRNA expression (H-score ≥35) in tumor cells as defined by CLIA-certified central laboratory testing of a fresh biopsy (preferred) or biopsy specimen obtained (See footnote 8).
8. Tumor tissue is mandatory for pre-treatment evaluation. Fresh biopsy is preferred; archived specimen may be acceptable. The tumor tissue will be tested for DKK1 mRNA expression to determine eligibility to proceed with Screening (See footnote 7). The tumor biopsy will also be tested for PD-L1, which is not required for eligibility. In addition, should sufficient tumor sample be available, the biopsy may be tested for MSS assessment, genomic profiling, RNA profiling (e.g., RNA-Seq), immunohistology, EBV, infiltrating immune cells, and additional IHC analysis as applicable.
9. An additional biopsy to evaluate the effects of treatment on the tumor tissue may be collected at any time during the study if a repeat biopsy is required clinically and the patient consents to the biopsy. Patients will be allowed to continue on treatment until they require discontinuation for any reason (i.e., progression, AE) or until a patient reaches 2 years of treatment (as measured from C1D1).
10. Refer to Appendix 2. After two years on treatment, safety labs will only be required on Day 1 of each new treatment cycle unless clinically indicated.
11. Hematology, chemistry, pregnancy testing, and ECG must be resulted, and eligibility confirmed prior to dosing.
12. 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. If a female patient is of childbearing potential, she will be followed monthly with a urine pregnancy test up to 6 months following last dose of study drug. This testing can occur at with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.
13. Sampling, handling, and processing procedures are outlined in the Laboratory Manual. Predose (within 60 min before start infusion) samples are required to be collected at Day 1 of C1, C2, C5, C9 and C17; post-dose/ End of Infusion (EOI) (within 30 minutes after completing tislelizumab infusion) samples are required to be collected at Day 1 of C1 and C5. An additional PK sample is required to be collected at the Safety Follow-Up Visit. If a patient presents with any immune-related adverse event, additional blood PK samples may be taken to determine the concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/IECs.
14. If a patient has known positive ADA (to DKN-01 or tislelizumab) at the EOT visit, he or she should have repeat testing, where feasible, performed in the PD Follow-up Period and/or Survival Follow-up Period until the patient is no longer positive.
15. Blood used to test for anti-tislelizumab antibodies should be collected within 60 minutes before beginning the Day 1 infusion of C1, C2, C5, C9, and C17 and at the mandatory Safety Follow-Up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs.
16. ctDNA is to be obtained upon PD (at EOT if discontinuing due to PD, or otherwise in PD follow-up).
17. Study drug is to be administered in the following order: DKN-01 → tislelizumab (see Section 5.2.2).

18. DKN-01 will be administered IV over a minimum of 30 minutes and up to a maximum of 2 hours on Days 1 and 15 of each cycle without interruption. Tislelizumab will be administered IV over 60 minutes on C1D1 and then over 30 minutes on D1 of each cycle if well tolerated (note: tislelizumab must not be concurrently administered with any other drug).
19. Baseline imaging studies may be performed within 28 days before C1D1. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to first dose of study drug may be used for the purposes of Screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 6 weeks (± 7 days), from Cycle 1 Day 1, for the first 24 weeks, then every 9 weeks (± 7 days) after 24 weeks. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted on the planned schedule. Screening assessments and each subsequent assessment of the tumor must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc.). All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at Screening is required to be used throughout the study (e.g., the same contrast protocol for CT scans).
20. Disease response is to be assessed every 6 weeks (± 7 days), from Cycle 1 Day 1, for the first 24 weeks, then every 9 weeks (± 7 days) after 24 weeks based on RECIST v1.1. After first documentation of response (CR or PR), confirmation of tumor response should occur at a minimum of 4 weeks after the first response or at the next scheduled assessment time point.
21. Tumor response and progression will be assessed by the Investigator using the iRECIST, 2017. RECIST v1.1 will be used to determine treatment decisions.
22. A safety event that occurs during the Pre-screening (Part B Only) Period (i.e., after the patient has signed the informed consent form for Pre-screening but prior to consent for the main study), will be reported as an SAE only if the event is related to a protocol-mandated procedure. After the patient signs informed consent form for the main study, all safety events that meet the serious criteria will be reported as SAEs. AE collection will begin after the administration of study drugs(s). (Note: An SAE narrative will not be required for SAEs that occur prior to study drug administration unless the event was related to a protocol mandated procedure). After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after last dose of study drug(s) (including comparator drug/other IMP) or initiation of new anticancer therapy, whichever occurs first. Reporting will also discontinue if the patient withdraws consent. Immune-related AEs (serious or non-serious) should be reported until 90 days after the last dose of DKN-01 and tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the Investigator should be reported regardless of time since the last dose of treatment
23. At the Screening visit, collect concomitant medications and procedures taken during the last 30 days.
24. If the EOT and Safety Follow-up Visits are planned to be conducted within 7 days of one another, the visit procedures from the visits may be combined and completed at the EOT visit, and the Safety Follow-up visit may be conducted instead as a telephone call to document AEs and concomitant medications/procedures. Telephone contacts with patients also should be conducted to assess immune-related AEs and concomitant medications (if appropriate, i.e., associated with an immune-related AE or is a new anticancer therapy) at 60 days and 90 days (± 14 days) after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected immune related AE at a telephone follow-up contact, the Investigator should arrange an unscheduled visit if further assessment is indicated.
25. DKN-01 ADA blood will be collected on C1D1 pre-dose and on all ODD cycles (C3D1pre-dose, C5D1 pre-dose, C7D1pre-dose, etc). After two years on treatment, DKN-01 ADA samples will not be collected during routine visits except for at the safety follow visit unless the subject had a known positive ADA at the EOT visit, then they should have repeat testing, where feasible, performed in the PD Follow Up and/or Survival Follow Up period until it is no longer positive.
26. **Sample collection windows: Pre-Dose:** Samples should be drawn within 60 minutes of the start of the DKN-01 infusion. **End of Infusion (EOI):** samples should be collected ± 5 minutes after the end of DKN-01 infusion. **3-12 hr Post-Dose**: Samples should be drawn a minimum of 3 hours after the DKN-01 infusion is completed. The sample can be drawn up to 12 hours after the DKN-01 sample is complete. After two years on treatment, DKK1 PK and serum samples will only be required at the safety follow up visit.
27. May be collected and resulted up to day 2 days prior to C1D1 to confirm eligibility and permit dosing on C1D1
28. Enrolled patients who have a history of radiation pneumonitis will receive Pulmonary Function Tests (PFT) at baseline and every 6 cycles ± 14 days during treatment and once either at the end of treatment visit (EOT) or at the Safety Follow-up Visit upon completion of therapy.
29. The ophthalmic assessments including eye exam, visual acuity test and optical coherence tomography (or equivalent diagnostic test) should be performed during Screening, every 6 cycles ± 14 days during treatment and once at either the EOT Visit or Safety Follow-up Visit.
30. Assessment of Amylase and Lipase and FT3 and FT4 will be conducted at Screening, every 3 cycles (i.e., Day 1 of Cycles 4, 7, 10 etc.) during therapy and once at either the EOT Visit or Safety Follow-up Visit
31. Vital signs and ECG should be performed prior to the collection of laboratory (blood) samples at all visits.

32. A fresh biopsy will be collected during the Screening period (+14 days) from patients who did not undergo a biopsy during the Pre-screening period for evaluation of DKK1 mRNA levels (unless it is clinically contraindicated per Investigator and after consultation with the Medical Monitor) for a retrospective DKK1 mRNA analysis.
33. Assessment of FT3 and FT4 will be conducted at Screening, every 3 cycles (i.e., Day 1 of Cycles 4, 7, 10 etc.) during therapy and once at either the EOT Visit or Safety Follow-up Visit

NOTE: All assessments should be performed prior to administration of study drugs (within -2 days) unless stated otherwise.

Schedule of Activities – Part C CAPOX Regimen (21-Day Cycle)

Procedure	Screening[1]	Treatment Period: Cycle 1 C1D1	Treatment Period: Cycle 1 C1D15	Treatment Period: at or after Cycle 2 D1	End-of-Treatment[22]	Safety Follow-Up[22]	PD Follow-up[2]	Survival Follow-up[3]	Unscheduled Visits[4]
	Days -28 to 0		±3D	+3D		30 Days Post Last Dose +7D	Q12 Weeks from EOT ± 14D	Q12 Weeks from EOT ± 14D	
Screening informed consent	X								
Medical history	X								
Cancer history, including treatment history[5] and, if available, genomics	X								
Demographics	X								
Randomization [29]		X							
Tumor tissue collection/biopsy[7]	X[6]			X[7]					X[7]
Height	X								
Weight	X	X	X	X	X	X			
Body surface area		X		X					
Vital signs[25]	X	X	X	X	X	X			X
Electrocardiogram [25, 9]	X	X		X	X	X			X
ECOG performance status	X	X		X	X	X			X
Physical examination	X	X			X	X			
Abbreviated physical examination				X					X
Laboratory sample collection:									
Hematology[8, 9]	X	X[9]	X	X	X	X			X
Coagulation	X	X			X	X			X
Clinical chemistries[8, 9]	X	X[9]	X	X	X	X			X
TSH	X	X		X	X	X			X
Urinalysis[8]	X	X		X	X	X			X
Pregnancy testing[9,10]	X	X[9]		X	X	X	X[10]	X[10]	X

Procedure	Screening[1]	Treatment Period: Cycle 1 C1D1	Treatment Period: Cycle 1 C1D15	Treatment Period: at or after Cycle 2 D1	End-of-Treatment[22]	Safety Follow-Up[22]	PD Follow-up[2]	Survival Follow-up[3]	Unscheduled Visits[4]
	Days -28 to 0		±3D	+3D		30 Days Post Last Dose +7D	Q12 Weeks from EOT ± 14D	Q12 Weeks from EOT ± 14D	
Plasma biomarker Analysis [30]	X	X		X	X				
Serum biomarker Analysis[30]	X	X		X	X				
Serum DKK1[24]		pre-dose, EOI, 3-12h post-dose		pre-dose, EOI		X			X
Serum DKN-01 PK [31]		pre-dose, EOI, 3-12h post-dose		pre-dose, EOI		X			
Serum tislelizumab PK[11]		pre-dose EOI		pre-dose EOI		X			
Serum DKN-01 ADA[23]		pre-dose		pre-dose (every ODD cycle)		X	X[12]	X[12]	
Serum tislelizumab ADA[13]		pre-dose		pre-dose		X	X[12]	X[12]	
ctDNA		pre-dose			X[14]		X[14]		
Study drug administration[15]									
DKN-01[16]		X	X	X					
Tiselelizumab[16]		X		X					
Oxaliplatin[16]		X		X					
Capecitabine[16]		X		X					
Baseline head imaging (MRI preferred)[17]	X								
Tumor imaging[17]	X			X	X		X		X
Dispense capecitabine		X		X					
Compliance diary-train/distribute		X		X					
Compliance diary-collect/monitor				X	X				
RECIST disease response assessment[18]				X	X		X		X
iRECIST assessment[19]				X	X		X		

Procedure	Screening[1]	Treatment Period: Cycle 1 C1D1	Treatment Period: Cycle 1 C1D15	Treatment Period: at or after Cycle 2 D1	End-of-Treatment[22]	Safety Follow-Up[22]	PD Follow-up[2]	Survival Follow-up[3]	Unscheduled Visits[4]
	Days -28 to 0		±3D	+3D		30 Days Post Last Dose +7D	Q12 Weeks from EOT ± 14D	Q12 Weeks from EOT ± 14D	
AEs, including infusion-related reactions and irAEs[20]	X	X		X	X	X			X
Concomitant medications and procedures[21]	X	X		X	X	X			X
Survival and subsequent therapies					X		X	X	
Pulmonary Function Tests (Korea only) [26]		X		X	X	X			
FT3 and FT4 (Korea only) [27]	X	X		X	X	X			
Ophthalmic Examination (Korea only) [28]	X			X	X	X			
Amylase and Lipase (Korea only) [27]	X	X		X	X	X			

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; BID = twice daily; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; DKK1 = Dickkopf-1; ECOG = Eastern Cooperative Oncology Group; EBV = Epstein Barr virus; EOI = end of infusion; EOT = end of treatment; IEC = independent ethics committee; IHC = immunohistochemistry; irAE = immune-related adverse event; IRB = institutional review board; iRECIST = Immune-related Response Evaluation Criteria in Solid Tumors; IV = intravenous; MRI = magnetic resonance imaging; MSI-H/MSI-L = microsatellite instability-high/low; MSS = microsatellite stable; PD = progressive disease; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; PI = Principal Investigator; PO = oral; Q12 weeks = once every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid-stimulating hormone.

Table footnotes:

1. Screening consent must be obtained prior to undergoing any Screening procedures. All Screening assessments must be performed within 28 days before C1D1 (except imaging which can be within 35 days). The results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to enrollment (C1D1) may be used for the purposes of screening rather than repeating the standard-of-care tests. Safety labs and physical exam must be performed within 3 days prior to dosing on C1D1 to confirm patient still meets treatment and eligibility criteria.
2. PD Follow-up Period applies only to patients who discontinue study treatment without documented PD. Follow-up assessments will be every 12 weeks (±14 days).
3. All patients will be followed in the Survival Follow-up Period 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 every 12 weeks ±14 days after the EOT visit or PD Follow-up Period discontinuation visit, as applicable. If a female patient is of childbearing potential, she will be followed monthly with a urine pregnancy test up to 6 months following last dose of study drug. This testing can occur at with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.

4. Unscheduled visits may be performed at any time during the study whenever necessary to assess or follow-up on Aes as deemed necessary by the PI or designee. The PI or designee may perform assessments outside of the study schedule (unscheduled visits) for safety purposes based on his/her clinical judgment. Only assessments deemed necessary by PI will be performed. The date and reason for the Unscheduled visit should be recorded in the source documentation, including recording of Aes and concomitant medications.
5. Cancer treatment history is to include documentation of prior cancer therapies, radiation therapy, surgery, and use of blood products, including red cell and platelet transfusions and growth factors within the previous 3 months.
6. Tumor tissue is mandatory. Fresh biopsy is preferred; archived specimen may be acceptable. The tumor tissue will be tested for DKK1 mRNA expression and PD-L1. In addition, should sufficient tumor sample be available, the biopsy may be tested for MSS assessment, genomic profiling, RNA profiling (e.g., RNA-Seq), immunohistology, EBV, infiltrating immune cells, and additional IHC analysis as applicable.
7. An on-treatment biopsy to evaluate the effects of treatment on the tumor tissue is required at Day 21 (+7 days) unless clinically not feasible. An additional biopsy may be collected at any other time during the study if a repeat biopsy is required clinically and the patient consents to the biopsy. Patients will be allowed to continue on-treatment until they require discontinuation for any reason (i.e., progression, AE) or until a patient reaches 2 years of treatment (as measured from C1D1).
8. Refer to Appendix 2. After two years on treatment, safety labs will only be required on Day 1 of each new treatment cycle unless clinically indicated.
9. Hematology, chemistry, pregnancy testing, and ECG must be performed, within 3 days prior to dosing at each cycle, to confirm patient meets requirements to receive study drug treatment.
10. 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. If a female patient is of childbearing potential, she will be followed monthly with a urine pregnancy test up to 6 months following the last dose of study drug. This testing can occur at with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.
11. Sampling, handling, and processing procedures are outlined in the Laboratory Manual. Predose (prior to the start of infusion) samples are required to be collected at Day 1 of C1, C2, C5, C9 and C17; post-dose/end of infusion (EOI) (within 30 minutes after completing tislelizumab infusion) samples are required to be collected at Day 1 of C1 and C5. An additional PK sample is required to be collected at the Safety Follow-Up Visit. If a patient presents with any immune-related adverse event, additional blood PK samples may be taken to determine the concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/IECs.
12. If a patient has known positive ADA (to DKN-01 [experimental group only] or tislelizumab) at the EOT visit, he or she should have repeat testing, where feasible, performed in the PD Follow-up Period and/or Survival Follow-up Period until the patient is no longer positive.
13. Blood used to test for anti-tislelizumab antibodies should be collected before beginning the Day 1 infusion of C1, C2, C5, C9, and C17 and at the mandatory Safety Follow-Up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs.
14. ctDNA is to be obtained upon PD (at EOT if discontinuing due to PD, or otherwise in PD follow-up).
15. Study drug is to be administered in the following order: premedications → DKN-01 (experimental group only) → tislelizumab → chemotherapy (see Section 5.2.2).
16. Patients in the **experimental group** will receive DKN-01 (600 mg, IV) and tislelizumab (200 mg, IV) on Day 1 of each 21-day cycle. For Cycle 1 only, an additional loading dose of DKN-01 (600 mg, IV) will be administered on Day 15. The CAPOX regimen will include oxaliplatin on Day 1 and capecitabine BID on Days 1-15 (for a total of 28 doses) of each 21-day cycle. Patients in the **control group** will follow the same administration order for tislelizumab and CAPOX but will not receive DKN-01 treatment. **Note**: Capecitabine should be taken after food (within 30 minutes of a meal) with water (morning and evening) and at the same time each day (±60 minutes). Chemotherapy dosing is to be administered per institutional standard of care.
17. Baseline imaging studies will be performed within 35 days of C1D1. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to enrollment may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 6 weeks (± 7 days), from Cycle 1 Day 1, for the first 24 weeks, then every 9 weeks (± 7 days) after 24 weeks. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted on the planned schedule. Screening assessments and each subsequent assessment of the tumor must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc.). All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at Screening is required to be used throughout the study (e.g., the same contrast protocol for CT scans).

18. Disease response is to be assessed every 6 weeks (± 7 days), from Cycle 1 Day 1, for the first 24 weeks, then every 9 weeks (± 7 days) after 24 weeks based on RECIST v1.1. After first documentation of response (CR or PR), confirmation of tumor response should occur at a minimum of 4 weeks after the first response or at the next scheduled assessment time point.
19. Following progression using RECIST 1.1, tumor response and progression will be assessed by the Investigator using iRECIST, 2017. RECIST v1.1 will be used to determine treatment decisions.
20. After the patient signs informed consent form for the study, all safety events that meet the serious criteria will be reported as SAEs. AE collection will begin after the administration of study drugs(s). (Note: An SAE narrative will not be required for SAEs that occur prior to study drug administration unless the event was related to a protocol mandated procedure). After initiation of study drug, all Aes and SAEs, regardless of relationship to study drug, will be reported until 30 days after last dose of study drug(s) (including comparator drug/other IMP) or initiation of new anticancer therapy, whichever occurs first. Reporting will also discontinue if the patient withdraws consent. Immune-related Aes (serious or non-serious) should be reported until 90 days after the last dose of DKN-01 and tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the Investigator should be reported regardless of time since the last dose of treatment
21. At the Screening visit, collect concomitant medications and procedures taken during the last 30 days.
22. If the EOT and Safety Follow-up Visits are planned to be conducted within 7 days of one another, the visit procedures from the visits may be combined and completed at the EOT visit, and the Safety Follow-up visit may be conducted instead as a telephone call to document Aes and concomitant medications/procedures. Telephone contacts with patients also should be conducted to assess immune-related Aes and concomitant medications (if appropriate, i.e., associated with an immune-related AE or is a new anticancer therapy) at 60 days and 90 days (± 14 days) after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected immune related AE at a telephone follow-up contact, the Investigator should arrange an unscheduled visit if further assessment is indicated.
23. **Experimental group only:** DKN-01 ADA blood will be collected on C1D1 pre-dose and on all ODD cycles (C3D1pre-dose, C5D1 pre-dose, C7D1 pre-dose, etc). If a patient has known positive ADA at the EOT visit, repeat testing, where feasible, will be performed in the PD Follow-up Period and/or Survival Follow-up Period until the patient is no longer positive. After two years on treatment, DKN-01 ADA samples will not be collected during routine visits except for at the safety follow visit unless the subject had a known positive ADA at the EOT visit, then they should have repeat testing, where feasible, performed in the PD Follow Up and/or Survival Follow Up period until it is no longer positive.
24. **Sample collection windows for the experimental group**: Pre-Dose: Samples should be drawn prior to the start of the DKN-01 infusion. End of Infusion (EOI): samples should be collected ± 5 minutes after the end of DKN-01 infusion. 3-12 hr Post-Dose: Samples should be drawn a minimum of 3 hours after the DKN-01 infusion is completed. The sample can be drawn up to 12 hours after the DKN-01 infusion sample is complete. After two years on treatment, DKK1 PK and serum samples will only be required at the safety follow up visit. **Sample collection windows for the control group**: Only Pre-Dose sample collection is required. Samples should be drawn prior to the start of treatment.
25. Vital signs and ECG should be performed prior to the collection of laboratory (blood) samples at all visits if possible per sites standard process.
26. Enrolled patients who have a history of radiation pneumonitis will receive Pulmonary Function Tests (PFT) at C1D1 and every 6 cycles ± 14 days during treatment and once either at the end of treatment visit (EOT) or at the Safety Follow-up Visit upon completion of therapy.
27. Assessment of Amylase and Lipase and FT3 and FT4 will be conducted at Screening, every 3 cycles (i.e., Day 1 of Cycles 1, 4, 7, 10 etc.) during therapy and once at either the EOT Visit or Safety Follow-up Visit
28. The ophthalmic assessments including eye exam, visual acuity test and optical coherence tomography (or equivalent diagnostic test) should be performed during Screening, every 6 cycles ± 14 days during treatment and once at either the EOT Visit or Safety Follow-up Visit.
29. Randomization may occur up to 3 days prior to C1D1 as long as safety labs for dosing are resulted.
30. Sampling, handling, and processing procedures are outlined in the Laboratory Manual for plasma and serum biomarker analysis. Samples are required to be collected at Screening and pre-dose at Day 1 of C1, C2, C3, and EOT.
31. **Sample collection windows for the experimental group only**: Pre-Dose: Samples should be drawn prior to the start of the DKN-01 infusion. End of Infusion (EOI): samples should be collected ± 5 minutes after the end of DKN-01 infusion. 3-12 hr Post-Dose: Samples should be drawn a minimum of 3 hours after the DKN-01 infusion is completed. The sample can be drawn up to 12 hours after the DKN-01 infusion sample is complete. After two years on treatment, DKK1 PK and serum samples will only be required at the safety follow up visit.

NOTE: All assessments should be performed prior to administration of study drugs (within -2 days) unless stated otherwise.

Schedule of Activities – Part C mFOLFOX6 Regimen (14-Day Cycle)

		Treatment Period							
		Cycle 1		at or after Cycle 2	End-of-Treatment[22]	Safety Follow-Up[22]	PD Follow-up[2]	Survival Follow-up[3]	Unscheduled Visits[4]
Procedure	**Screening[1]**	**C1D1**	**C1D8**	**D1**		**30 Days Post Last Dose**	**Q12 Weeks from EOT**	**Q12 Weeks from EOT**	
	Days -28 to 0		**±3D**	**+3D**		**+7D**	**± 14D**	**± 14D**	
Screening informed consent	X								
Medical history	X								
Cancer history, including treatment history[5] and, if available, genomics	X								
Demographics	X								
Randmization[29]		X							
Tumor tissue collection/biopsy[7]	X[6]			X[7]					X[7]
Height	X								
Weight	X	X	X	X	X	X			
Body surface area		X		X					
Vital signs[25]	X	X	X	X	X	X			X
Electrocardiogram[25, 9]	X	X		X	X	X			X
ECOG performance status	X	X		X	X	X			X
Physical examination	X	X			X	X			
Abbreviated physical examination				X					X
Laboratory sample collection:									
Hematology[8,9]	X	X[9]	X	X	X	X			X
Coagulation	X	X			X	X			X
Clinical chemistries[8, 9]	X	X[9]	X	X	X	X			X
TSH	X	X		X	X	X			X
Urinalysis[8]	X	X		X	X	X			X
Pregnancy testing[9,10]	X	X[9]		X	X	X	X[10]	X[10]	X

Procedure	Screening[1]	Treatment Period: Cycle 1 C1D1	Treatment Period: Cycle 1 C1D8	Treatment Period: at or after Cycle 2 D1	End-of-Treatment[22]	Safety Follow-Up[22]	PD Follow-up[2]	Survival Follow-up[3]	Unscheduled Visits[4]
	Days -28 to 0		±3D	+3D		30 Days Post Last Dose +7D	Q12 Weeks from EOT ± 14D	Q12 Weeks from EOT ± 14D	
Plasma biomarker Analysis[30]	X	X		X	X				
Serum biomarker Analysis[30]	X	X		X	X				
Serum DKK1[24]		pre-dose, EOI, 3-12h post-dose		pre-dose, EOI		X			X
Serum DKN-01 PK [31]		pre-dose, EOI, 3-12h post-dose		pre-dose, EOI		X			
Serum tislelizumab PK [11]		pre-dose EOI		pre-dose EOI		X			
Serum DKN-01 ADA[23]		pre-dose		pre-dose (every ODD cycle)		X	X[12]	X[12]	
Serum tislelizumab ADA[13]		pre-dose		pre-dose		X	X[12]	X[12]	
ctDNA		pre-dose			X[14]		X[14]		
Study drug administration[15]:									
DKN-01[16]		X	X	X					
Tiselelizumab[16]		X		X					
Leucovorin calcium [16]		X		X					
Fluorouracil[16]		X		X					
Oxaliplatin[16]		X		X					
Baseline head imaging (MRI preferred)[17]	X								
Tumor imaging[17]	X			X	X		X		X
RECIST disease response assessment[18]				X	X		X		X
iRECIST assessment[19]				X	X		X		
AEs, including infusion-related reactions and irAEs[20]	X	X		X	X	X			X

Procedure	Screening[1]	Treatment Period: Cycle 1 C1D1	Treatment Period: Cycle 1 C1D8	Treatment Period: at or after Cycle 2 D1	End-of-Treatment[22]	Safety Follow-Up[22]	PD Follow-up[2]	Survival Follow-up[3]	Unscheduled Visits[4]
						30 Days Post Last Dose	Q12 Weeks from EOT	Q12 Weeks from EOT	
	Days -28 to 0		±3D	+3D		+7D	± 14D	± 14D	
Concomitant medications and procedures[21]	X	X		X	X	X			X
Survival and subsequent therapies					X		X	X	
Pulmonary Function Tests (Korea only)[26]		X		X	X	X			
FT3 and FT4 (Korea only)[27]	X	X		X	X	X			
Ophthalmic Examination (Korea only)[28]	X			X	X	X			
Amylase and Lipase (Korea only)[27]	X	X		X	X	X			

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; BID = twice daily; C = cycle; CT = computed tomography; ctDNA = circulating tumor DNA; D = day; DKK1 = Dickkopf-1; ECOG = Eastern Cooperative Oncology Group; EBV = Epstein Barr virus; EOI = end of infusion; EOT = end of treatment; IEC = independent ethics committee; IHC = immunohistochemistry; irAE = immune-related adverse event; IRB = institutional review board; iRECIST = Immune-related Response Evaluation Criteria in Solid Tumors; IV = intravenous; MRI = magnetic resonance imaging; MSI-H/MSI-L = microsatellite instability-high/low; MSS = microsatellite stable; PD = progressive disease; PD-L1 = programmed cell death ligand 1; PK = pharmacokinetics; PI = Principal Investigator; PO = oral; Q12 weeks = once every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid-stimulating hormone.

Table footnotes:

1. Screening consent must be obtained prior to undergoing any Screening procedures. All Screening assessments must be performed within 28 days before C1D1 (except imaging which can be within 35 days). The results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to enrollment (C1D1) may be used for the purposes of screening rather than repeating the standard-of-care tests. Safety labs and physical exam must be performed within 3 days prior to dosing on C1D1 to confirm patient still meets treatment and eligibility criteria.
2. PD Follow-up Period applies only to patients who discontinue study treatment without documented PD. Follow-up assessments will be every 12 weeks (±14 days).
3. All patients will be followed in the Survival Follow-up Period 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 every 12 weeks ±14 days after the EOT visit or PD Follow-up Period discontinuation visit, as applicable. If a female patient is of childbearing potential, she will be followed monthly with a urine pregnancy test up to 6 months following the last dose of study drug. This testing can occur at with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.
4. Unscheduled visits may be performed at any time during the study whenever necessary to assess or follow-up on AEs as deemed necessary by the PI or designee. The PI or designee may perform assessments outside of the study schedule (unscheduled visits) for safety purposes based on his/her clinical judgment. Only assessments deemed necessary by PI will be performed. The date and reason for the Unscheduled visit should be recorded in the source documentation, including recording of AEs and concomitant medications.

5. Cancer treatment history is to include documentation of prior cancer therapies, radiation therapy, surgery, and use of blood products, including red cell and platelet transfusions and growth factors within the previous 3 months.
6. Tumor tissue is mandatory. Fresh biopsy is preferred; archived specimen may be acceptable. The tumor tissue will be tested for DKK1 mRNA expression and PD-L1. In addition, should sufficient tumor sample be available, the biopsy may be tested for MSS assessment, genomic profiling, RNA profiling (e.g., RNA-Seq), immunohistology, EBV, infiltrating immune cells, and additional IHC analysis as applicable.
7. An on-treatment biopsy to evaluate the effects of treatment on the tumor tissue is required at Day 21 (+7 days). An additional biopsy may be collected at any other time during the study if a repeat biopsy is required clinically and the patient consents to the biopsy. Patients will be allowed to continue on-treatment until they require discontinuation for any reason (i.e., progression, AE) or until a patient reaches 2 years of treatment (as measured from C1D1).
8. Refer to Appendix 2. After two years on treatment, safety labs will only be required on Day 1 of each new treatment cycle unless clinically indicated.
9. Hematology, chemistry, pregnancy testing, and ECG must be performed within 3 days prior to dosing at each cycle, to confirm patient meets requirements to receive study drug treatment.
10. 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. If a female patient is of childbearing potential, she will be followed monthly with a urine pregnancy test up to 6 months following the last dose of study drug. This testing can occur at with a primary care physician and documentation made available to the study team. Male subjects will be asked during the PD and/or survival follow up period, if their female partners have experienced a pregnancy.
11. Sampling, handling, and processing procedures are outlined in the Laboratory Manual. Predose (prior to the start of infusion) samples are required to be collected at Day 1 of C1, C4, C7, C13 and C25and EOT/Safety Follow-up; post-dose/end of infusion (EOI) (within 30 minutes after completing tislelizumab infusion) samples are required to be collected at Day 1 of C1, C7, and 30 days ± 7days after the last dose. An additional PK sample is required to be collected at the Safety Follow-Up Visit. If a patient presents with any immune-related adverse event, additional blood PK samples may be taken to determine the concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/IECs.
12. If a patient has known positive ADA (to DKN-01 or tislelizumab) at the EOT visit, he or she should have repeat testing, where feasible, performed in the PD Follow-up Period and/or Survival Follow-up Period until the patient is no longer positive.
13. Blood used to test for anti-tislelizumab antibodies should be collected before beginning the Day 1 infusion of C1, C4, C7, C13 and C25 and at the mandatory Safety Follow-Up Visit. All samples should be drawn at the same time as blood collection for predose PK analysis. These tests are required when it is allowed by local regulations/IRBs/IECs.
14. ctDNA is to be obtained upon PD (at EOT if discontinuing due to PD, or otherwise in PD follow-up).
15. Study drug is to be administered in the following order: premedications → DKN-01 (experimental group only) → tislelizumab followed by chemotherapy (see Section 5.2.2).
16. Patients in the **experimental group** will receive DKN-01 (400 mg, IV) on D1 of each 14-day cycle and tislelizumab (400 mg, IV) will be administered every 6 weeks starting on C1D1 and continuing every third 14-day cycle (e.g., C4D1, C7D1, etc). For Cycle 1 only, an additional loading dose of DKN-01 (400 mg, IV) will be administered on Day 8. The mFOLFOX6 regimen will be administered every 14 days and may include leucovorin calcium (folinic acid) IV on Day 1, fluorouracil IV bolus on Day 1, then fluorouracil IV/day (Days 1 and 2), and oxaliplatin IV on Day 1. Patients in the **control group** will follow the same administration order for tislelizumab and mFOLFOX6 but will not receive DKN-01 treatment. Chemotherapy dosing is to be administered per institutional standard of care.
17. Baseline imaging studies will be performed within 35 days before C1D1. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤28 days prior to enrollment may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 6 weeks (± 7 days), from Cycle 1 Day 1, for the first 24 weeks, then every 9 weeks (± 7 days) after 24 weeks. If a tumor assessment is missed or conducted outside of the specified assessment window, all subsequent scans should be conducted on the planned schedule. Screening assessments and each subsequent assessment of the tumor must include CT scans (with oral/intravenous contrast, unless contraindicated) or MRI of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc.). All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at Screening is required to be used throughout the study (e.g., the same contrast protocol for CT scans).
18. Disease response is to be assessed every 6 weeks (± 7 days), from Cycle 1 Day 1, for the first 24 weeks, then every 9 weeks (± 7 days) after 24 weeks based on RECIST v1.1. After first documentation of response (CR or PR), confirmation of tumor response should occur at a minimum of 4 weeks after the first response or at the next scheduled assessment time point.
19. Following progression using RECIST 1.1, tumor response and progression will be assessed by the Investigator using iRECIST, 2017. RECIST v1.1 will be used to determine treatment decisions.

20. After the patient signs informed consent form for the main study, all safety events that meet the serious criteria will be reported as SAEs. AE collection will begin after the administration of study drugs(s). (Note: An SAE narrative will not be required for SAEs that occur prior to study drug administration unless the event was related to a protocol mandated procedure). After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after last dose of study drug(s) (including comparator drug/other IMP) or initiation of new anticancer therapy, whichever occurs first. Reporting will also discontinue if the patient withdraws consent. Immune-related AEs (serious or non-serious) should be reported until 90 days after the last dose of DKN-01 and tislelizumab, regardless of whether or not the patient starts a new anticancer therapy. All SAEs considered related to the study drug(s) that are brought to the attention of the Investigator should be reported regardless of time since the last dose of treatment
21. At the Screening visit, collect concomitant medications and procedures taken during the last 30 days.
22. If the EOT and Safety Follow-up Visits are planned to be conducted within 7 days of one another, the visit procedures from the visits may be combined and completed at the EOT visit, and the Safety Follow-up visit may be conducted instead as a telephone call to document AEs and concomitant medications/procedures. Telephone contacts with patients also should be conducted to assess immune-related AEs and concomitant medications (if appropriate, i.e., associated with an immune-related AE or is a new anticancer therapy) at 60 days and 90 days (± 14 days) after the last dose of study treatment, regardless of whether or not the patient starts a new anticancer therapy. If patients report a suspected immune related AE at a telephone follow-up contact, the Investigator should arrange an unscheduled visit if further assessment is indicated.
23. **Experimental group only:** DKN-01 ADA blood will be collected on C1D1 pre-dose and on all ODD cycles (C3D1pre-dose, C5D1 pre-dose, C7D1 pre-dose, etc). If a patient has known positive ADA at the EOT visit, repeat testing, where feasible, will be performed in the PD Follow-up Period and/or Survival Follow-up Period until the patient is no longer positive. After two years on treatment, DKN-01 ADA samples will not be collected during routine visits except for at the safety follow visit unless the subject had a known positive ADA at the EOT visit, then they should have repeat testing, where feasible, performed in the PD Follow Up and/or Survival Follow Up period until it is no longer positive.
24. **Sample collection windows for the experimental group**: Pre-Dose: Samples should be drawn prior to the start of the DKN-01 infusion. End of Infusion (EOI): samples should be collected ± 5 minutes after the end of DKN-01 infusion. 3-12 hr Post-Dose: Samples should be drawn a minimum of 3 hours after the DKN-01 infusion is completed. The sample can be drawn up to 12 hours after the DKN-01 infusion sample is complete. After two years on treatment, DKK1 PK and serum samples will only be required at the safety follow up visit. **Sample collection windows for the control group**: Only Pre-Dose sample collection is required. Samples should be drawn prior to the start of treatment.
25. Vital signs and ECG should be performed prior to the collection of laboratory (blood) samples at all visits if possible per sites standard process.
26. Enrolled patients who have a history of radiation pneumonitis will receive Pulmonary Function Tests (PFT) at C1D1 and every 6 cycles ± 14 days during treatment and once either at the end of treatment visit (EOT) or at the Safety Follow-up Visit upon completion of therapy.
27. Assessment of Amylase and Lipase and FT3 and FT4 will be conducted at Screening, every 3 cycles (i.e., Day 1 of Cycles 1, 4, 7, 10 etc.) during therapy and once at either the EOT Visit or Safety Follow-up Visit.
28. The ophthalmic assessments including eye exam, visual acuity test and optical coherence tomography (or equivalent diagnostic test) should be performed during Screening, every 6 cycles ± 14 days during treatment and once at either the EOT Visit or Safety Follow-up Visit.
29. Randomization may occur up to 3 days prior to C1D1 as long as safety labs for dosing are resulted.
30. Sampling, handling, and processing procedures are outlined in the Laboratory Manual for plasma and serum biomarker analysis. Samples are required to be collected at Screening and pre-dose (prior to the start of infusion) at Day 1 of C1, C2, C3, and EOT.
31. **Sample collection windows for the experimental group only**: Pre-Dose: Samples should be drawn prior to the start of the DKN-01 infusion. End of Infusion (EOI): samples should be collected ± 5 minutes after the end of DKN-01 infusion. 3-12 hr Post-Dose: Samples should be drawn a minimum of 3 hours after the DKN-01 infusion is completed. The sample can be drawn up to 12 hours after the DKN-01 infusion sample is complete. After two years on treatment, DKK1 PK and serum samples will only be required at the safety follow up visit.

NOTE: All assessments should be performed prior to administration of study drugs (within -2 days) unless stated otherwise.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Serum Chemistry[a]	**Hematology**	**Urinalysis**
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Direct bilirubin Blood urea nitrogen or urea Potassium Sodium Total calcium[b] Creatinine Glucose Lactate dehydrogenase Total protein Creatine kinase[c] Phosphorus Carbon dioxide Chloride Lipase[f] Amylase[f]	Hematocrit Hemoglobin Platelet counts WBC count Monocytes Eosinophils Basophils Lymphocytes Neutrophils NLR[d]	Glucose Protein Blood Ketones
Coagulation	**Other Laboratory Assessments**	**Pregnancy Testing**
Prothrombin time Partial thromboplastin time International normalized ratio	TSH FT3[f] FT4[f]	For women of childbearing potential[e]

Abbreviations: NLR = neutrophil-to-lymphocyte ratio; TSH = thyroid-stimulating hormone; WBC = white blood cell.

a. It is acceptable to use the automated differential for complete blood count.
b. Total calcium values will be corrected for patients with hypoproteinemia.
c. All patients will have creatine kinase and CK-MB testing at Screening, and to be repeated at all scheduled visits during the first 3 treatment cycles, all predose assessments from C4 onwards, and at the End of Treatment/Safety Follow-up visit. If CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Refer to Section 7.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.
d. Calculated only once at C1D1 (baseline).
e. 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. Please see Appendix 10.
f. For patients enrolled in the Republic of Korea only

APPENDIX 3. EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

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

Source: (Oken, Creech et al. 1982). Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

APPENDIX 4. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

Source: (Eisenhauer, Therasse et al. 2009).

Definitions

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (v1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT and magnetic resonance imaging (MRI) (no less than double the slice thickness and a minimum of 10 mm). Assumes a scan slice thickness no greater than 5 mm.
- 10 mm caliper measurement by clinical examination (when superficial)
- 20 mm by chest Xray (if clearly defined and surrounded by aerated lung)

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 recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. 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 are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- 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 as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, 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.
- Lesions with prior local treatment:
- Tumor lesions 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. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm by 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.

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. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

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. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.
- Chest Xray: Chest CT is preferred over chest Xray, particularly when progression is an important endpoint, since CT is more sensitive than Xray, particularly in identifying new lesions. However, lesions on chest Xray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date, and because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials

where recurrence following complete response (CR) or surgical resection is an endpoint.

- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report form may be designed to have target

nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

- 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 (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded on the electronic case report form (eCRF). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat, such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that measurement should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When nonnodal 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

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
- NonCR/NonPD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression (as detailed below) of existing nontarget lesions. (Note: The appearance of one or more new lesions is also considered progression.)
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an

overall level of substantial worsening in nontarget 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 nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

- When the patient has only non-measurable disease: This circumstance arises in some phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept applies here as noted above; however, in this instance 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 (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to wide-spread, or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, 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 (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain scan ordered that reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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.

While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning 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 FDGPET at baseline, with a positive FDGPET at followup, is a sign of PD based on a new lesion.
- No FDGPET at baseline and a positive FDGPET at followup: If the positive FDGPET at followup corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDGPET at followup is not confirmed as a new site of disease on CT, additional followup 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 FDGPET scan). If the positive FDGPET at followup corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- Timepoint Response
- It is assumed that at each protocol specified time point, a response assessment occurs. The following table provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline:

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

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

When patients have nonmeasurable (therefore nontarget) disease only, the following table is to be used:

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	SD (Non-CR/non-PD)
Not all evaluated	No	NE

Nontarget Lesions	New Lesions	Overall Response
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; SD = stable disease.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later).

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero."

In trials where confirmation of response is required, repeated "NE" (not evaluable) time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as

"symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

Conditions that define "early progression, early death, and inevaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If progression is confirmed at the next scheduled assessment, the date of progression should be the earlier date when progression was suspected.

Confirmation of Measurement/Duration of Response

Confirmation

In nonrandomized 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 trials (phase 2 or 3) or trials 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 trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 5. PREEXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

Prospective patients should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease.

Please contact the Medical Monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

Acute disseminated encephalomyelitis	Addison disease
Ankylosing spondylitis	Antiphospholipid antibody syndrome
Aplastic anemia	Autoimmune hemolytic anemia
Autoimmune hepatitis	Autoimmune hypoparathyroidism
Autoimmune hypophysitis	Autoimmune myocarditis
Autoimmune oophoritis	Autoimmune orchitis
Autoimmune thrombocytopenic purpura	Behcet disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn disease
Dermatomyositis	Dysautonomia
Epidermolysis bullosa acquisita	Gestational pemphigoid
Giant cell arteritis	Goodpasture syndrome
Granulomatosis with polyangiitis	Graves disease
Guillain-Barré syndrome	Hashimoto disease
Immunoglobulin A (IgA) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki disease
Lambert-Eaton myasthenic syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren ulcer
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodosa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren syndrome
Stiff person syndrome	Takayasu arteritis
Ulcerative colitis	Vogt-Kovangai-Harada disease

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Adapted from (Dolgin, Association et al. 1994).
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

APPENDIX 7. MANAGEMENT OF POSSIBLE DKN-01-ASSOCIATED ADVERSE EFFECTS

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 5.2.3): • Resume DKN-01 as per Table 10 or Table 11 as applicable 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 × ULN • ALT >2.5 × ULN • Total bilirubin >1.5 × ULN	**Moderate:** • AST or ALT >2.5 to <5.0 × ULN and/or • Total bilirubin >1.5 to <3.0 × 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 5.2.3): • Resume DKN-01 as per Table 10 or Table 11 as applicable if liver function tests are <2.5 × ULN or return to BL and bilirubin is <1.5 × ULN or returns to BL. Symptoms Ongoing: • If AST or ALT elevation continues to be >5 × ULN OR total bilirubin >3 × ULN, see below.
	Severe or life-threatening • AST or ALT >5.0 × ULN and/or • Total bilirubin >3.0 × 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 5.2.3): • Resume DKN-01 as per Table 10 or Table 11 as applicable 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 5.2.3): • Resume DKN-01 as per Table 10 or Table 11 as applicable 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 5.2.3): • Resume DKN-01 as per Table 10 or Table 11 as applicable when: • Patient is stable on hormone-replacement therapy (as indicated) Symptoms Ongoing: • Permanently discontinue DKN-01

Abbreviations: ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; ULN = upper limit of normal.

APPENDIX 8. IMMUNE-RELATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any irAE are intended as a guidance. This document should be used in conjunction with expert clinical judgement (by specialist physicians experienced in the treatment of cancer using immunological agents), and individual institutional guidelines or policies.

Criteria used to diagnose irAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, disease progression, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an irAE diagnosis:

- What was the temporal relationship between initiation of tislelizumab and the AE?
- How did the patient respond to withdrawal of tislelizumab?
- Did the event recur when tislelizumab was reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is disease progression or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the irAE field associated with the AE in the eCRF should be checked. If further diagnostic evaluations change the assessment, the eCRF should be updated accordingly.

Recommended Diagnostic Tests in the Management of Possible Immune-related Adverse Events

Immune-related Toxicity	Diagnostic Evaluation Guideline
Thyroid Disorders	Scheduled and repeated thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath, or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including DLCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological Toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.

Recommended Diagnostic Tests in the Management of Possible Immune-related Adverse Events

Immune-related Toxicity	Diagnostic Evaluation Guideline
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium difficile* toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, e.g., X-ray, CT scan. If a patient experiences bleeding, pain, or distension, consider colonoscopy with biopsy and surgical intervention as appropriate.
Eye Disorders	If a patient experiences acute, new onset, or worsening of eye inflammation; blurred vision; or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (e.g., daily if Grade 3 to 4; every 2 to 3 days if Grade 2, until recovering). Review medications (e.g., statins, antibiotics) and alcohol history. Perform liver screen including Hepatitis A/B/C serology, Hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (e.g., ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to a nephrologist for further management assistance.
Dermatology	Consider other causes by conducting a physical examination. Consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin, and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, CK/CK-MB, troponin (I and/or T), and refer to a cardiologist.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibody; AST = aspartate aminotransferase; CK = creatine kinase; CK-MB = creatine kinase cardiac isoenzyme; CNS = central nervous system; CRP = C-reactive protein; CT = computed tomography; DLCO = diffusing capacity for carbon monoxide; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; FBC = full blood count; HIV = human immunodeficiency virus; INR = international normalized ratio; LCI = liver cytosolic antigen; LFT = liver function test; LKM = liver kidney microsomal antibody; LP = liver pancreas antigen; MRA = magnetic resonance angiogram; MRI = magnetic resonance imaging; PCR = polymerase chain reaction; SLA = soluble liver antigen; SMA = smooth muscle antibody; T4 = thyroxine; TFT = thyroid function tests; TSH = thyroid-stimulating hormone; UEC = urea electrolytes and creatinine.

Treatment of Immune-Related Adverse Events

- Immune-related AEs can escalate quickly. Study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention as appropriate is required.

- Immune-related AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the study Medical Monitor.
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug may be considered if there is evidence of a clinical response to study treatment, after consultation with the study Medical Monitor.
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory irAEs, consider use of steroid-sparing agents (e.g., mycophenolate mofetil [MMF]).
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving longterm immunosuppressive therapy.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Thyroid Disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker, and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with comorbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
Hypophysitis	**1-2** Mild-moderate symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4.	Continue study treatment.
	3-4 Severe or life-threatening symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse intravenous methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinologist's advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to ≤Grade 2. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: e.g., blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe or life-threatening symptoms: breathless at rest	Admit to a hospital and initiate treatment with intravenous methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, e.g., blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological Toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening symptoms	Initiate treatment with oral prednisolone or intravenous methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/Diarrhea	**1** Mild symptoms: ≤3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for >14 days, manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (nonenteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks. Consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Severe symptoms: >6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, e.g., blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Class III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/ sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study Medical Monitor.
	4 Life-threatening symptoms		Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, <10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers >30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: intravenous methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study Medical Monitor.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Skin sloughing >30% BSA with associated symptoms (e.g., erythema, purpura, epidermal detachment)	Initiate intravenous methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.
Hepatitis	**1** ALT or AST >ULN to 3 x ULN	Check LFTs within 1 week and before the next dose; check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5 x ULN	Recheck LFTs every 48-72 hours. For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days, then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline Grade and prednisolone tapered to ≤10 mg.
	3 ALT or AST 5-20 x ULN	ALT/AST <400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST >400 IU/L or raised bilirubin/INR/low albumin: Initiate intravenous (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study Medical Monitor.
	4 ALT or AST >20 x ULN	Initiate intravenous methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	Worsening LFTs despite steroids: • If on oral prednisolone, change to pulsed intravenous methylprednisolone. • If on intravenous methylprednisolone, add mycophenolate mofetil (MMF) 500 to 1000 mg twice a day. • If worsens on MMF, consider addition of tacrolimus. Duration and dose of steroid required will depend on severity of event.		
Nephritis	**1** Creatinine 1.5 x baseline or >ULN to 1.5 x ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.
	2 Creatinine >1.5-3 x baseline or >1.5-3 x ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to <10 mg prednisolone.
	3 Creatinine >3 x baseline or >3-6 x ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate intravenous (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine >6 x ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ Hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value >500 mg/dL; >27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
Ocular Toxicity	**1** Asymptomatic eye examination/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study Medical Monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate intravenous (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study Medical Monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment, manage as a Grade 3 event.	Continue treatment or, if symptoms continue to worsen, hold study treatment until symptoms improve to baseline or Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study Medical Monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate intravenous (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improve to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider intravenous corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ Rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 x ULN or worse, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus intravenous (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve, add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	For Grade 3: Hold study treatment until improved to Grade 0-1. Discontinue upon any evidence of myocardial involvement.
Myocarditis[a]	**<2** Asymptomatic but significantly increased CK-MB or increased troponin OR clinically significant intraventricular conduction delay	Initiate cardiac evaluation under close monitoring with repeat serum testing and including ECG, cardiac echo/MUGA, and/or other interventions per institutional guidelines; consider referral to a cardiologist. If diagnosis of myocarditis is confirmed, treat as Grade 2.	Hold study treatment. If a diagnosis of myocarditis is confirmed and considered immune-related, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study Medical Monitor.
	2 Symptoms on mild-moderate exertion	Admit to hospital and initiate oral prednisolone or intravenous (methyl)prednisolone at 1-2 mg/kg/day. Consult with a cardiologist and manage symptoms of cardiac failure according to local guidelines. If no immediate response, change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab, or anti-thymocyte globulin.	
	3 Severe symptoms with mild exertion		Hold study treatment. If a diagnosis of

Autoimmune Toxicity	Grade	Treatment Guidelines (Subject to Clinical Judgement)	Study Drug Management
	4 Life-threatening		myocarditis is confirmed and considered immune related, permanently discontinue study treatment in patients with moderate or severe symptoms. Patients with no symptoms or mild symptoms may not restart tislelizumab unless cardiac parameters have returned to baseline and after discussion with the study Medical Monitor.

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSA = body surface area; CHF = congestive heart failure; CK = creatine kinase; CK-MB = creatine kinase cardiac isoenzyme; ECG = electrocardiogram; INR = international normalized ratio; LFT = liver function test; MMF = mycophenolate mofetil; MUGA = multigated acquisition scan; NYHA = New York Heart Association; T4 = thyroxine; TB = tuberculosis; TFT = thyroid function test; TSH = thyroid-stimulating hormone; U&E = urea and electrolytes; ULN = upper limit of normal.

[a] If clinically significant cardiac enzyme abnormalities are detected during laboratory assessment and serial cardiac enzyme assessments pose logistical hardship for the patient, then patient hospitalization should strongly be considered until immune-related myocarditis has been ruled out.

Note: Recommendation for diagnostic evaluation and management of irAEs is based on European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines (Haanen, Carbonnel et al. 2017, Brahmer, Lacchetti et al. 2018), and common immune-related toxicities are detailed in this appendix. For any AEs not included in this appendix, please refer to the ASCO Clinical Practice Guideline (Brahmer, Lacchetti et al. 2018) for further guidance on diagnostic evaluation and management of immune-related toxicities.

APPENDIX 9. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate (eGFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey, Stevens et al. 2009) and the Modification of Diet in Renal Disease (MDRD) Study equation. The National Kidney Disease Education Program (NKDEP) calculators rely on creatinine determinations which are isotope dilution mass spectrometry (IDMS) traceable. All laboratories should be using creatinine methods calibrated to be IDMS traceable.

This CKD-EPI equation calculator should be used when serum creatinine (S_{cr}) is reported in mg/dL.

$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{cr}/κ or 1, and

max indicates the maximum of S_{cr}/κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found here:
https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators

APPENDIX 10. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

The Clinical Trials Facilitation Group recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control (CTFG 2014). These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
    - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation
    - Oral, injectable, implantable
      Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide.
- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner
  Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study patient and there has been a medical assessment confirming surgical success.
    - A sterile male is one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility.
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment)
  Note: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception, and if used, this method must be used in combination with one of the highly effective forms of birth control listed above.

Definitions of "Women of Childbearing Potential," "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant.

Conversely, “women of no childbearing potential” are defined as female patients meeting any of the following criteria:

- Surgically sterile (i.e., through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
    - ≥55 years of age with no spontaneous menses for ≥12 months OR
    - <55 years of age with no spontaneous menses for ≥12 months AND with postmenopausal follicle-stimulating hormone concentration >30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If a follicle-stimulating hormone measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from (CTFG 2014).

APPENDIX 11. NCI-CTCAE V5.0 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, IV 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.					

Abbreviations: IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; O2 = oxygen.

APPENDIX 12. 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-related 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-related 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-related 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-related reaction with or without premedication will not receive further DKN-01 treatment but will continue to be followed on the protocol.

Abbreviations: IV = intravenous

APPENDIX 13. Management of Tislelizumab Infusion-Related Reaction and Hypersensitivity Reaction

Managing Infusion-Related Reactions

Patients should be closely monitored for infusion-related reactions. Immediate access to an Intensive Care Unit (ICU) or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions.

Treatment modifications for symptoms of infusion-related reactions due to study drug(s) is provided in Table 18.

Table 18: Treatment Modifications for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE Grade	Treatment Modification for Tislelizumab
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, intravenous fluids); prophylactic medications indicated for ≤24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described below. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe 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.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described below. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

Abbreviations: NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Once the tislelizumab infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions and be administered with

premedication. If the patient has a second infusion-related reaction (≥Grade 2) on the slower infusion rate, infusion should be discontinued, and the patient should be withdrawn from tislelizumab treatment.

NCI-CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted as indicated per the type of reaction. This includes, but is not limited to, an antihistamine (e.g., diphenhydramine or equivalent), antipyretic (e.g., paracetamol or equivalent), and if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. In the next cycle, patients should receive oral premedication with an antihistamine (e.g., diphenhydramine or equivalent) and an antipyretic (e.g., paracetamol or equivalent), and they should be closely monitored for clinical signs and symptoms of an infusion reaction.

NCI-CTCAE Grade 3 or 4 infusion reaction: Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes, but is not limited to, oral or intravenous antihistamines, antipyretics, glucocorticoids, epinephrine, bronchodilators, and oxygen.

Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice as described in the complete guideline for emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (UK) (Soar, Pumphrey et al. 2008). Patients should be instructed to report any delayed reactions to the Investigator immediately.

In the event of a systemic anaphylactic/anaphylactoid reaction the infusion must be immediately stopped, and the patient discontinued from the study. Systemic anaphylactic/anaphylactoid reactions typically manifest within minutes following administration of the drug/antigen and are characterized by respiratory distress; laryngeal edema; and/or intense bronchospasm; and often followed by vascular collapse or shock without antecedent respiratory difficulty; cutaneous manifestations such as pruritus and urticaria with/without edema; and gastrointestinal manifestations such as nausea, vomiting, crampy abdominal pain, and diarrhea.

The patient will be administered epinephrine injection and dexamethasone infusion if hypersensitivity reaction is observed. The patient should then be placed on monitor immediately, and ICU should be alerted for possible transfer if needed.

For prophylaxis of flu-like symptoms, a dose of 25 mg indomethacin or a comparable dose of nonsteroidal anti-inflammatory drugs (i.e., 600 mg ibuprofen, 500 mg naproxen sodium) may be administered 2 hours before and 8 hours after the start of each dose of study drugs(s) infusion. Alternative treatments for fever (i.e., paracetamol) may be given to patients at the discretion of the Investigator.