Leap Therapeutics, Inc.

SAP Part A+B

- **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**)
- **SAP Part A+B,** Version 3.0, 03 October 2022
- **Protocol Identifier:** DEK-DKK1-P205
- **NCT04363801**

STATISTICAL ANALYSIS PLAN

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)

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SIGNATURE PAGE

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REVISIONS HISTORY LOG

Changes to the approved SAP should be logged in this table.

Version	Revision Date**	Author of Revision*	Section(s) Modified	Description and/or Reason(s) for Revision	Reason for Revision
2.0	14OCT2021	[redacted]	2	Addition of Time to Response (TTR) as secondary objective/endpoint including the definition of TTR	Based on Protocol Amendment 1
			2	Addition of iRECIST exploratory objectives and endpoints	Based on Protocol Amendment 1
			3.3	Text added to clarify sample size	Based on Protocol Amendment 1
			4.1	Updated hypothesis wording	Simplified
			5	Define study drug versus study treatment	Clarification
			5	Response Evaluable Population definition has been updated	Based on Protocol Amendment 2
			5	Analysis populations	Updates to wording to align with Protocol Amendment 2.0 and for further clarification, including clarification of distinct Biomarker Populations
			6.1 and 8.0	Added language for Part B2 to be further divided by Immunotherapy (Naïve and Experienced) for certain outputs	Based on new decision
			6.5	Split into 6.4.1 and 6.4.2 to add details for handling of external vendor data	Needed to clarify programming conventions
			6.7	Clarification to subgroups for genetic alterations and	Definition needed for properly grouping subgroups

Version	Revision Date**	Author of Revision*	Section(s) Modified	Description and/or Reason(s) for Revision	Reason for Revision
				RNAscope dichotomization	
			7.1	Revisions to disposition presentation	Based on need for further data points and clarifications
			7.3	Time to diagnosis to be reports in months rather than days; prior systemic cancer therapy type to include immunotherapy; details added to historic and baseline characteristics presentation	Decisions based on data and further clarifications needed
			7.5	Added immunotherapy to subsequent cancer therapy type	Based on recent database changes
			8.1	Added text regarding tumor imaging	Additional information
			8.1.1	Updated definition for disease control benefit (DCB)	Further clarification to the protocol definition
			8.1.1	Response rates and best overall response will also be presented for the Safety Populations	Based on new decision
			8.1.2	Added KM plots for mITT population; added additional TTR endpoint (TTR_First and TTR_Best)	Based on new decision
			8.2	Added additional language for iRECIST endpoints, including requirement for at least 5 patients for certain outputs	Clarification
			8.4	Eliminated some exploratory endpoints	Based on availability of data

Version	Revision Date**	Author of Revision*	Section(s) Modified	Description and/or Reason(s) for Revision	Reason for Revision
			9.1	Added 5-FU data listing	Based on Protocol Amendment 1
			9.2.1	Removed combined CAPOX tables from adverse events	Not needed
			9.3	Removed shift table for urinalysis abnormalities	Data will be listed
			9.3 and 9.8	Added South Korea specific items	To be consistent with protocol changes
			Table 2	Updated	Clarifications
			General	Changes in language	Based on Protocol Amendments 1 and 2
			General	Clarifying language	Clarification
3.0	22SEP2022	[redacted]	General	Updates made based on Protocol Amendment 3	Protocol Amendment 3
			Table 1	Revisions to abbreviations	Protocol Amendment 3
			1.0	Explained this SAP will only be for Study Parts A and B	Clarification
			5.0	Addition of Intent to Treat Population	Protocol Amendment 3
			6.4.2	Added that zero scores for vCPS included in <1, <5, and <10 categories	Clarification
			6.7	Added that any analysis based on optimal cut will be exploratory in nature	Sponsor request
			7.1	Updates to disposition	Consistency and clarification
			7.3	Updates to conventions used for presentation	Consistency and clarification
			8.3	Updates to PFS censoring	Clarification of special scenarios and on conventions

Version	Revision Date**	Author of Revision*	Section(s) Modified	Description and/or Reason(s) for Revision	Reason for Revision
			9.1	Added actual dose intensity and other updates	Clarification

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Table 1: List of Abbreviations

Abbrev	Definition
5-FU	fluorouracil
AE	adverse event
ADA	anti-drug-antibody
AMA	American Medical Association
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	anatomical-therapeutic-chemical
BOR	best overall response per RECIST 1.1 criteria
C1D1	Cycle 1 Day one
CAPOX	capecitabine + oxaliplatin
CISH	chromogenic in situ hybridization
CI	confidence interval
CR	complete response per RECIST 1.1 criteria
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CSR	clinical study report
DCB	durable clinical benefit
DCR	disease control rate
DKK1	Dickkopf-1
DoCB	duration of clinical benefit
DoCR	duration of complete response
DoR	duration of response
EBV	Epstein Barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	End of Study
EOT	End of Treatment
G/GEJ	gastric or gastroesophageal junction

GC	gastric cancer
HER2	human epidermal growth factor receptor 2
iBOR	best overall response per iRECIST criteria
ICF	informed consent form
ICH	International Council for Harmonisation
iCPD	confirmed progressive disease per iRECIST criteria
iCR	complete response per iRECIST criteria
iDCB	durable clinical benefit per iRECIST criteria
iDCR	disease control rate per iRECIST criteria
IHC	Immunohistochemistry
INR	international normalized ratio
IO	immunotherapy
iORR	objective response rate per iRECIST criteria
iPR	partial response per iRECIST criteria
iRECIST	Immune-related Response Criteria in Solid Tumors
iSD	stable disease per iRECIST criteria
irAE	immune-related adverse events
ITT	intent-to-treat
iUPD	unconfirmed progressive disease per iRECIST criteria
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
mRNA	messenger ribonucleic acid
MSI	microsatellite instability
MSS	microsatellite stability status
n	number of patients with data
N	number of patients in a population
NCI	National Cancer Institute
NE	Not evaluable
OR	objective response
ORR	objective response rate

OS	overall survival
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PP	per protocol
PR	partial response per RECIST 1.1 criteria
PT	preferred term
PT	prothrombin time
PTT	partial thromboplastin time
QTcF	Fridericia-corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
REP	Response Evaluable Population
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease per iRECIST criteria
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TLF	tables, listings, and figures
TMB	Tumor Mutation Burden
TPS	tumor proportion score
TTR	Time to response
ULN	upper limit of normal
vCPS	visually estimated combined positive score
WHODRUG	World Health Organization Drug Dictionary
yyyy-MM-dd	year-Month-day

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Leap Therapeutics Protocol DEK-DKK1-P205, entitled "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)".

This is a Phase 2 nonrandomized, open-label, multicenter study to be conducted concurrently in 3 Parts:

- Part A will enroll gastric or gastroesophageal junction (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 have 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 Dickkopf-1 (DKK1)-high G/GEJ adenocarcinoma (second-line treatment).
- Part C is an 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.

This SAP will only present the planned analysis for Parts A and B. Part C will be presented separately. Part A enrolled patients in the USA, and Part B enrolled patients in the USA and in South Korea.

The primary objective of Parts A and B is 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. This study will also evaluate other secondary, safety, and exploratory endpoints as enumerated in Section 2 of this SAP.

This SAP conveys the planned analyses for Parts A and B of the primary and secondary endpoints and other analyses mentioned in the protocol, as well as the presentation of study data to be included in the clinical study report (CSR) for Protocol DEK-DKK1-P205. A discussion of the steps taken to prepare the data for analysis, such as study milestones, data partitioning, and derived data, is provided. Examples of tables and figures that will be used to summarize the data are included in the companion document *Tables, Listings and Figures Shells.* External data from specialized vendors which is not received at the time of the clinical database lock will not be included in the CSR and may be part of a separate exploratory Biomarker Report.

This SAP has been developed according to Ce3 SOP 700: Developing and Maintaining a Statistical Analysis Plan, and accordingly, this plan and any deviations from this plan must be finalized, approved, and placed on file before the study database is frozen.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of Parts A and B of this study is 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.

2.1.2. Secondary Objectives

The secondary objectives of this study are:

- 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 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, and 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.

2.1.3. Exploratory Objectives

The exploratory objectives of Parts A and B of this study are:

- 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, best overall response (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

2.2. Part A and B Study Endpoints

2.2.1. Safety Endpoints

2.2.1.1. Primary 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

2.2.1.2. 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

2.2.2. Efficacy Endpoints

- ORR (the proportion of patients with best overall response (BOR) 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., Cycle 1 Day 1 (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., Cycle 1 Day 1 (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

2.2.3. 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 messenger RNA (mRNA) by in situ hybridization (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

3. STUDY DESIGN

3.1. General Study Design and Plan

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). This SAP will only address non-randomized Parts A and B.

- 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 (±HER2 therapy if applicable) for locally advanced/metastatic DKK1-high G/GEJ adenocarcinoma (second-line treatment)

Part A will enroll approximately 24 patients to achieve 20 evaluable patients, and follow a study schema is as follows:

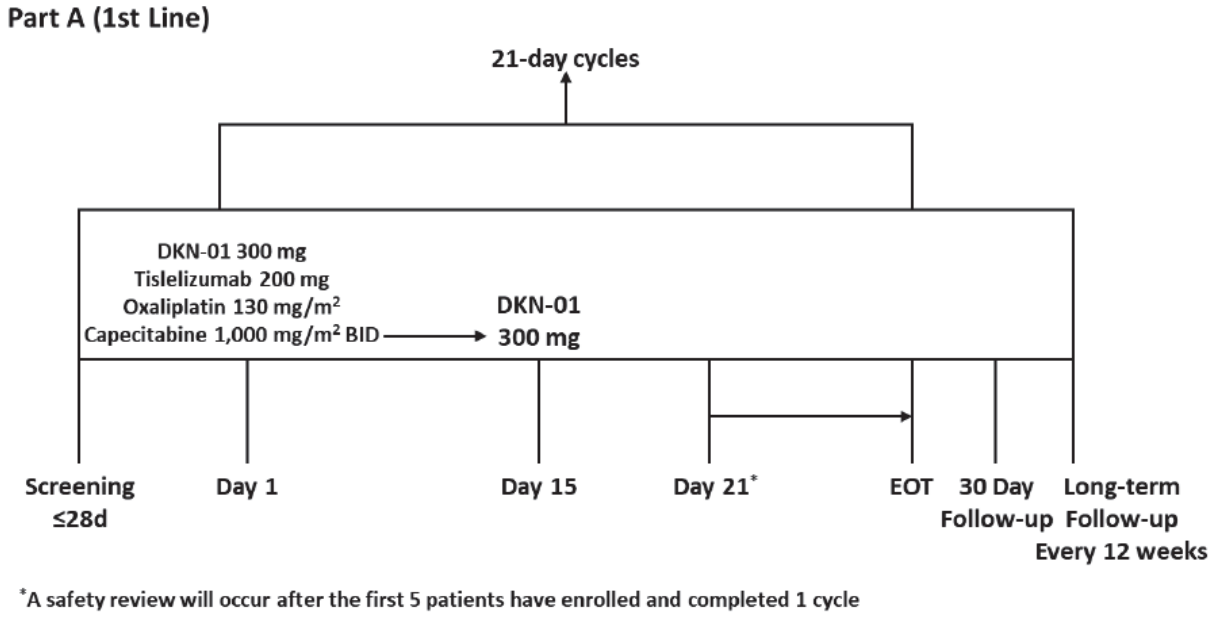

Figure 1: Study Schema Part A

All 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 will enroll approximately 48 patients to ensure 40 evaluable patients and is comprised of 2 components:

- Approximately 24 enrolled patients (20 evaluable) (Part B1) will receive DKN-01 300 mg
- Approximately 24 enrolled patients (20 evaluable) (Part B2) will receive DKN-01 600 mg

The study schemas for Parts B1 and B2 are as follows:

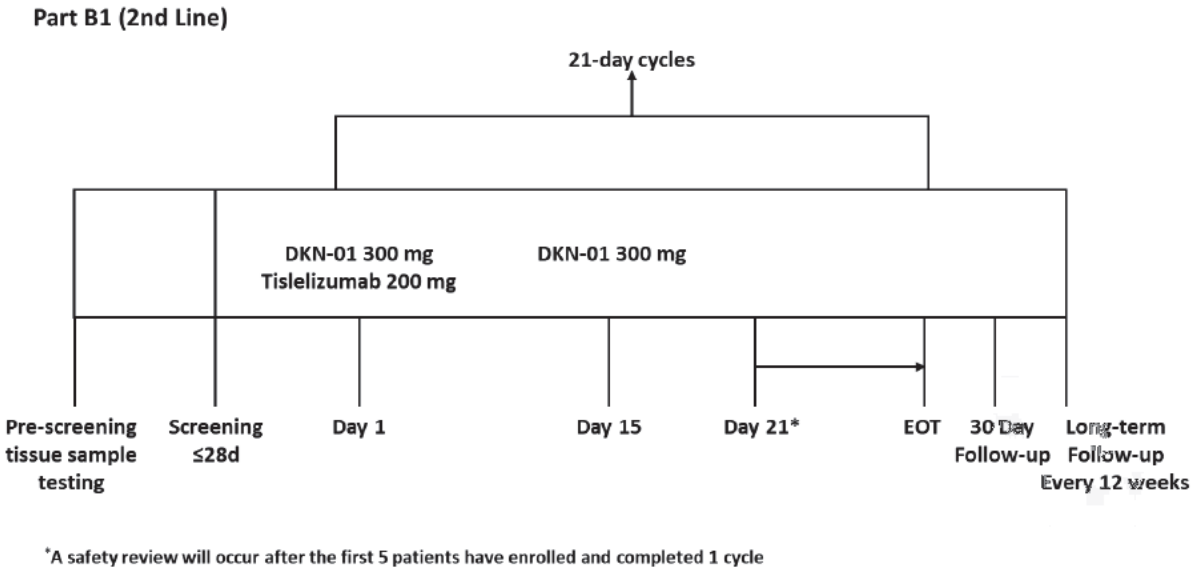

Figure 2: Study Schema Part B1

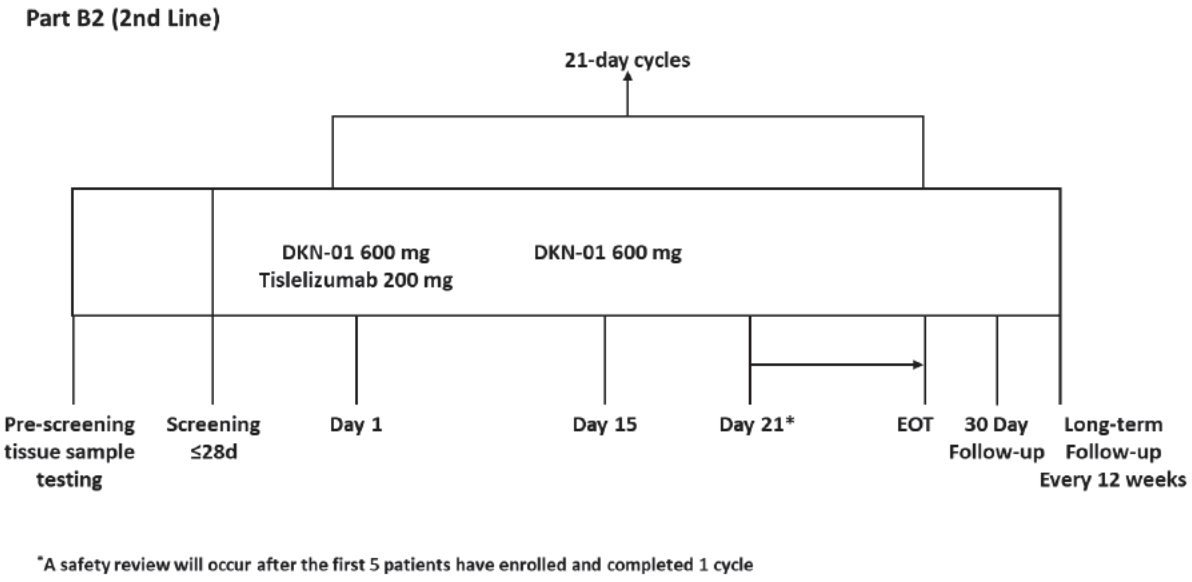

Figure 3: Study Schema Part B2

Further details on the study design and conduct are provided in the study protocol.

3.2. Definition of Study Drug

The study drug, DKN-01, 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.

3.3. Sample Size Considerations

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.

3.4. Randomization and Blinding

Not Applicable.

3.5. Study Assessments

Details of scheduled assessments are presented in Section 6 of the study Protocol.

4. PLANNED ANALYSIS

4.1. Hypotheses

The emphasis of the final analyses will be on estimation of key summary statistics. No formal hypotheses will be tested.

4.2. Interim Analyses

No interim analyses are planned for this study.

4.3. Final Analysis

Final tables, listings, and figures (TLFs) for Parts A and B will be provided once both study parts have ended. Each part ends when its last patient dies, withdraws consent, completes all study assessments or is lost to follow-up. Alternatively, the two parts end when the sponsor decides to terminate the study.

5. ANALYSIS POPULATIONS

The following terms will be used to define the analysis populations for Parts A and B:

- Study drug: DKN-01
- Study treatment: any of DKN-01, tislelizumab, capecitabine, oxaliplatin (Part B does not include capecitabine or oxaliplatin)

Per protocol DKN-01 is administered first, followed by the other study treatment components. Any patient who received any study medication will have received DKN-01. Safety information will be provided for each component of the study treatment.

Patients who did not meet inclusion/exclusion criteria and/or were not treated with any study drug (i.e., screen failure patients) will not be included in any analysis. The following analysis populations will be used for presentation of the data:

- *Enrolled:* All patients who signed the main study informed consent form (ICF)

- *Safety Population*: All patients who signed the ICF and received at least one dose of DKN-01. This is the primary population for the safety analysis (the safety population represents the ITT population in the context of this study).
- *Intent-to-Treat (ITT) Population*: : In the context of this study the ITT population is the same as the safety population. The term ITT population will preferentially (but not always) be used in the context of efficacy summaries and analyses, while safety population is used for safety summaries and analyses.
- *Modified Intent-to-Treat Population (mITT)*: All patients who received more than one dose of DKN-01. This is the primary efficacy population used for the determination of PFS and OS and other efficacy measures.
- *Response Evaluable Population*: All patients who received any amount of DKN-01 and who have a measurable disease at baseline and at least 1 evaluable post-baseline RECIST v1.1 tumor response assessment.
- *Per-Protocol (PP) Population:* All enrolled patients without important protocol deviations that necessitates exclusion from this population or compliance issues, as applicable.
- *Pharmacokinetics Population DKN-01:* All enrolled patients dosed with DKN-01 with available DKN-01 serum-time concentration data.
- *Pharmacokinetics Population Tislelizumab:* All enrolled patients dosed with tislelizumab with available tislelizumab serum-time concentration data
- *Biomarker Populations:* 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) in the tumor microenvironment by IHC
  - circulating tumor deoxyribonucleic acid (ctDNA)
  - serum DKK1

Each biomarker population consists of the patients with an evaluable central vendor baseline value of the corresponding biomarker.

6. GENERAL STATISTICAL CONSIDERATIONS

All analyses will be performed using SAS® Version 9.4 or higher. Continuous variables (e.g., age) are summarized using descriptive statistics. Categorical variables (e.g., race) are summarized using counts and percentages.

6.1. General Reporting Conventions

The following data conventions are applied to all data presentations and summaries.

- Data will be described and summarized separately for Part A and Part B of the study. Within Part B, data will be summarized for Parts B1 and B2, and overall. For some outputs, Part B2 patients will be further summarized as Immunotherapy (IO) – Naïve and IO-Experienced.
- For assessments performed at defined time points, the data summary will be reported for each time point.
- Summary tables for continuous variables will contain the following statistics: N (number of patients in the population); n (number of patients with data); mean; standard deviation; median; minimum; and maximum; 25th and 75th percentiles when applicable. Selected statistics may also include a 2 sided 95% normal approximation confidence intervals (CIs) on the mean.
- Summary tables for categorical variables will include: N (number of patients in the denominator); n (number of patients in the numerator); and percent. This will be presented in the format XX (XX.X%), where the percentage is in parentheses. Selected statistics also may include 2-sided 95% CIs for the percent based on the exact Clopper-Pearson methodology for binomial proportions.
- Unless specifically noted to the contrary, the denominator used for the calculation of percentages will be the number of patients in the specified analysis population who are in the Study Part being summarized.
- Date variables are formatted as yyyy-MM-dd (for example, 2021-09-12 for 12th of September 2021) for presentation. Time is formatted in military time as HH:MM for presentation.
- The baseline value for a given parameter is the last non-missing value prior to the first dose. A value is post-baseline if it is obtained after the first study drug administration.
- Change from baseline is calculated as (post-baseline result – baseline result). Percent change from baseline is calculated as (change from baseline/baseline results) * 100. If either the baseline or post-baseline result is missing, the change from baseline and/or percent change from baseline is set to missing as well.
- Data from study centers will be pooled for all analyses.
- Study day is defined as calendar date – date of first treatment + 1 if the calendar date is on or after the date of first treatment, and calendar date – date of first treatment if the calendar date is before the date of first treatment.
- Duration will be calculated by the difference of start and stop date + 1, if not otherwise specified.
- 1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

- Age [years] is defined as (year of given informed consent – year of birth).
- Measurements from unscheduled visits will be included in listings, but not summary tables with exception of specific laboratory results noted in Section 6.4.2.
- Missing data conventions for individual endpoints are described in detail below for each endpoint.
- Listings will be provided of all data collected in the electronic case report form (eCRF).
- Wherever possible, data will be decimal aligned.
- For continuous variables, use the following conventions for significant digits: mean (xx.x), median (xx.x), standard deviation (xx.xx), minimum (xx.x) and maximum (xx.x). If data results are less than 1, format decimal points to one more place than the measured value for all summary variables except format to two more places for standard deviations.
- Version 23.1 of the Medical Dictionary for Regulatory Activities (MedDRA) will be used for this study.
- Version B3 Global September 1, 2020, of the World Health Organization Drug Dictionary (WHODRUG) will be used for this study.

The accompanying TLF document to this SAP provides the expected layout and titles of the tables, figures, and listings. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP, nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation.

6.2. Multi-Center Studies

This is a multi-center study in the USA and South Korea. Given the small sample size of the study, no site effect will be considered in any statistical analysis, and data from all study centers will be pooled for the analysis.

6.3. Multiple Comparisons / Multiplicity

Not applicable to this descriptive study.

6.4. Handling of Dropouts or Missing Data

6.4.1. Missing Data and Dropouts

Unless otherwise specified in this SAP, all data will be evaluated as reported and no imputation of missing values will be done.

Where individual data points are missing, the data will be analyzed based on reduced denominators. For survival analysis, dropouts without confirming events will be treated as censored.

6.4.2. Flagship and Ventana Data

Flagship Data (H-score):

- If a site sends multiple specimens for the Part A retrospective analysis, all samples will be tested. If the samples are from the same lesion, the most recent sample will be used in the analysis to determine whether the patient is DKK1 high or low. If the samples are from two different lesions, the patient will be deemed as DKK1 high if either result in an H score ≥ 35.
- If a first run of tissue does not yield a result, results from a separate, unscheduled biopsy may be used.
- For Part A patients the H-score values used in the analysis and the figures will come from the baseline/screening biopsy. Other on-study results will be listed but not used for analysis.
- For Part B patients, the H-score value from the Pre-screening timepoint regardless of whether it is archival or fresh will be used in the study tables, figures, and analyses. For Part B patients who are required to have repeat biopsy during screening due to the use of an archived specimen to determine eligibility, there may be an exploratory analysis evaluating the difference of DKK1 expression over time.

Ventana Data (vCPS):

- If a patient has multiple samples tested, the result included in analyses will match the tissue sample used to provide the H score result.
- A score of 0 indicates absence of staining. Zero scores will be presented in the < 1%, < 5%, and < 10% categories.
- A score of < 1 indicates staining > 0, but < 1%. The < 1-score will be mapped to a value of 0.5 for plotting to distinguish it from true 0. Both values, 0 and 0.5, will be classified as negative.

6.4.3. Handling of Missing and Partial Dates

All missing and partial start dates will be queried for a value. If a complete start date cannot be obtained, the following imputation rules apply to calculate duration of adverse event, concomitant medication use, or prior cancer history endpoints:

Missing month and day:

- If the year of the incomplete start date is the same as the year of the date of study drug administration, then the missing month and day of the start date will be imputed to be the month and day of the start of study drug administration.
- If the year of the incomplete start date is before the year of the date of study drug administration, December 31 will be assigned to the missing fields.

- If the year of the incomplete start date is after the year of the date of study drug administration, January 1 will be assigned to the missing fields.

Missing month only:

- If only the month is missing, the day will also be treated as missing, and both month and day will be replaced according to the above procedure.

Missing day only:

- If the month and year of the incomplete start date are the same as the month and year of the date of study drug administration, the start date of study drug will be assigned to the missing field (i.e., AEs will be assumed treatment-emergent, and medications will be assumed concomitant).
- If the month and year of the incomplete start date are before the month and year of the date of study drug administration, the last day of the month will be assigned to the missing field.
- If the month and year of the incomplete start date are after the month and year of the date of study drug administration, the first day of the month will be assigned to the missing field.

If the stop date is complete and the imputed start date, when imputed as instructed above, is after the stop date, the start date will be imputed to equal the stop date.

Incomplete Date of Initial Cancer Diagnosis

- If day is missing and month is non-missing, day will be set to 15th of the month.
- If month is missing and day is non-missing, then month will be set to July.
- If month and day are both missing, month and day will be set to July 1st.
- If complete date is missing, then impute it as the date of informed consent -1.

6.5. Outlier Handling

Data entry errors may manifest as outliers and will be handled in the data management process through edit checks. An analysis may be performed to assess the effect of extreme outliers on the results and determine if the patient should be excluded from the Per Protocol Analysis. Review of extreme observations for parameters of interest generated by proc univariate in SAS will take place and a final adjudication of exclusions will be determined.

6.6. Adjustments for Covariates

Not applicable to this study.

6.7. Subgroup Analyses

If meaningful data are available, the following subgroups may be assessed for Part A, Part B1, Part B2, and Part B overall:

- DKK1 expression H-score (e.g., DKK1 High ≥ 35 vs DKK1 Low < 35, and < optimal cut point versus ≥ optimal cut point statistically derived based on the PFS analysis) for Part A
- DKK1 expression H-score (e.g., optimal cut point based on the PFS analysis) Part B only
- DKK1 expression percent positive tumor cells (e.g., < 20% vs ≥ 20%, < optimal cut point versus ≥ optimal cut point statistically derived based on PFS analysis) for Part A and Part B
- PD-L1 expression (Ventana), vCPS (visually estimate combined positive score) of 0, < 1 vs ≥ 1; < 5 vs ≥ 5; and < 10 vs ≥ 10
- HER2 status (positive or negative, part B only based on historical data)
- ctDNA (baseline historic):
  - TMB (< 10 vs ≥ 10 mutations/Mb)
  - Microsatellite Status (MSS and MSI-H)
- Genetic alterations (present, absent, unknown; based on FMI data):
  - Wnt Activating Mutations (CTNNB1, APC, AXIN1, RNF43, RSPO2)
  - PI3K/AKT Signaling Mutation (AKT1, AKT2, AKT3, PIK3CA, PIK3CB, PIK3R1, PIK3C2B, PIK3C2G, PTEN, PDK1)
  - CTNNB1
  - PIK3CA mutations
  - ARID1A mutations
- Baseline circulating serum DKK1 (two subgroups, below median and above median)
- Tumor type (GC versus GEJ)
- Geographical region analysis of baseline characteristics i.e., USA versus South Korea. If differences are noted, further analysis of other endpoints may be performed
- Type of Prior Therapies (Neoadjuvant or Adjuvant)
- Prior Systemic Therapies (Yes versus No). Part B only

DKK1-RNAscope H-score will be dichotomized as high (≥ statistically derived optimal cut point) and low (< statistically derived optimal cut point) based on the Williams method from 2006, using progression free survival as the optimization endpoint. In these derived cut point analyses, a cut point for a Baseline DKK1-RNAscope H-score will be derived for PFS for each reporting group for the forest plot and subgroup figure production; this cut point creates a two--level categorical variable (e.g., X < cut point vs. X ≥ cut point) by which the groups are determined to be maximally different from one another on the basis of a log rank test; the PFS cut points will be used for all subgroup analyses. An analysis showed that with the data

available, an optimal cut point cannot be identified reliably. Any results using the optimal cut point will be considered exploratory.

6.8. Statistical Considerations Due to Covid-19

A sensitivity analysis on study endpoints may be conducted separately for patients significantly impacted by Covid-19. If the analysis is deemed necessary, any modification to the definition and/or ascertainment of trial endpoints will be described.

7. SUMMARY OF STUDY POPULATION DATA

Tables related to the study population will be in Section 14.1 and listings in Section 16.2 of the TLF Shell document.

7.1. Patient Disposition

A summary will be presented for patient disposition, including number of patients who signed informed consent, number of screen failures and reason for screen failure, number of patients enrolled but not treated, number of patients in each analysis population, number of patients remaining on treatment, number of patients who discontinued all study drug treatment, and reason for discontinuation, number of patients remaining on study, and number of patients who discontinued the study, with reasons. In addition, summary statistics will be presented in months for duration of treatment, duration on study, and duration on post-treatment follow-up. The following definitions will apply:

- Duration of Treatment = Minimum of ((Date of End of Treatment, Death, or Last Contact Date – First Treatment Date) + 1)/30.4375
- Duration on Study = Minimum of ((Last Contact Date, Date of End of Study) – First Treatment Date) + 1)/30.4375
- Duration of Post-Treatment Follow-up = ((Date of End of Study – Date of End of Treatment) +1)/30.4375.

Enrollment is defined as any patient who signs informed consent. Screen failure is defined as patients who provided informed consent but did not dose with study drugs as he/she did not fulfill the inclusion or exclusion criteria according to the protocol. Enrolled but not treated patients refers to those who signed informed consent, were found eligible for the study, but discontinued study prior to receiving first dose. A separate summary will display number of patients enrolled by site and study part.

Separate listings will be provided for patient disposition, inclusion/exclusion eligibility, and analysis population assignment.

7.2. Protocol Deviations

The number and percentage of enrolled patients with at least one important protocol deviation will be presented in a summary table. All protocol deviations captured in the database are

categorized as either major or minor. Sponsor will review and categorize each deviation as either important or not important. These adjudicated designations will be summarized and provided in the listing. In addition, the number and percentage of enrolled patients who had at least one Covid-related deviation will be presented.

All protocol deviations will be listed.

7.3. Demographics and Baseline Characteristics

Descriptive statistics will be used to summarize demographics and baseline characteristics for the Safety and modified Intent-to-Treat (mITT) Populations. If the modified ITT and the per protocol populations differ by more than 10%, the demographics and baseline characteristics will also be presented for the Per Protocol population. In addition, select baseline characteristics will be analyzed with respect to geographic region, i.e., USA versus South Korea.

Patient demographic characteristics will include age (years), gender, race, ethnicity, height (cm), weight (kg), body surface area (m^2), and baseline ECOG performance status (0, 1, or not reported).

Tables will display descriptive statistics for the following baseline and historic characteristics:

- Medical and surgical history
- Cancer diagnosis at screening, number, and frequency of patients in the following categories:
  - GEJ vs GC
  - Stage at initial diagnosis (Stage I to IV)
  - Category (Siewert I, II, III, unknown)- GEJ only
  - Time since diagnosis in months, defined as (Date of First DKN-01 treatment – Date of cancer diagnosis+1)/30.4375
  - Time since most recent cancer therapy in months, defined as (Date of first DKN-01 treatment – End date of last regimen+1)/30.4375
- Prior systemic cancer therapy, cancer surgery, and radiation therapy
  - Prior systemic cancer therapy
    - Setting (adjuvant/neoadjuvant, adjuvant only, neoadjuvant only, or advanced/metastatic)
    - Best overall response
    - Type (biological, chemotherapy (including specific therapy type), targeted therapy, immunotherapy, other)
  - Cancer surgery
    - Number of procedures
    - Reasons for surgery

  - Radiation therapy
    - Number of therapies
    - Intent for therapy
    - Anatomical location
    - Type
    - Response
- Liver involvement (Yes/No), defined as any patient with a screening lesion location = liver
- Historic tumor characteristics
  - Prior Genetics: ZNRF3, RSPO2, RSPO3, RNF43, CTNNB1, AX1N1, AXIN2, APC, AR1D1A, PIK3CA, Other
  - Tumor mutational burden (TMB)
  - Microsatellite stability status (MSS, MSI or MMR deficient, Undetermined, Not tested) and MSI phenotype (MSI-L, MSI-H, Unknown)
  - Epstein Barr Virus (positive/negative/undetermined)
  - Human epidermal growth factor receptor 2 (HER2) (positive/amplified negative/non-amplified, undetermined)
  - PD-L1 expression status (positive/negative/undetermined)
- Other Baseline characteristics from central vendors on study include but are not limited to:
  - Circulating tumor deoxyribonucleic acid ctDNA: Number and percent of APC, ARIDIA, AXIN1, CTNNB1, PIK3CA, RNF43, and RSPO2 will be presented (FMI)
  - Tumor mutation burden (TMB): Summarized and categorized as < 10 vs ≥ 10 mutations/Mb) (FMI)
  - Serum DKK1 (ng/mL): Number and percent above and below the median results will be presented (Nexelis)
  - Programmed cell death protein ligand-1 (PD-L1) expression in the tumor microenvironment by immunohistochemistry (IHC): Status (Negative/Positive) and summary statistics for positive results will be presented (Ventana)
  - DKK1 tumor expression in messenger RNA (mRNA) H-score by in situ hybridization (ISH): Summary statistics and High/Low categories will be presented (Flagship)
  - DKK1 RNAscope: Total positive percent cells categorized as $< 20\%$ vs $\geq 20\%$ (Flagship)
  - Microsatellite stability status: MSS, MSI, Undetermined (FMI)

  - Wnt activating mutations: Defined according to Section 6.7 and displayed as number and percent present/absent/unknown (FMI)
  - PI3K/AKT signaling mutations: Defined according to Section 6.7 and displayed as number and percent present/absent/unknown (FMI)

Listings will be provided for individual patient demographics and baseline medical and surgical history/physical findings, as well as cancer history at screening, historic tumor characteristics, baseline head imaging, prior systemic cancer therapy, prior cancer surgery and prior radiation therapies.

7.4. Prior and Concomitant Medications

Prior and concomitant medications were collected on the Prior and Concomitant Medications eCRF. The following conventions will be used:

- Prior medications will be defined as medications that stopped before the day of first dose of study drug. Concomitant medications will be defined as medications that 1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or 2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose (as of Safety Follow-up visit).

Summaries for prior medications, and for concomitant medications will be provided by Study Part for patients in the Safety population. In these, medications will be classified by WHODRUG Anatomical-Therapeutic-Chemical (ATC) Level 4 Class and Preferred Drug Name. ATC Level 3 Class will be used for any medications that do not have an ATC4 Class.

For each summary (prior and concomitant), for each study part, the summary will provide the number and percentage of patients who used any medication; the number and percentage who used any medications within each ATC Class; and the number and percentage who used any medications by Preferred Drug Name (within each ATC class). Patients who used multiple medications within each level of summarization will be counted once in the summary for that level.

Data reported for prior and concomitant medications will be listed. This listing will include indications for prior use, for concomitant use, and the duration of therapy.

7.5. Subsequent Systemic Cancer Treatments and Procedures

Data on subsequent systemic cancer treatments and procedures will be summarized as follows:

- Subsequent systemic cancer therapy
  - Best overall response
  - Type (biological, chemotherapy, targeted therapy, immunotherapy, other)
  - Reason for stopping
  - Duration of treatment
- Cancer surgery

  - Number of procedures
- Radiation therapy
  - Number of therapies
  - Intent for therapy
  - Anatomical location
  - Type
  - Response

Data on systemic cancer therapies, cancer surgeries, and radiation therapies administered subsequent to the discontinuation of study treatment will be listed.

7.6. Non-Drug Treatments and Procedures

Data on reported non-drug treatments and procedures will be listed.

8. EFFICACY ANALYSES

The primary efficacy analyses for Part A and B will be conducted on the modified Intent-to-Treat Population. In addition, separate analyses may be conducted on the Response Evaluable Population, the Per-Protocol Population, and the Safety Population. Efficacy endpoints will also be assessed for subgroups. For the primary efficacy endpoint of ORR, data will also be presented by demographic and geographic subgroups. Data will be presented by study part for the mITT, Safety and REP (when noted), and if needed, the PP population. All data presentation will include results for Part A, Part B1, Part B2, and Part B Overall. Part B2 subjects will be further presented as IO-naïve, IO-experienced, and B2-overall. Subgroups may be combined. If the PP population is < 10% different from mITT, only the mITT will be presented as the primary efficacy population. Any statistical results will be interpreted in the perspective of the exploratory nature of the study.

8.1. Tumor Response per RECIST Version 1.1

Tumor imaging will be performed within 28 days before first dose of study treatment. During the study tumor imaging will be performed every 6 weeks (± 7 days) from C1D1, for the first 24 weeks, then every 9 weeks (± 7 days) after 24 weeks based on RECIST v1.1.

Data listings will be provided for the assessment of target tumor lesions and non-target tumor lesions both RECIST v1.1 and iRECIST.

8.1.1. Tumor Response Rates

For each patient, the best overall response (BOR) will be determined in accordance with RECIST v1.1, and the following response rates achieved during the study will be presented for the mITT, REP, and Safety populations:

- Objective response rate (ORR) is defined as the proportion of patients achieving a best overall response (BOR) of complete response (CR) or partial response (PR). Responses evaluated after switching to another anti-cancer therapy will be excluded.
- Durable Clinical Benefit (DCB) rate is defined as the proportion of patients presenting a duration of clinical benefit (DoCB) for ≥ 180 days from initiation of DKN-01. Patients who have a best overall response (BOR) of PD or those having clinical benefit, but DoCB lasting < 180 days will be considered as "non-DCB".
- Disease control rate (DCR) is defined as the proportion of patients presenting with a best overall response (BOR) of complete response, partial response, or stable disease for a duration of at least 6 weeks from initiation of DKN-01.

The distribution of patients according to best overall response per RECIST v1.1 will be presented by study part. For Part A patients there will be a further sub-division by DKK1 RNAscope H-score indicator (High/Low/Unknown) and PD-L1 vCPS (< 5, ≥ 5) from Ventana. Additionally, the ORR, the DCB rate, and the DCR will be presented by study part and subgroups from Section 6.7, along with accompanying 95% exact Clopper-Pearson confidence intervals.

Forest Plots of Duration of Response and Objective Response Rate by study part will be developed using the subgroups from Section 6.7 if at least 5 subjects are present in each subgroup category.

Waterfall plots for the best percent change from baseline (i.e., maximum decrease) in sum of diameters of target lesions of each patient will be presented by study part and selected subgroups. Spider plots will display the percent change from baseline in sum of diameters of each patient by date of visit, study part and subgroup.

8.1.2. Time-to-Event Endpoints

For each patient, the following time-to-event endpoints will be evaluated per RECIST v1.1 for the mITT and REP populations:

- Duration of response (DoR) is defined only for responders (patients with a BOR of CR or PR) as the time from initial response (CR or PR) until radiographically documented progressive disease or death due to any cause, whichever is earlier. Patients who do not experience PD or death at the time of the analysis will be censored using the same rules as described for PFS (see Section 8.3).
- Duration of complete response (DoCR) is defined only for responders as the time from initial CR until radiographically documented progressive disease or death due to any cause, whichever occurs first. Patients who do not experience PD or death at the time of the analysis will be censored using the same rules as described for PFS (see Section 8.3).
- Duration of clinical benefit (DoCB) is defined as the time from the initiation of DKN-01 to the time of progressive disease or death due to any cause, whichever

occurs first. Patients who do not experience PD or death at the time of the analysis will be censored using the same rules as described for PFS (see Section 8.3).

- Time to best response (TTR_Best) for patients with a BOR of CR or PR, is defined as the time from the first dose of study treatment to the assessment date of the BOR of either CR or PR. If the BOR occurs on multiple time points, TTR_Best refers to the first instance. The time to the first response will also be displayed, and it is defined as the time from first dose of study treatment to the assessment date of the first instance of an overall response of CR or PR (TTR_First).

Per-patient summaries for the determination of each time-to-event endpoint will be provided. Additionally, a summary for each time-to-event endpoint will be presented, which will include the following statistics obtained from the Kaplan-Meier summaries: the number of patients; the median, 25th percentile, and 75th percentile; the standard error; and a 95% confidence interval. Kaplan Meier curves for DoR and DoCB may be presented for the Response Evaluable and the mITT population by study part, geographic region, and subgroup. Swimmer plots showing duration of patient treatment and follow-up with Objective Tumor Response and Death Over Time and will be presented by study part and by vCPS category and study part.

8.2. Tumor Response per iRECIST

All information and formulas presented in this section are only applicable to patients who continue treatment beyond the initial assessment of progressive disease.

8.2.1. Tumor Response Rates

iRECIST efficacy endpoints are exploratory in nature and will be displayed for the mITT population. Analysis of iRECIST endpoints follows the same pattern as RECIST 1.1, up until the first instance of iUPD, where RECIST ends, but iRECIST continues to monitor response. If iUPD is not confirmed with a further increase in size or sum of measures, then the bar is reset so that iUPD needs to occur again and then be confirmed. iBOR is the best timepoint response recorded form the start of the study treatment until the end of treatment, considering any requirement for confirmation. The duration of iCR and iPR is from the timepoint when the criteria for iCR or iPR are first met.

For each patient, the best overall response according to iRECIST will be determined and the following response rates achieved during the study will be presented:

- iORR is defined as the proportion of patients achieving a tumor assessment of complete response (iCR) or partial response (iPR) and who have all necessary iRECIST measurements. Responses evaluated after switch to another anti-cancer therapy will be excluded.
- iDCB rate is defined as the proportion of patients presenting with a duration of clinical benefit for ≥ 180 days from the first tumor assessment of iCR, iPR, or iSD disease. Patients who have a best overall response (iBOR) of iCPD or those having clinical benefit, but DoCB lasting < 180 days, will be considered as “non-iDCB”.

- iDCR, disease control rate, is defined as the proportion of patients presenting with iCR, iPR, or iSD for a duration of at least 6 weeks from initiation of study treatment.

The distribution of patients according to best overall response per iRECIST will be presented if there are at least 5 patients who continue treatment after first instance of iUPD. Additionally, the iORR, the iDCB rate, and the iDCR will be presented, along with accompanying 95% exact binomial confidence intervals.

8.2.2. Time-to-Event Endpoints

For each patient, the following time-to-event endpoints will be evaluated per iRECIST if there are at least 5 patients who continue treatment after first instance of iUPD:

- Duration of response (DoR), defined as the time from initial response (iCR or iPR) until the first radiographically documented unconfirmed progressive disease (iUPD) that is followed at next assessment by confirmed progressive disease (iCPD) or death due to any cause. Patients who do not experience iCPD or death at the time of the analysis will be censored using the same rules as described for PFS (Section 8.3).
- Duration of complete response (DoCR), defined as the time from initial iCR until the first radiographically documented iUPD that is followed at next assessment by iCPD or death due to any cause. Patients who do not experience iCPD or death at the time of the analysis will be censored using the same rules as described for PFS (Section 8.3).
- Duration of clinical benefit (DoCB), defined as the time from the initiation of DKN01 to the time of iUPD that is followed at next assessment by iCPD or death due to any cause, whichever occurs first. Patients who do not experience iCPD or death at the time of the analysis will be censored using the same rules as described for PFS (Section 8.3).
- Time to best response (iTTR_Best) for patients with a BOR of iCR or iPR, defined as the time from the first dose of study treatment to the assessment date of the BOR of either iCR or iPR. If the BOR occurs on multiple time points, iTTR_Best refers to the first instance. The time to the first response will also be displayed and it is defined as the time from first dose of study treatment to the assessment date of the first instance of an overall response of iCR or iPR (iTTR_First).

Per-patient summaries for the determination of each time-to-event endpoint will be provided. Additionally, a summary for each time-to-event endpoint will be presented, which will include the following statistics obtained from the Kaplan-Meier summaries: the number of patients; the median, 25th percentile, and 75th percentile; the standard error; and a 95% confidence interval.

8.3. Progression Free Survival (PFS) and Overall Survival (OS)

Progression free survival (PFS) and overall survival (OS) will be calculated on the mITT Population and the Safety Population. For RECISTv1.1, PFS is defined as the time from first study drug dose (i.e., C1D1) to first radiographically documented progressive disease or death due to any cause, whichever comes earlier. For iRECIST, PFS is defined as the time from first

study drug dose (i.e., C1D1) to first radiographically documented iUPD that is followed at next assessment by iCPD or death due to any cause. OS is defined as the time from first study drug dose (i.e., C1D1) to death due to any cause. If the patient is alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the patient is known to be alive. For each patient, this time-to-event endpoint will be evaluated.

Per-patient summaries for the determination of PFS and OS will be provided. Additionally, a summary for OS and PFS will be presented, which will include the following statistics obtained from the Kaplan-Meier summaries: the number of patients; the median, 25th percentile, and 75th percentile; the standard error; and a 95% confidence interval. Kaplan-Meier curves based on the mITT Population and Safety Population for PFS, OS, DoR, etc. will be presented for each study part and by selected subgroups from section 6.7, including Part A: H-score and vCPS ($< 5, \geq 5$) and Part B: vCPS ($< 5, \geq 5$). For time-to-event endpoints having missing dates, the censoring rules described below will be applied. Forest Plots of PFS and OS by study part will be developed using the subgroups from Section 6.7 if at least 5 subjects are present in each subgroup category.

Censorship for OS:

- Patients last known to be alive will be censored at the time of last contact.

Censorship for PFS and time-to-event analysis (except for OS):

- Patients last known to be Progression-free, and who have a baseline and at least one disease assessment after dosing, are censored at the date of the last objective disease assessment that verified lack of disease progression. This applies to patients who drop out for any reason.
- Patients with no disease assessment after dosing are censored at the first dose date unless death occurred prior to first planned assessment (in which case the death is an event).
- Patients starting new anti-cancer treatment, including chemotherapy, surgery, or radiation not allowed per protocol, prior to progression are censored at the date of last objective disease assessment documenting no progression prior to the new treatment. Aside from overall survival status, no further progression analyses will be conducted for these patients, even if they restart study treatment.
- Patients with documentation of progression or death after an unacceptably long interval (i.e., 2 missed or indeterminate assessments, $\geq$ 12 weeks up until 6 months on study when this would change to $\geq$ 9 weeks) since the last tumor assessment will be censored at the time of last objective assessment documenting no progression.

Table 2: Censoring Rules

		None	Date of Last Non-PD Assessment	Date of Last Assessment	Censored on Day 1	Last Known Alive Date	Maximum Day of Response of Any Patient + 1 Day
DoR/ DoCR	Surviving and no PD			X			
	Either PD or death preceded by 2 missing or NE tumor assessments		X				
TTR	Responders	X					
DoCB	Surviving and no PD			X			
PFS	Surviving and no PD			X			
	Either PD or death preceded by two or more missing or NE tumor assessments or initiation of other antitumor treatment		X				
	Surviving but no tumor assessments after baseline				X		
OS	Surviving					X	

8.4. Exploratory Endpoints

Exploratory analyses may be evaluated for the following exploratory endpoints and their correlation with efficacy outcomes where sufficient data (≥ 5 patients) is available, and is not limited to those listed here:

- 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 messenger RNA (mRNA) by chromogenic in situ hybridization (CISH)
  - Programmed cell death protein ligand-1 (PD-L1) in the tumor microenvironment by IHC
  - circulating tumor deoxyribonucleic acid (ctDNA), including genetics, TMB and microsatellite stability status
  - serum DKK1

8.5. Data Listings

Data for all efficacy endpoints will be provided.

9. SAFETY ANALYSES

Safety analyses will be conducted on the Safety Population. The safety data will be summarized descriptively. The safety population will be used to summarize drug exposure, treatment compliance, and dose modifications, including dose interruptions.

9.1. Study Drug Exposure and Compliance

Study drug administration tables will present descriptive statistics on the number of cycles, duration of exposure (days), total cumulative dose (mg), actual dose intensity (%), and relative dose intensity (%) for DKN-01, tislelizumab, and oxaliplatin (Part A only) by study part and overall. For capecitabine (Part A only), number of doses, cumulative dose, and relative dose intensity will be described. The number of patients with at least one dose delayed, number of doses delayed per patient, length of delay and reason for dose delay will be reported. Additionally, a study drug modification table will summarize the number, types, and reasons of modifications for each drug, the number of infusion interruptions and the reasons for interruptions.

Data on the administration of DKN-01, tislelizumab, oxaliplatin, and capecitabine including reasons for any deviations from the planned administration schedule will be listed. DKN-01, tislelizumab and oxaliplatin are administered as infusions. For tislelizumab, oxaliplatin and DKN-01, the number of dose interruption by cycle and all cycles will be reported. The total

number of infusions administered will also be summarized with mean, median, standard deviation, minimum, and maximum.

Data on the administration of intravenous 5-FU, including reasons for changing from treatment with capecitabine after completing Cycle 2, will be listed.

Capecitabine will be measured by pill counts and summarized by cycle. The total assigned dose for a patient with no adjustments or omissions is 1000 mg/m2 twice daily [BID]) on Days 1 - 15 (for 28 total doses) of each 21-day cycle i.e., 1000 mg/m2 per dose × 2 doses per day × 14 days = 28000 mg/m2 per cycle. Within each cycle relative dose intensity will be calculated as the ratio of total dose taken to the total assigned dose (minus any dose adjustments and doses omitted/withheld for medical or logistical reasons). A complete cycle of study treatment is defined as completing 21 days of treatment in compliance with the study treatment for the respective part as per Table 3 below.

Table 3: Study Treatment

Part	DKN-01	Tislelizumab	Oxaliplatin	Capecitabine
Part A	300 mg IV D1, D15	200 mg IV D1	70, 100, 130, or other 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		

BID = twice daily; D = day; IV = intravenous; PO = orally

Actual dose intensity will be calculated as the actual amount of drug taken divided by the amount of drug prescribed, with units equal to mg/visit for DKN-01 and tislelizumab, mg/m^2/visit for oxaliplatin and mg/m^2/day for capecitabine. Relative dose intensity will be calculated as the actual amount of drug taken divided by the amount of drug prescribed times 100% (that is, expressed as a percentage). If a patient has discontinued study drug due to toxicity or PI decision, these days will not be included as expected (i.e., prescribed).

Exposure data and infusion details will be listed together.

9.2. Adverse Events

9.2.1. Conventions for Reporting Adverse Events

Patients will be assessed for adverse events at each clinic visit while on the study. Adverse events (AEs) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and coded to preferred term and system organ class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) using version 23.1.

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. 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.

Adverse event summaries will be based on treatment-emergent adverse events (TEAEs) and will be presented by study part and overall. TEAEs are 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. AEs on study day 1 that do not have a time recorded to confirm the event occurred prior to administration of study drug will be counted as treatment emergent. Immune-related AEs (serious or non-serious) can occur until 90 days after the last dose of tislelizumab whether or not the patient starts a new anticancer therapy. Drug-related categories will be reported as DKN-01-related, tislelizumab-related, Regimen-related, capecitabine-related, and oxaliplatin-related. Regimen-related is defined as an adverse event deemed related to any one of the study treatments.

Summaries of TEAEs will be presented by MedDRA system organ class (SOC) and preferred term (PT) in order of decreasing frequency of total SOC count, followed by decreasing frequency of total PT count. The following conventions will be followed in summarizing multiple occurrences of an AE for a certain assessment period when summarizing data from individual patients by SOC and PT:

- Each patient will be counted only once within SOC or PT
- The highest known severity within an SOC or a PT will be assigned to the event
- The strongest relationship within an SOC or a PT will be assigned to the event

Within each SOC or PT, the summary will include the number and percentage of patients who experienced an event.

In addition, each AE summary will include the total number of AEs reported. In this tally, for patients who presented multiple occurrences of an AE, the total number of such occurrences will be included. Each AE summary will also include the number and percentage of patients who reported one or more event.

The denominator used for calculation of percentages will be the number of patients in the Safety Population for the Study Part(s) being summarized, unless otherwise specified.

9.2.2. AE Summaries to be Provided

An overall summary table will be provided that presents the total number of TEAEs, and the number of and percent of patients who presented with one or more TEAE of each of the listed types below, where capecitabine and oxaliplatin tables are only relevant for Part A subjects:

- All TEAEs
- Grade ≥ 3 TEAEs
- DKN-01-Related TEAEs
- Tislelizumab-Related TEAEs
- Capecitabine-Related TEAEs
- Oxaliplatin-Related TEAEs
- Regimen-Related TEAEs
- DKN-01-Related TEAEs that has occurred in ≥ 10% of patients
- Tislelizumab-Related TEAEs that has occurred in ≥ 10% of patients
- Oxaliplatin-Related TEAEs that has occurred in ≥ 10% of patients
- Regimen-Related TEAEs that has occurred in ≥ 10% of patients
- DKN-01-Related Grade ≥ 3 TEAEs
- Tislelizumab-Related Grade ≥ 3 TEAEs
- Capecitabine-Related Grade ≥ 3 TEAEs
- Oxaliplatin-Related Grade ≥ 3 TEAEs
- Regimen-Related Grade ≥ 3 TEAEs
- DKN-01-Related TEAE leading to study drug discontinuation
- Tislelizumab-Related TEAE leading to study drug discontinuation
- Capecitabine-Related TEAE leading to study drug discontinuation
- Oxaliplatin-Related TEAE leading to study drug discontinuation
- Regimen-Related TEAE leading to study drug discontinuation
- TEAEs leading to any drug discontinuation
- TEAEs leading to DKN-01 drug discontinuation
- TEAEs leading to DKN-01 dose reduction
- Infusion-Related TEAEs
- Immune Related TEAE (irAE)

- Grade ≥ 3 Immune Related TEAE (irAE)
- Grade ≥ 3 Infusion-Related TEAE
- Grade ≥ 3 Hematology Abnormality
- Grade ≥ 3 Clinical Chemistry Abnormality
- Treatment-emergent Serious Adverse Event (TESAE)
- DKN-01-Related TESAE
- Tislelizumab-Related TESAE
- Capecitabine-Related TESAE
- Oxaliplatin-Related TESAE
- Regimen-Related TESAE
- DKN-01-Related TESAEs leading to study drug discontinuation
- Tislelizumab-Related TESAEs leading to study drug discontinuation
- Capecitabine-Related TESAEs leading to study drug discontinuation
- Oxaliplatin-Related TESAEs leading to study drug discontinuation
- Regimen-Related TESAEs leading to study drug discontinuation
- Covid 19-Related TEAEs
- TEAEs Leading to Death

In addition, summaries by SOC and PT (unless specified as by PT only) as described above will be provided for selected groups from the list above.

A summary of all TEAEs by SOC, PT, and maximum severity will be presented for each study part and part B overall.

9.2.3. AE Data Listings to be Provided

The following data listings of TEAEs will be provided:

- All TEAEs
- Grade ≥ 3 TEAEs
- TEAEs leading to study drug discontinuation
- SAEs
- Deaths

Hematologic abnormalities reported as AEs that were coded to preferred terms in the Blood and Lymphatic Systems Disorders SOC have been mapped to the appropriate laboratory preferred

term in the Investigations SOC for summary counts in relevant tables and listings, including the following:

Table 4: Mapping of Hematologic Abnormalities

Blood and Lymphatic Systems Disorder SOC	Investigations SOC
Thrombocytopenia	Platelet count decreased
Neutropenia	Neutrophil count decreased
Leukopenia	White blood cell count decreased
Lymphopenia	Lymphocyte count decreased
Leukocytosis	White blood cell count increased
Anemia	Hemoglobin decreased

Any additional terms added to this list will be noted in the Clinical Study Report.

Abnormalities reported as AEs that were coded to preferred terms in the Metabolism and nutrition disorders SOC have been mapped to the appropriate laboratory preferred term in the Investigations SOC for summary counts in relevant tables and listings, including the following:

Table 5: Mapping of Metabolism and Nutrition Disorders

Metabolism and Nutrition Disorders SOC	Investigations SOC
Hyperglycaemia	Blood glucose increased
Hypernatraemia	Blood sodium increased
Hyperphosphataemia	Blood phosphorus increased
Hypophosphataemia	Blood phosphorus decreased
Hyperuricaemia	Blood uric acid increased
Hypoalbuminaemia	Blood albumin decreased
Hypercalcaemia	Blood calcium increased
Hypocalcaemia	Blood calcium decreased
Hypoglycaemia	Blood glucose decreased
Hyperkalaemia	Blood potassium increased
Hypokalaemia	Blood potassium decreased
Hyponatraemia	Blood sodium decreased
Hypothyroidism	Thyroid stimulating hormone increased

Any additional terms added to this list will be noted in the Clinical Study Report.

9.3. Clinical Laboratory Evaluations

Clinical laboratory values will be displayed in SI units (Système Internationale d'Unités; International System of Units). Clinical laboratory evaluations performed during the study will include the following:

Table 6: Clinical Laboratory Evaluations to be Performed During the Study

Hematology	Chemistry	Coagulation	Urinalysis (Dipstick)
Hematocrit	Alkaline phosphatase	Prothrombin time (PT)/ Partial thromboplastin time (PTT)	Glucose
Hemoglobin	Alanine aminotransferase	International normalized ratio (INR)	Protein
Platelets	Aspartate aminotransferase	Activated partial thromboplastin time (aPTT)	Blood
White blood cells (absolute)	Albumin		Ketones
Monocytes (absolute)	Total bilirubin		
Eosinophils (absolute)	Direct bilirubin		
Basophils (absolute)	Blood urea nitrogen or urea nitrogen		
Lymphocytes (absolute)	Potassium		
Neutrophils (absolute)	Sodium		
	Total calcium		
	Corrected total calcium		
	Creatinine		
	Glucose		
	Lactate dehydrogenase		
	Total protein		
	Creatine kinase		
	Phosphorus		
	Carbon dioxide		
	Chloride		
	Thyroid-stimulating hormone		
	Creatinine-kinase cardiac isoenzyme		
	Troponin I		
	Troponin T		
	Lipase (South Korea only)		
	Amylase (South Korea only)		
Other Laboratory Assessments	TSH		
	FT3 (South Korea only)		
	FT4 (South Korea only)		
	Pregnancy Test (for women of childbearing potential)		

Laboratory measures will also be compared with their corresponding normal ranges and the incidence of abnormally high and abnormally low laboratory values will be calculated for each relevant protocol-specified laboratory test.

Hematology and chemistry laboratory results will be graded according to the NCI CTCAE v5.0 guidelines, where calculable. Severity grades will be programmatically calculated using standard American Medical Association's (AMA) laboratory normal ranges [AMA Manual of Style, AMA 2009] and the quantitative NCI CTCAE v5.0 criteria (when available for a specific laboratory abnormality). Laboratory values considered to be normal by CTCAE criteria, meaning they do not qualify as Grade 1 to 4, will be assigned a severity Grade of 0.

Descriptive summaries of hematology, chemistry, and coagulation laboratory parameters, of the observed values, as well as absolute changes from the baseline value, will be provided by study part and scheduled assessment time point. Shift tables of baseline grade by the worst post-baseline NCI-CTCAE grades for hematology, chemistry, and coagulation will also be provided, and treatment emergent Grade 3/4 abnormalities for hematology, chemistry and coagulation laboratory tests will be summarized.

For the shift tables a lab test will only be included if the direction is relevant according to CTCAE grading. For example, will represent Alanine Aminotransferase Increased, but not Alanine Aminotransferase Decreased.

Summaries will be displayed by group and the clinical laboratory parameters presented in alphabetical order. In the event of multiple evaluations for the same parameter at the same visit, the last non-missing value per study day/time will be used.

The data for all clinical laboratory evaluations will be presented in listings. A subset listing will be presented for all clinically significant abnormal laboratory values. Pregnancy test results will not be listed but will be included in datasets. Urinalysis results will only be listed.

9.4. Vital Signs

Vital signs measurements will include height, weight, systolic/diastolic blood pressure, pulse, respiratory rate, and temperature. Descriptive summaries for each parameter, as well as changes from the baseline (screening) value, will be provided by assessment time point.

The data for vital signs evaluations will be presented in listings.

9.5. ECGs

Electrocardiogram (ECG) measurements will include ventricular heart rate, PR interval, QRS duration, QT interval, corrected QT interval, and RR interval. The physician's overall interpretation will also be determined.

Descriptive summaries for each quantitative ECG parameter, as well as changes from the baseline (screening) value, will be provided by assessment time point.

The following abnormal QTc values (including QTcF, QTcB) will be reported by a frequency table.

- Absolute value at any post-baseline visit: > 450 msec, > 480 msec, > 500 msec
- Change from baseline: > 20 msec > 30 msec, > 60 msec

Shift tables will be provided for baseline vs. worst on study QTcF and QTcB using maximum NCI-CTCAE Grade. Data for ECG assessments will be presented in a listing.

9.6. Physical Examination

Physical exams will be performed at specified timepoints throughout the study to determine the presence of any clinically significant abnormal findings.

Data on physical exams will be presented in a listing.

9.7. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be displayed at specified timepoints throughout the study. Shift from baseline to worst post-baseline ECOG PS grade will also be presented.

Data for ECOG assessments will be presented in a listing.

9.8. Other Safety Measures

Information on transfusions or growth factor support in the 3 months prior to screening, during treatment, or following treatment will be listed. Where transfusion products are defined as: packed red blood cells, whole blood, platelets, fresh frozen plasma, other. Growth Factors products are defined as: Granulocyte colony-stimulating factor (G-CSF), Granulocyte macrophage colony-stimulating factor (GM-CSF), Erythropoiesis-Stimulating Agents (ESA), other.

For South Korean patients the following additional data will be listed:

- Pulmonary Function Test (PFT) for patients with radiation pneumonitis
- Ophthalmic Examination: Best Corrected Visual Acuity, Spectral Domain Optical Coherence

10. CLINICAL PHARMACOLOGY ANALYSES

Not applicable.

11. OTHER ANALYSES

11.1. Pharmacokinetic Analysis

A separate pharmacokinetic analysis plan will be developed for this study.

11.2. Biomarker Analysis

Exploratory biomarker analyses may be performed to understand the association of these study markers with study drug response, including efficacy and/or adverse events. Results will be presented in a separate report.

11.3. Anti-Drug Antibody Analysis

A separate plan will be generated to detail the analysis of anti-drug antibody endpoints for this study.

12. REPORTING CONVENTIONS

All tables, figures, and data listings will be presented in landscape orientation for easy visual comparison of different study parts. Legends will be used for all figures with more than one variable or item displayed. Figure lines should be wide enough to see the line after being copied. The tables, listings, and figure reporting layout will be detailed in the companion document DEK-DKK1-P205 Table, Listing and Figure Shells.

All titles will be centered on a page. The International Conference on Harmonization (ICH) numbering convention will be used for all TLFs. All tables, figures, and data listings will have the name of the relevant SAS program. Data Listing or Table source, and a date-time stamp at the time the program was run on the bottom of each output.

13. CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL

The following clarifications or changes from the protocol should be noted:

- The Response Evaluable Population has been updated and is now the same for Part A and Part B
- Introduced ‘enrolled population
- Per protocol population will use ‘without important protocol violations’ instead of ‘major deviations’ to determine exclusions
- Biomarker population split into distinct populations based on biomarker
- Pharmacokinetic population split into DKN-01 and Tislelizumab

14. REFERENCES

Eisenhauer, E.A., et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). European Journal of Cancer, 2009.

Brent A. Williams, MS, Jayawant N. Mandrekar, Sumithra J. Mandrekar, Stephen S. Cha, MS, Alfred F. Furth. “Finding Optimal Cutpoints for Continuous Covariates with Binary and Time-to-Event Outcomes”. Department of Health Sciences Research Mayo Clinic Rochester, Minnesota. Technical Report Series #79, June 2006.

Klempner, S, Bendell J, et al. DKN-01 in combination with pembrolizumab in patients with advanced gastroesophageal adenocarcinoma (GEA): Tumoral DKK1 expression as a predictor of response and survival. ASCO 2020. 2020.

15. TABLES, FIGURES, LISTINGS

Tables, figures, and listings will be generated according to the companion document which details the layout of the output. Minor style deviation from specification defined in the shell document in the final production is permissible.