Leap Therapeutics, Inc.

SAP Part C

- **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 C**, Version 2.0, 06 February 2025
- **Protocol Identifier:** DEK-DKK1-P205
- **NCT04363801**

NOVOTECH
The Asia Pacific CRO

STATISTICAL ANALYSIS PLAN

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 NO.: DEK-DKK1-P205 (Part C)

PRODUCT CODE: DKN-01 (Leap Therapeutics, Inc.)
tislelizumab (BGB A317) (BeiGene, Ltd.)

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SAP APPROVAL

By my signature, I confirm that this SAP has been reviewed by Leap Therapeutics, Inc. and has been approved for use on the DEK-DKK1-P205 (Part C) study:

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Document History

Date	Version number	Summary of changes
21Sep2023	Final v1.0	Initial SAP
06Feb2025	Final V2.0	Analyses for PFS and ORR are added based on the Blinded Independent Central Review (BICR) assessments for exploratory purposes. For the determination of stable disease (SD) for the confirmed best overall tumor response, the previous cut-off was 6 weeks (42 days) from randomization. This is changed to 5 weeks (35 days) to account for the data collection visit window. Leap made the decision on 31 January 2025 to terminate the study early based on a preliminary data analysis suggesting that the experimental treatment will not be more efficacious than its comparator in the primary endpoint of progression-free survival as assessed by the investigators. Therefore, only a subset of the TLFs will be selected from the full list for an abbreviated CSR. Other wording changes to avoid confusion.

Table of Contents

List of Abbreviations

Abbreviation	Description
ADA	anti-drug antibody
AE	adverse event
ATC	Anatomical Therapeutic Chemical
BLQ	below limit of quantification
BOR	best overall response
CAPOX	capecitabine + oxaliplatin
CI	confidence interval
CPS	combined positive score
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CV	coefficient of variation
CX	cycle X
D	day
DCB	durable clinical benefit
DCR	disease control rate
DKK1	Dickkopf-related protein 1
DoCB	duration of clinical benefit
DoCR	duration of complete response
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
G/GEJ	gastric or gastroesophageal junction
GCP	Good Clinical Practice
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
IV	intravenous
LLoQ	lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	leucovorin calcium, fluorouracil, and oxaliplatin
NE	Not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD	pharmacodynamics
PD-L1	programmed cell death protein ligand-1
PFS	progress-free survival
PFT	pulmonary function tests
PK	pharmacokinetics
PN	preferred name
PR	partial response
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

Abbreviation	Description
SD	stable disease
SOC	System Organ Class
SOP	standard operating procedure
TEAE	treatment emergent adverse event
TPS	tumor percentage score
TTR	time to response
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Leap Therapeutics Protocol DEK-DKK1-P205 (Protocol version 6.0, dated 29Jun2023), 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 open-label, multicenter study to be conducted concurrently in 3 Parts:

- Part A will enroll approximately 24 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 approximately 48 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 will enroll approximately 160 patients G/GEJ adenocarcinoma patients who have received no prior systemic treatment in the locally advanced/metastatic setting (first-line treatment)

This SAP will present the planned analysis for Part C only. Examples of tables and figures that will be used to summarize the data are included in the companion document 'Mock Tables, Listings, and Figures'. The SAP for Parts A and B was documented separately.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post hoc, or unplanned, exploratory analyses performed will be clearly identified as such in the final CSR.

2. PROJECT OVERVIEW

2.1 Study Design of Part C

General Design

Part C of this study 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.

Approximately 160 patients will be randomized in a 1:1 ratio to receive:

- Experimental: DKN-01 + tislelizumab + chemotherapy regimen (CAPOX or mFOLFOX6) (n=80), or
- Control: tislelizumab + 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)

For Part C, a review by the Safety Review Team (SRT) will occur after the first 5 patients on each chemotherapy regimen (CAPOX and mFOLFOX6) have completed Cycle 1 from both the experimental arm and the control arm.

Dosing Schedule

Patients in both arms 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 Cycle Day 1 and capecitabine 1000 mg/m^2 BID on Cycle Days 1-15 of each 21-day cycle for a total of 28 doses. Patients in the experimental arm 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 arm will not receive DKN-01 treatment.

In summary, the treatments are planned as follows for CAPOX chemotherapy regimen, where Cn stands for each cycle.

- Experimental arm:
  - DKN-01 (600 mg IV) on CnD1 and C1D15
  - tislelizumab (200 mg IV) on CnD1, Oxaliplatin 130 mg/m^2 IV on CnD1 and Capecitabine 1000 mg/m^2 PO BID on CnD1-15 (for a total of 28 doses)
- Control arm:
  - tislelizumab (200 mg IV) on CnD1, Oxaliplatin 130 mg/m2 IV on CnD1 and Capecitabine 1000 mg/m^2 PO BID on CnD1-15 (for a total of 28 doses)

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 Cycle Day 1, fluorouracil 400

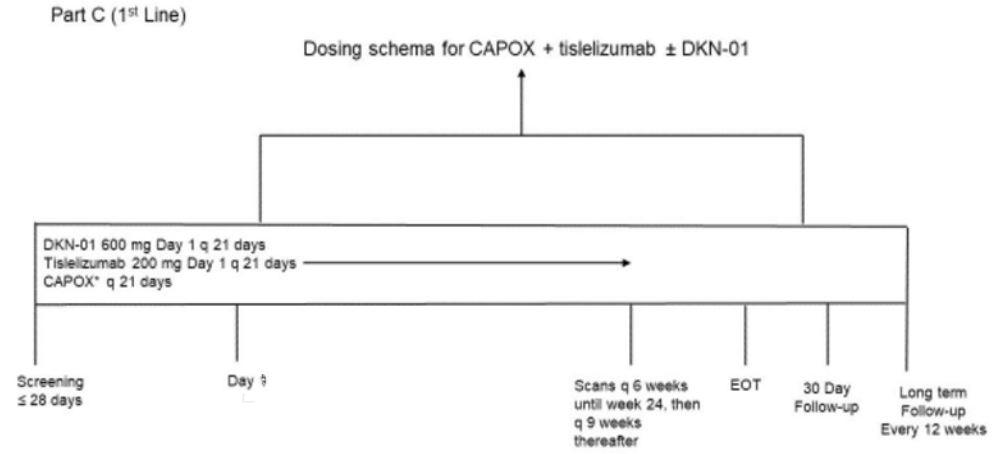
mg/m^2 IV bolus on Cycle Day 1 followed by fluorouracil 2400 mg/m^2 IV continuous infusion over 48 hours, and oxaliplatin 85 mg/m^2 IV on Cycle Day 1. Patients in the experimental arm will receive DKN-01 (400 mg, IV) on Day 1 of each cycle. For Cycle 1 only, an additional loading dose of DKN-01 (400 mg, IV) will be administered on Day 8. Patients in the control group will not receive DKN-01 treatment.

In summary, the treatments are planned as follows for mFOLFOX6 chemotherapy regimen.

- mFOLFOX6 Experimental arm:
  - DKN-01 (400 mg IV) on CnD1 and C1D8
  - tislelizumab (400 mg, IV) every 6 weeks starting on C1D1, Leucovorin calcium (folinic acid) 400 mg/m^2 IV on CnD1, Fluorouracil 400 mg/m^2 IV/day on CnD1 followed by fluorouracil 2400 mg/m^2 IV continuous infusion over 48 hours, and Oxaliplatin 85 mg/m^2 IV on CnD1
- mFOLFOX6 Control arm:
  - tislelizumab (400 mg, IV) every 6 weeks starting on C1D1, Leucovorin calcium (folinic acid) 400 mg/m^2 IV on CnD1, Fluorouracil 1200 mg/m^2 IV/day on CnD1 and Oxaliplatin 85 mg/m^2 IV on CnD1

Figure 1: Study Schemas

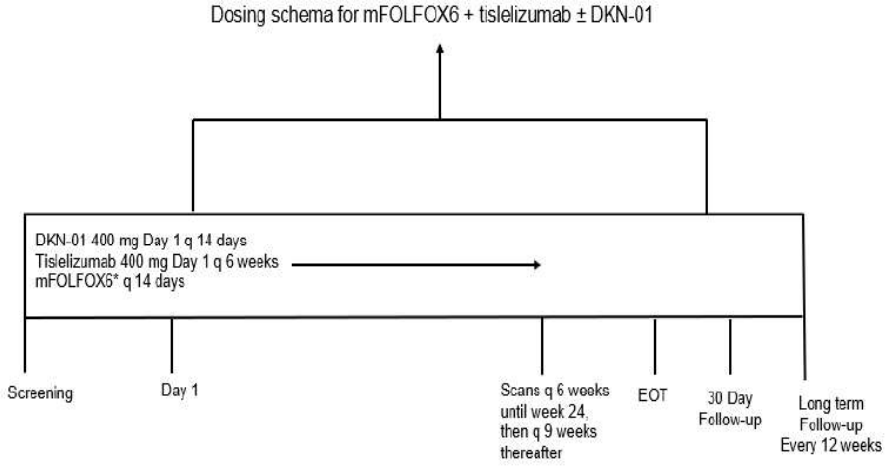
Study Design Part C (CAPOX regimen)



*CAPOX : oxaliplatin 130 mg/m2 on Day 1 + capecitabine 1000mg/m2 BID on Days 1-15

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.

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.

2.2 Objectives

2.2.1 Primary Objective

To assess whether the addition of DKN-01 to the combination of tislelizumab + chemotherapy regimen (CAPOX [capecitabine + oxaliplatin] 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.

2.2.2 Secondary Objectives

The secondary objectives of the study are:

- To estimate the objective response rate (ORR), according to RECIST v1.1 as assessed by the Investigator, the duration of response (DoR), according to RECIST v1.1 as assessed by the Investigator, 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 $\geq$ 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 $\geq$Grade 3 treatment-related adverse events (TRAE) associated with each of the treatment arms.

2.2.3 Exploratory Objective

The exploratory objectives of the study are:

- 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 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.

2.3 Endpoints

2.3.1 Primary Endpoints

- 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 overall patients

2.3.2 Secondary Efficacy 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)

2.3.3 Exploratory Efficacy 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 exploratory studies.
- iORR = (number of subjects with iCR + iPR)/all subjects) 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 exploratory 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

2.4 Sample Size

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.

2.5 Randomization

This is an open label study, the randomization for treatment assignment will not be blinded.

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

The stratification variable values for each patient are reported under Stratification Factor from 'Eligibility' eCRF page. Randomization may occur up to 3 calendar days prior to C1D1. The Interactive Response Technology (IRT) system will be used to assign a study subject to the experimental or the control group. The randomization block size will be defined in the IRT system.

The enrollment assumptions, including percentage of PD-L1+ patients, will be monitored during the enrollment period; thus, sample size and analysis timeline could be adjusted accordingly.

3. STATISTICAL CONSIDERATIONS

Data will be handled and processed per the sponsor's representative (Novotech) Standard Operating Procedures (SOPs), which are written based on the principles of good clinical practice (GCP). In general, the following considerations are applicable for the data analyses.

3.1 General Considerations

All data collected on the electronic case report form (eCRF) will be presented in the data listings and sorted by treatment group, subject number and study visit, where applicable. All descriptive summaries will be presented by treatment group and nominal visit/time point (where applicable).

Unless otherwise stated, the following methods will be applied:

- Continuous variables: Descriptive statistics will include the number of non-missing values (n), arithmetic mean, standard deviation (SD), median, minimum and maximum values.

  The minimum and maximum values will be displayed to the same decimal precision as the source data, the arithmetic mean, SD and median values and other derived values will be displayed to one more decimal than the source data for the specific variable.

  95% Confidence Intervals (CIs) and mean differences (change from baseline) will be displayed to one more decimal than the source data for a specific variable. Where applicable, p-values will be displayed to 4 decimal places (i.e. 0.1234).

  The appropriate precision for derived variables will be determined based on the precision of the data on which the derivations are based, and statistics will be presented in accordance with the aforementioned rules.

- Categorical variables: Descriptive statistics will include counts and percentages per category. The denominator in all percentage calculations will be the number of subjects in the relevant analysis population with non-missing data, unless specifically stated otherwise. Percentages will be displayed to one decimal place.

- Repeat/unscheduled assessments: Only values collected at scheduled study visits/time points will be presented in **by-visit** summary tables. If a repeat assessment was performed, the result from the original assessment will be presented as the result at the specific visit/time point for the summary. All collected data will be included in the data listings. For **time to event** analyses, all collected data from scheduled and unscheduled visits will be used for the data derivation and analyses. All collected data will be included in the data listings.

- Assessment windows: All assessments will be included in the data listings and no derived visit windows will be applied to exclude assessments that were performed outside of the protocol specified procedure windows. Data from unscheduled visits will be included in data listings, but will not be included in the by-visit summary tables.

- Result display convention: Results will be center aligned in all summary tables and listings. Subject identifiers, visit and parameter labels may be left-aligned if required.

- Date and time display conventions: The following display conventions will be applied in all outputs where dates and/or times are displayed:

  - Date only: YYYY-MM-DD
  - Date and time: YYYY-MM-DD HH:MM

- If only partial information is available, unknown components of the date or time will be presented as 'NK' (not known), i.e., '2022-NK-NK'. Times will be reported in military time.

3.2 General Key Definitions

The following definitions will be used:

- Baseline: The baseline value is defined as the last available valid (quantifiable continuous or categorical value), non-missing observation for each subject prior to the first study treatment administration. Repeat and unscheduled assessments will be included in the derivation of the baseline values.
- Change from Baseline: The change from baseline value is defined as the difference between the result collected/derived at a post-baseline visit/time point and the baseline value.

  The change from baseline value at each post-baseline visit/time point will be calculated for all continuous parameters using the following formula, unless stated otherwise:

  Change from Baseline Value = Result at Visit/Time Point – Baseline Value

  A positive change reflects an increase; a negative change reflects a decrease. The change from baseline value will only be calculated if the specific post-baseline visit/time point result and the baseline value for the parameter are both available and will be treated as missing otherwise.

  Similarly, Fold Change from Baseline will be calculated as:

  Result at Visit/Time Point divided by Baseline Value

  The corresponding Percentage Change from Baseline will be calculated as:

  Percentage Change from Baseline Value = 100* ((Result at Visit/Time Point – Baseline Value)/Baseline)
- Study day: The study day of an event is defined as the relative day of the event starting with the date of **randomization** (reference date) as Day 1 (there will be no Day 0).

  The study day of events occurring before the randomization will be calculated as:

  Study Day = (Date of Event - Date of Randomization)

  For events occurring on or after Day 1, study day will be calculated as:

  Study Day = (Date of Event - Date of Randomization) + 1

  Study days will only be calculated for events with complete dates and will be undefined for events that are 'Ongoing' at the end of the study.

  Relative days compared to an alternative reference point will be calculated similarly, but the alternative starting reference start date will be used instead of the date of the first study drug dosing.
- Cycle day: will be calculated using the first dosing date of each treatment cycle as the reference date. The date of interest can only occur on or after the first dosing date of each treatment cycle. The cycle day will be calculated as (date of interest – date of first dosing of each treatment cycle) + 1.
- Adverse event (AE) duration: AE End Date – AE Start Date + 1. Duration will only be calculated for events with complete (non-imputed) dates.

3.3 Multiple Comparisons and Multiplicity Adjustments

PFS is the primary endpoint of this study. The comparisons of PFS between the experimental and control groups will be tested in DKK1-high patients and in all patients respectively at the significance level of 0.10 (one-sided test). No multiplicity adjustment is planned for the treatment comparisons of PFS in DKK1-high patients and in all patients as this is a Phase 2 study for exploratory and for signal finding purpose. All other efficacy analyses will be considered exploratory. No multiplicity adjustments will be made and nominal one-sided p-values will be provided. The significance level of 0.10 (one-sided) is considered as a reference for decision making purpose in this Phase 2 study.

3.4 Handling of Missing Data

For the classification of treatment emergent adverse event (TEAE) and concomitant medication, treatment emergent is defined as post the first treatment administration, and the following will be applied in the following order:

- If all dates/times (start and stop) missing, the event/medication will automatically be classified as a TEAE/Concomitant medication.
- For AEs with a missing start date/time, if the event end date/time is prior to first study treatment administration, the event will not be classified as a TEAE.
- If only the AE start year/medication end year is present and is the same or is after the first study treatment administration year unit, the event/medication will be classified as a TEAE/Concomitant medication.
- If the AE start month and year/medication end month and year are present and are the same or after the first study treatment administration month and year units, the event/medication will be classified as a TEAE/Concomitant medication.

Conversion of categorical values

In some instances, continuous variables are expressed as a range (e.g., < 10). In such cases, values may be converted to the range boundary (upper or lower limit as applicable). As an example, a value of <10 may be converted to 10. Such substitutions will be clearly documented in the footnotes of relevant outputs. In listings such values will be represented as recorded in the eCRF, e.g. <10.

3.5 Coding of Events and Medications

Medical history and AE verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 25.1). Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred terms (PT) will be of primary interest for the analysis.

Prior and concomitant medications will be coded using the dictionary of WHODrug Global Sep2021. Medications will be mapped to the full WHO Drug Global Anatomical Therapeutic Chemical (ATC) class hierarchy, but ATC Level 4 and PNs (preferred names) will be of primary interest in this analysis.

3.6 Treatment Groups

As a general rule for the Part C analyses, all summaries will be provided separately for the following patient populations:

- DKK1-high Patients

- All Patients

DKK1-high patients are those with a DKK1 RNAscope tumor percentage score (TPS) of ≥ 20%. DKK1 RNAscope TPS data are reported from 'Eligibility' eCRF page. For each patient population, the following treatment group labels will be generally used for the data analyses:

- DKN-01 + tislelizumab + (CAPOX/mFOLFOX6), known as experimental arm
- tislelizumab + (CAPOX/mFOLFOX6), known as the control arm
- Overall

Overall is the pool of patients from experimental and control groups. This Overall group is only used for the summary of patient disposition, demographics, baseline characteristics, and safety.

4. ANALYSIS POPULATIONS

In this study, seven analysis populations are defined: Enrolled, Safety, Intent-to-Treat (ITT), Per-Protocol (PP), Pharmacokinetics DKN-01, Pharmacokinetics Tislelizumab, and Biomarker. The protocol defined analysis populations such as Modified Intent-to-Treat (mITT), and Response Evaluable (RE) are not applicable in this SAP. Furthermore, any additional exploratory analysis not identified in the SAP will be identified in the final CSR as exploratory post hoc analyses, including analyses for additional study analysis populations or subgroups of interest.

4.1 Enrolled Analysis Population (Enrolled)

Enrolled analysis population is defined as all patients who signed the main study informed consent form (ICF). Enrolled analysis population will be used for the analyses of patient disposition.

4.2 Safety Analysis Set (Safety)

Safety analysis population is defined as all patients who are randomized and receive at least one dose of study treatment. Patients will be analysed according to the treatment group actually received. The Safety analysis population will be used for the summaries of all safety endpoints.

4.3 Intent-to-Treat Analysis Population (ITT)

Intent-to-Treat analysis 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. The ITT analysis population will be used for the summary of efficacy endpoints.

4.4 Per-Protocol (PP) Analysis Population (PP)

The Per-Protocol analysis population is defined as 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. Patients will be included in the treatment group assigned at randomization. PP analysis will be run only if >10% ITT population is excluded, and would only be needed for the primary and key secondary efficacy endpoints.

4.5 Pharmacokinetics DKN-01 Analysis Population (PK DKN-01)

Pharmacokinetics DKN-01 analysis population is defined as all enrolled patients with available serum-time concentration data from patients dosed with DKN-01. A separate pharmacokinetic analysis plan will be developed for this study. No summaries or listings will be provided as part of this SAP.

4.6 Pharmacokinetics Tislelizumab Analysis Population (PK Tislelizumab)

Pharmacokinetics Tislelizumab analysis population is defined as all enrolled patients with available serum-time concentration data from patients dosed with tislelizumab. Pharmacokinetics A separate pharmacokinetic analysis plan will be developed for this study. No summaries or listings will be provided as part of this SAP.

4.7 Biomarker Analysis Population (Biomarker)

There is one biomarker population for each of the following biomarkers:

- DKK1 tumor expression in messenger RNA (mRNA) by chromogenic in situ hybridization (CISH) (provided by Flagship)

- Programmed cell death protein ligand-1 (PD-L1) in the tumor microenvironment by IHC (provided by Flagship)
- serum DKK1 (ng/mL) (provided by Nexelis)

Each biomarker population consists of the patients with an evaluable central vendor baseline value of the corresponding biomarker. A separate biomarker and pharmacodynamics analysis plan will be developed for this study.

5. PARTICIPANT DISPOSITION AND ANALYSIS POPULATIONS

Summary of subject disposition and analysis populations will be based on the Enrolled analysis population. Subject disposition and analysis populations will be summarized descriptively as described in section 3.1 (categorical descriptive analysis).

The following patient enrollment, disposition and analysis population information will be reported for this study:

- Number of patients screened
- Number of screen failures
- Reason for screen failures (only if data available)
- Number of patients randomized
- Number of patients treated
- Number of patients who received CAPOX Regimen
- Number of patients who received mFOLFOX6 Regimen
- Number of patients who permanently discontinued ALL study drug treatment
- Primary reason for ALL study drug treatment discontinuation
- Number of patients who discontinued study
- Primary reason for study discontinuation
- Duration on study, duration on treatment, and duration on post-treatment follow-up (months)
- Number of patients in each analysis population (Safety and ITT)

Counts and percentages will be reported descriptively for the summary of patient screening, randomized, treated, disposition, and analysis populations by treatment group. By-participant data listings will also be provided, inlcuding date of informed consent, date of randomization, date of treatment, and date of ALL study drug treatment discontinuation, and date of study discontinuation.

6. PROTOCOL DEVIATIONS

All important protocol deviations will be categorized and summarized descriptively as per data collected by the protocol deviation tracking database, based on the ITT analysis population. Protocol deviations will be presented for each patient in a by-participant data listing and summarized in a separate table.

Prior to database lock, all protocol deviations will be reviewed by medical monitors and assigned a status of Important Deviation based on clinical or study judgement on their possible impact on study outcomes. As these data are not collected in eCRF, if data format is not suitable for summary, only data listing will be provided.

7. DEMOGRAPHIC AND BASELINE INFORMATION

Demographic and baseline information analysis will be based on the ITT. Demographic and baseline information will be summarized descriptively as described in section 3.1.

7.1 Demographics

The following demographic parameters will be analyzed:

- Age (years) at consent
- Age group (<65 and >=65)
- Sex
- Ethnicity
- Race
- Height (cm) at baseline
- Weight (kg) at baseline
- BMI (kg/m^2)
- Body Surface Area (m^2)
- Baseline ECOG performance status
- Randomisation stratification factors
  - TPS ≥ 20% and CPS ≥ 5
  - TPS < 20% and CPS ≥ 5
  - TPS ≥ 20% and CPS <5
  - TPS < 20% and CPS <5
- DKK1-High patients (TPS ≥ 20%)
- Serum DKK1 (ng/mL) (provided by Nexelis)

7.2 Historic Tumor Characteristics

Historic tumor characteristics will be summarized for the followings. All data will be listed.

- Prior Genetics test results available (yes/no)
- Prior Genetic mutations: ZNRF3, RSPO2, RSPO3, RNF43, CTNNB1, AX1N1, AXIN2, APC, AR1D1A, PIK3CA, Other
- Source of sample (ctDNA, Tumor Biopsy)
- Prior tumor mutation burden assessed (yes/no)
- Tumor mutational burden (TMB) (mutations per megabase)
- Was prior microsatellite stability or mismatch repair status done? (yes/no)
- Microsatellite stability status (MSS or MMR proficient, MSI or MMR deficient, and Undetermined) and MSI phenotype (MSI-L, MSI-H, Unknown)
- Was prior EBV testing done? (yes/no)
- Epstein Barr Virus (Positive, Negative, and Undetermined)

- Was prior HER2 testing done? (yes/no)
- Human epidermal growth factor receptor 2 (HER2) (Positive/Amplified, Negative/Non-amplified, and Undetermined)
- Was a prior PD-L1 status done? (yes/no)
- PD-L1 Numeric Results (CPS <5 and CPS ≥5)

7.3 Medical and Surgical History/Physical Findings

Medical and surgical history/physical findings will be coded using MedDRA®. Medical history and surgical history/physical findings will be summarized together descriptively by treatment group and by system organ class (SOC) and preferred term (PT). When patients are counted in each category of SOC/PT, each patient will be only counted once in each category. All data will be presented in a by-participant data listing.

7.4 Cancer Diagnosis at Study Entry

Cancer diagnosis data will be presented in a by-participant data listing. The following data items will be summarized descriptively by treatment group.

- Primary cancer diagnosis (GEJ, GC)
- Cancer category (Siewert I, II, III, unknown) - GEJ only
- Duration since initial pathological diagnosis (months)
- Stage at initial diagnosis (Stage I to IV)
- Any metastatic disease to the liver (Yes/No)
- Any Ascites (Yes/No)

7.5 Prior Systemic Cancer Therapy, Cancer Surgery and Radiation Therapy

Prior systemic cancer therapy, prior cancer surgery, and prior radiation therapy will be presented in separate by-patient data listings. Separate descriptive summaries will be conducted for prior systemic cancer therapy, prior cancer surgery, and prior radiation therapy.

For prior systemic cancer therapy, data items such as any prior systemic cancer therapy (Yes/No), number of therapies, duration of treatment (weeks), setting (Adjuvant/Neoadjuvant), and any other prior systemic cancer therapy will be summarized descriptively by treatment group. For prior cancer surgery, data items such as any prior cancer surgery (Yes/No) and reason for surgery will be summarized. For prior radiation therapy, data items such as any prior radiation therapy (Yes/No), duration of radiation therapy (weeks), intent, given concurrent with other therapy (Yes/No), anatomical location, radiation type, and dose received (cGy) will be summarized.

7.6 Eligibility

Subject eligibility will be listed in a data listing.

7.7 Tumor Biopsy

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. All reported biopsy data will be listed.

8. TREATMENT EXPOSURE

The following treatments are administrated in Part C of the study according to the schedule of dosing below:

Chemo Regimen	DKN-01	Tislelizumab	Oxaliplatin[1]	Capecitabine[1]	Leucovorin calcium[1, 6]	Fluorouracil
Experimental arm						
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/m^2 IV bolus on D1 then 2400 mg/m^2 IV continuous infusion over 48 hours D1 and D2
Control arm						
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/m^2 IV bolus on D1 then 2400 mg/m^2 IV continuous infusion over 48 hours D1 and D2

Abbreviations: BID = twice daily; D = day; IV = intravenously; PO = orally; q = every
[1] Standard regimen as supported by (Bang, Kim et al. 2012).
[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.

The duration for each cycle is based on the chemotherapy regimen: CAPOX is 21 days and mFOLFOX6 is 14 days. Treatment exposure to DKN-01, tislelizumab, Leucovorin calcium, Oxaliplatin, Fluorouracil, and Capecitabine will be summarized separately in separate table by treatment group based on Safety analysis population. The following variables will be summarized.

- Number of treatment Cycles initiated
- Duration of Exposure (Months): (last dosing date -first dosing date + 1) /30.4375
- Cumulative Dose (mg)
- Compliance (%): (Cumulative actual doses received (mg) / Cumulative planned doses for the same treatment period (mg)) *100
  - The actual doses received and planned dose for each infusion for DKN-01, tislelizumab, Oxaliplatin, Leucovorin calcium, and Oxaliplatin are recorded in the corresponding treatment administration eCRF pages.

- For Capecitabine, the actual doses received (mg) need to be calculated based on number of tablets taken for each cycle and converted to mg unit, and the planned doses is calculated as 1000 mg/m^2 * BSA*28 for each cycle. If a cycle is treated for <15 days, the planned doses is calculated as 1000 mg/m^2 * BSA*2*(days treated) for the cycle.

DKN-01, tislelizumab, Leucovorin calcium, Oxaliplatin, and Fluorouracil will be administered by IV, and the following drug modification events will be summarized for these 5 treatments:

- Any treatment delay and reasons
- Any dose reduction and reasons (except for tislelizumab)
- Infusion prematurely discontinued and reasons
- Study drug permanently discontinued and reasons
- Any infusion interruption and reasons
- Any infusion reaction
- Any infusion slowed (except for DKN-01)

Capecitabine will be administered orally, and the following drug modification events will be summarized:

- Any treatment delay and reasons
- Any missed dose and reasons
- Study drug permanently discontinued and reasons

9. PRIOR AND CONCOMITANT MEDICATIONS

9.1 General Prior and Concomitant Medications

Prior and concomitant medications will be coded by WHODrug Global Sep 2021. Medications will be mapped to the Anatomical Therapeutic Chemical (ATC) **Level 4** and preferred name (PN), as the primary interest for the analysis. Data from 'Prior and Concomitant Medications' eCRF page will be included for the analysis.

The prior and concomitant medications and therapies are defined as follows.

- Prior Medications: Prior medications are defined as any medication where the use was stopped prior to the first administration of the study treatment regimen.
- Concomitant Medications: Concomitant medications are defined as any medication (other than the study treatment regimen) that was used at least once after the first administration of the study treatment regimen. Medications that were stopped on the same date (with end time missing) as the first study treatment regimen administration will be defined as concomitant medications. If a clear determination cannot be made (partial medication end dates) the medication will be classified as concomitant.

The prior and concomitant medications/therapies are exclusive with each other. The number and percentage of patients using at least one prior or concomitant medication/therapy will be tabulated and displayed together with the number and percentage of patients using at least one medication/therapy within each therapeutic class and preferred name. For the summaries of prior and concomitant medications, patients who take the same medication (in terms of the drug preferred name) more than once will be counted only once for that medication. These will be summarized under Safety analysis population by treatment group.

Listing of full details of prior and concomitant medications/therapy classification, medication taken, start and end date/time, ongoing status, indication, dose, unit, dose form, frequency, route, and premedication will be provided by treatment group for the Safety analysis population.

9.2 Non-Drug Treatments/Procedures, Radiation Therapy, and Transfusions and Growth Factor

Data for the following treatments received during the study period will be listed:

- Non-Drug Treatments/Procedures
- Radiation Therapy
- Transfusions and Growth Factor

9.3 Subsequent Anticancer Therapy

Data for the following subsequent anticancer therapies will be listed:

- Subsequent Systemic Cancer Therapy
- Subsequent Cancer Surgery
- Subsequent Radiation Therapy

10. EFFICACY

Efficacy analyses will be conducted by using ITT and PP analysis populations.

All the efficacy analysis results will be presented for DKK1-high patients first, followed by results for overall patients.

According to the study design, a one-sided test will be applied to PFS comparison between the experimental and control arms in DKK1-high patients and in overall patients. Accordingly, only one-sided p-values will be reported for PFS analysis as the primary endpoint for both DKK1-high and overall patients. For all other efficacy endpoint analyses, only nominal one-sided p-values will be reported as supportive evidence, without further multiplicity adjustment. For all efficacy endpoints, confidence intervals (CIs) will be reported as 95% CI (two-sided). For all time to event endpoint analyses, log-rank tests and Cox proportional hazards models will be conducted.

10.1 Analyses of Progress-free Survival (PFS)

Progress-free Survival (PFS)

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 that verified lack of disease progression, PFS will be censored at the most recent tumor assessment before the data cutoff or study withdrawal, whichever occurs first.

According to the study protocol, PFS is the primary endpoint when assessed in **DKK1-high and all patients** in Part C.

The specific censoring rules for PFS are:

- 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 randomization 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 (from Subsequent Systemic Cancer Therapies CRF page), surgery (from Subsequent Cancer Surgery CRF page), or radiation (from Radiation Therapy with curative intent only or from Subsequent Radiation Therapy) 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 immediately after an unacceptably long interval (i.e., $\geqslant$ 2 consecutive missing) since the last tumor assessment will be censored at the time of last objective assessment documenting no progression before missing assessments.

The censoring rules for PFS are also listed in Table 1.

Analyses of PFS

Descriptive Analysis

The analysis of PFS is based on the survival analysis method. Survivor function will be estimated for time to event data (time to PFS events), which is the probability to survive or, more generally, to stay event-free beyond a certain point in time. The survival function is estimated by the Kaplan-Meier method. The survival function will be summarized for 25th percentile, median, and 75th percentile and their respective 95% confidence intervals. The plot of Kaplan-Meier estimates for the two treatment groups will be presented. The event free (survival) rates of PFS at Months 6, 8, 12, and 24 (as appropriate) and their 95% confidence intervals will be derived based on their respective survival functions.

Log-rank Test

The stratified log-rank test is the main method of analysis. It will be used to compare survival functions between the two treatment groups. Log-rank test stratified by the protocol-specified stratification variables will be conducted:

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

The stratification variable values for each patient are reported under Stratification Factor from the 'Eligibility' eCRF page. The same stratification variables will be used for all stratified analyses.

Cox's Proportional Hazards Model

The survival data of the two treatment groups will be analyzed with a stratified Cox's proportional hazards model to estimate the hazard ratio and its 95% confidence interval. The stratification factors are those used for the randomization (TPS <20%, >=20%, and CPS <5, >=5). The hazard ratio will be used to compare the risk for PFS events (disease progression or death) between the two treatment groups. Tied events will be handled by Efron's approximation in partial likelihood.

According to the study design, p-values based on log-rank test will be presented as **one-sided** for superiority test.

Subgroup Analysis

An unstratified univariate Cox's proportional hazards model will be used to assess treatment effect in each subgroup, with the treatment group included as the only predictor. These analyses will not be stratified because subgroups may have small sample sizes. The hazard ratio and its 95% confidence interval between the two treatment groups will be reported separately for each subgroup, and no p-value will be reported for the subgroup analysis. A forest plot will also be used to present the results from subgroup analyses. The subgroup analyses will be conducted on each level of the following variables:

- DKK1 RNAscope TPS (≥20% vs <20%), where >=20% indicate DKK1-high patients
- PD-L1 immunohistochemistry CPS (≥5 vs <5)
- Serum DKK1 (ng/mL) (< median vs ≥ median), where median is based on ITT population for All Patients.
- Epstein Barr Virus (Positive vs Negative/Undetermined)

- Age (<60 years, ≥60 years)
- Region (Asia vs USA/Europe/Australia)
- Baseline ECOG performance status (0, ≥1)
- Cancer Diagnosis (Gastric adenocarcinoma, Gastroesophageal junction adenocarcinoma)
- Metastatic disease to the liver (Yes, No)

The same subgroups will be applied to subgroup analyses on other efficacy endpoints where applicable. Depending on the final available data, the above subgroups might be adjusted in the final analysis.

10.2 Analyses of Objective Response Rate (ORR)

Tumor assessments will be made based upon the RECIST version 1.1 criteria (Response Evaluation Criteria in Solid Tumors). Tumor response in target lesions, non-target lesions, and new lesions will be used to assess the 'overall response' at each assessment visit. 'Overall response' reported from 'Overall Response Assessment (RECIST 1.1)' eCRF page will be used for the data analysis:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)
- Non-Evaluable (NE)

The analysis of tumor response is based on the **best** overall response (BOR). BOR is defined as the best response recorded from the start of trial treatment until disease progression/recurrence, death, or end of study. Following RECIST v.1.1 guidelines for randomized trials, confirmation of tumor responses is not necessarily required for the analyses. However, the confirmed best overall tumor response will also be summarized for exploratory purpose. The following algorithm describes how the **confirmed best overall response** is determined from the 'overall response' at each assessment visit. The hierarchy used to determine the confirmed best overall response is CR>PR>SD>PD:

- A patient is assigned a best overall response of CR if they have a response assessment of CR at two consecutive visits at least 28 days apart.
- A patient is assigned a best overall response of PR if they have a response assessment of PR or CR at two consecutive visits at least 28 days apart, without being a confirmed CR.
- A patient is assigned a best overall response SD if they have a response assessment of SD, PR, or CR at one or more visits at least 35 days (5 weeks) after the randomization date, but are not a confirmed CR or PR. The choice of 5 weeks is because the first imaging assessment is scheduled at Week 6 with a 7 day window.
- A patient is assigned a best overall response of PD if they have a response assessment of PD at any visit, and not a best overall response of CR, PR or SD.
- Patients without any post baseline tumor assessments, or an assessment of SD, PR or CR in the first 56 days (8 weeks) after the randomization date and no further tumor assessments thereafter have insufficient post baseline information.

Objective Response Rate (ORR)

ORR is defined as the proportion of patients who achieve BOR of CR or PR per RECIST 1.1, assessed by the investigator. ORR is one of the secondary endpoints in Part C.

ORR based on confirmed best overall response will be summarized along with ORR based on unconfirmed best overall response. Confirmed best overall response will not be used for subgroup analysis or used to derive time to event endpoints (section 10.3).

Analyses of ORR

Descriptive Analysis

For the analysis of ORR, a summary table presenting the number and proportion of responders and non-responders in each treatment group, together with the two-sided Clopper-Pearson 95% confidence intervals (Clopper C, Pearson ES, 1934) for response rates, will be produced. The proportion and the corresponding 95% confidence interval for each of the response subcategories (CR, PR, SD, PD, and NE) by treatment group will also be presented.

For target lesion sum of diameters, the observed, absolute change from baseline, and percentage change from baseline will be summarized descriptively. Only the percentage change from baseline is meaningful in comparison among subjects because the sum of diameters of target lesions is affected by the number of target lesions for each subject and the size of each target lesion at baseline. A waterfall plot will be used to present the maximum percentage decrease from baseline in the sum of diameters of target lesions for each subject by treatment group. A spider (spaghetti) plot will be used to present the percentage decrease from baseline in the sum of diameters of target lesions during the course of study for each subject. Data will be shown as a swimmer's plot showing time to first response, duration of response, and time on efficacy assessment per RECIST v1.1 criteria.

Stratified Risk Difference

The comparison of ORR between the two treatment groups will be assessed by a risk difference, stratified by the same stratification factors as for the analysis of PFS. The stratification variable adjusted common risk difference of ORR and its 95% CI between the two treatment groups will be estimated by the stratified Newcombe method, weighted by minimum risk weights. The p-value to test the difference of the ORR between Experimental and Control will be based on the stratified Mantel and Haenszel method.

Subgroup Analysis

The same subgroups as per PFS will be included for the subgroup analysis of ORR. The risk difference between Experimental and Control will be used to assess the treatment effect on ORR in each subgroup. The subgroup analysis will not be stratified due to small sample size. The risk difference and its 95% confidence interval between the two treatment groups will be reported separately for each subgroup, and no p-value will be reported. The 95% confidence interval of the risk difference will be estimated by (unstratified) Newcombe method with continuity correction. A forest plot will also be used to present the risk differences from subgroup analyses.

Concordance between Investigator RECIST 1.1 Assessment and Central Imaging Assessment

Best overall response categories (CR, PR, SD, PD, and NE) based on investigator RECIST 1.1 assessment and those based on central imaging review will be paired for concordance analysis. Agreement rate and its Clopper-Pearson 95% CI will be estimated based on the paired data.

Agreement is defined as:

[(number of patients assessed the same by both methods)/(number of patients with paired data)]*100

A Cohen's Kappa and its 95% CI will also be calculated to measure the agreement between the two assessment methods. Cohen's Kappa measures the agreement between two assessment methods, corrected for agreement by chance.

ORR categories of responders (CR+PR) and non-responders based on the two assessment methods will also be paired. Agreement and Cohen's Kappa will be calculated based on the paired ORR data. To assess rater agreement, concordance analysis is only based on all patient population regardless of treatment groups.

For PFS and ORR, analyses will also be conducted on the Blinded Independent Central Review (BICR) assessments for exploratory purposes.

10.3 Analyses of Duration of Response (DoR), Overall Survival (OS), Duration of Complete Response (DoCR), Duration of Clinical Benefit (DoCB), and Time to Response (TTR)

Duration of Response (DoR)

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. This endpoint is only applicable to ORR responder (CR+PR) patients. For responders without PD or death, DoR will be censored at the most recent tumor assessment before the data cut-off or study withdrawal, whichever occurs first.

Overall Survival (OS)

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 at 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 at the date of randomization (i.e., OS duration of 1 day).

Duration of Complete Response (DoCR)

DoCR is defined only for complete responders as the time from initial CR until radiographically documented progressive disease or death due to any cause, whichever occurs first. This endpoint is only applicable to CR responder patients. For CR patients without PD or death, DoCR will be censored at the most recent tumor assessment before the data cut-off or study withdrawal, whichever occurs first.

Duration of Clinical Benefit (DoCB)

DoCB 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 from the randomization date. This endpoint is only applicable to CB patients, i.e., patients with a BOR of CR, PR, or SD. For CB patients without PD or death, DoCB will be censored at the most recent tumor assessment before the data cut-off or study withdrawal, whichever occurs first.

Time to Response (TTR)

TTR is 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. Patients without CR or PR will be excluded from the summary.

DoR and OS are the secondary endpoints in Part C. DoCR, DoCB and TTR are the exploratory endpoints in Part C. The censoring rules for these endpoints are also listed in Table 1.

The same survival analyses applied to PFS will be applied to DoR, OS, DoCR, and DoCB . That is descriptive survival analysis, stratified log-rank test, stratified Cox's proportional hazards model, and subgroup analysis (unstratified univariate Cox's proportional hazards model **for DoR and OS only**) will be conducted on these time-to-event endpoints. For DoR, OS, DoCR, and DoCB, the event free (survival) rates at Months 6, 12, 18, and 24 (as appropriate) and their 95% confidence intervals will be derived based on their respective survival functions. For TTR, only events will be included for simple descriptive analysis.

Table 1. Censoring Rules

		None	**Last Tumor Assessment prior to Antitumor Treatment**	**Last Tumor Assessment prior to PD**	**Last Tumor Assessment**	**Day 1 (Rand. Date)**	**Last Known Alive Date**
PFS/ DoR/ DoCR/ DoCB	Surviving and no PD				X		
	Without disease assessment (only applicable to PFS)					X	
	Initiation of other antitumor treatment		X				
	Either PD or death preceded by two or more missing or NE tumor assessments			X			
OS	Surviving						X
TTR	Responders (CR/PR)	X					

10.4 Analyses of Disease Control Rate (DCR) and Durable Clinical Benefit Rate (DCB)

Disease Control Rate (DCR)

DCR is defined as the proportion of patients who achieve BOR of CR, PR, or SD per RECIST 1.1, assessed by the investigator. The SD should be assessed ≥ 6 weeks since the randomization date.

Durable Clinical Benefit Rate (DCB)

DCB rate is defined as the proportion of patients who achieve a BOR of CR, PR, or SD and with a DoCB ≥ 180 days. The SD should be assessed ≥ 6 weeks since the randomization date. To define DCB, DoCB duration is calculated 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 from the randomization date (CB responders). For CB patients without PD or death, DoCB duration will end at the most recent tumor assessment before the data cut-off or study withdrawal, whichever occurs first. Patients who have best overall response of PD or those having clinical benefit (CB responders) but DoCB lasting <180 days will be considered as "non-DCB".

DCR and DCB are the exploratory endpoints in Part C.

The same categorical data analysis method applied to ORR will be applied to DCR and DCB. That is descriptive analysis (without analyses for response subcategories and sum of diameters) and stratified common risk difference measuring treatment effect will be estimated on these tumor response endpoints. Subgroup analysis will not be conducted for DCR and DCB as the exploratory endpoints.

10.5 iRECIST

While the current RECIST criteria are designed to assess tumor response in traditional chemotherapeutic regimens in solid tumor, iRECIST is a modified version of RECIST 1.1 for immunotherapy regimens. All responses defined using iRECIST guidelines are designated with a prefix 'i' which is indicative of 'immune based' therapies.

iRECIST 'overall' response assessments at each visit have the following categories:

- Complete Response (iCR)
- Partial Response (iPR)
- Progressive Disease, Unconfirmed (iUPD)
- Progressive Disease, Confirmed (iCPD)
- Stable Disease (iSD)
- Not Evaluable (iNE)

iRECIST is different from RECIST 1.1 only after the first progression is observed. The first PD is "unconfirmed" for iRECIST and termed as 'iUPD.' The occurrence of iUPD must be confirmed in the next scan between 4-8 weeks. If iUPD is confirmed in the subsequent assessment, then it becomes a 'confirmed' PD termed 'iCPD' with the date of progression being the date of iUPD that was initially observed. If iUPD is not confirmed in the subsequent assessment, i.e., if it is followed by an iSD, iPR, or iCR, then the bar is reset for iUPD. **In other words, the original iUPD will be ignored and it must occur again and confirmed at the subsequent assessment to be assigned as iCPD.**

iRECIST is exploratory in nature. iRECIST data will be listed only, and statistical summary analyses will not be conducted.

11. OTHER ANALYSES

11.1 Pharmacokinetics

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

11.2 Biomarker

Exploratory biomarker analyses may be performed to understand the association of these study markers with study drug response, including efficacy and/or adverse events. These analyses are not in the remit of this SAP and the results will be presented in a separate report.

11.3 Pharmacodynamics

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

12. SAFETY

Safety endpoints will be analyzed using the Safety analysis population, and will be summarized descriptively as described in section 3.1.

The main patient population in this study is DKK1-high patients. Therefore, all the safety analysis results will be presented for DKK1-high patients first, followed by results for all patients.

12.1 Adverse Events

All AE verbatim terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. Terms will be coded to the full MedDRA hierarchy, but the system organ class (SOC) and preferred terms (PT) will be of primary interest for the analysis.

Treatment Emergent Adverse Events (TEAEs) are defined as adverse events that occurred or became worsen in intensity following the first administration of the study treatment post randomization until 30 days within the last dose for general and serious AEs or 90 days within the last dose for immune or study treatment related AEs. If missing dates or time prevent a clear determination as to whether the AE is treatment emergent, the adverse event will be regarded TEAE.

For the summary of TEAEs, if a subject experienced the same adverse event multiple times, this will only be counted once for the purpose of counting the number of patients experiencing that adverse event. Summary tables will include the number of subjects (%) experiencing an adverse event and the number of adverse events. TEAEs will be summarised by Safety analysis population.

Immune related TEAEs (irTEAE) and infusion related reaction TEAEs will be identified by the corresponding checkbox from 'Adverse Events' eCRF page. irTEAE and infusion related reaction TEAEs will be summarized separately. COVID-19 vaccine related TEAEs will be summarized separately as well.

The TEAE summaries will include:

- Overall Summary of TEAEs
- Summary of TEAEs by SOC and PT
- Summary of Serious TEAEs by SOC and PT
- Summary of Immune Related TEAEs by SOC and PT
- Summary of Immune Related TEAEs by SOC, PT and Maximum Severity
- Summary of Serious Immune Related TEAEs by SOC and PT
- Summary of Infusion Related Reaction TEAEs by SOC and PT
- Summary of Infusion Related Reaction TEAEs by SOC, PT and Maximum Severity
- Summary of TEAEs by SOC, PT and Maximum Severity
- Summary of DKN-01 Related TEAEs by SOC, PT and Maximum Severity
- Summary of tislelizumab Related TEAEs by SOC, PT and Maximum Severity
- Summary of Chemotherapy Regimen (Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) Related TEAEs by SOC, PT and Maximum Severity
- Summary of TEAEs Leading to DKN-01 Withdrawal by SOC and PT
- Summary of TEAEs Leading to tislelizumab Withdrawal by SOC and PT
- Summary of TEAEs Leading to Chemotherapy Regimen (Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) Withdrawal by SOC and PT
- Summary of TEAEs Leading to DKN-01 Interrupted by SOC and PT

- Summary of TEAEs Leading to tislelizumab Interrupted by SOC and PT
- Summary of TEAEs Leading to Chemotherapy Regimen (Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) Interrupted by SOC and PT
- Summary of TEAEs leading to Death
- Summary of Most Common TEAEs (Incidence >=10% One or More Treatment Groups) by PT

For the 'Overall Summary of TEAEs', the following items will be included:

- Any TEAEs
- Any serious TEAEs
- Any severe TEAEs (Grade >=3)
- Any infusion related reactions (TEAEs)
- Any regimen (DKN-01, tislelizumab, Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) and each component related TEAEs
- Any regimen (DKN-01, tislelizumab, Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) and each component related serious TEAEs
- Any regimen (DKN-01, tislelizumab, Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) and each component related severe TEAEs (Grade >=3)
- Any TEAEs leading to any regimen (DKN-01, tislelizumab, Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) and each component withdrawn
- Any TEAEs leading to any regimen (DKN-01, tislelizumab, Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) and each component interruption
- Any TEAEs leading to any regimen (DKN-01, tislelizumab, Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) and each component dose reduced
- Any regimen (DKN-01, tislelizumab, Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) and each component related TEAEs leading to drug withdrawn
- Any TEAEs leading to death
- Any regimen (DKN-01, tislelizumab, Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) and each component related TEAEs leading to death
- Any immune related TEAEs

All AEs will be listed and will include the start and stop date and time of AEs, AE number, verbatim term, Preferred Term, System Organ Class, SAE/TEAE flag, actions taken with study treatments, relationship to study treatment and outcome. Separate listings will be created for SAEs, AEs leading to study treatment withdrawal, AEs leading to study discontinuation, and death. These listings will be presented by treatment group sorted by subject ID and AE start date/time for the Safety analysis population.

12.2 Safety Laboratory Assessments

Clinical laboratory testing samples will be collected at:

- Screening
- C1D1
- C1D15 (CAPOX)/C1D8 (mFOLFOX6) (hematology and chemistry only)
- CnD1 (hematology, chemistry and urinalysis only)
- End of Treatment
- Safety Follow-up

Assessments will be conducted for hematology, chemistry (including TSH, FT3 and FT4), and urinalysis. The following tests will be performed within each of the specified test panels. Parameters denoted with * should be graded according to the CTCAE term of 'Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, Published: November 27, 2017'. These laboratory parameters will be summarized according to the CTCAE grade.

Hematology:

- Hematocrit
- Hemoglobin *(CTCAE Term: Anemia/Hemoglobin increased)
- Lymphocytes (absolute) *(CTCAE Term: Lymphocyte count decreased/Lymphocyte count increased)
- Monocytes (absolute)
- Neutrophils (absolute) *(CTCAE Term: Neutrophils count decreased)
- Basophils (absolute)
- Eosinophils (absolute)
- WBC count * (CTCAE Term: White blood cell decreased)
- Platelet counts * (CTCAE Term: Platelet count decreased)
- NLR (C1D1 only)

Chemistry:

- Glucose
- Total calcium
- Corrected Total Calcium
- Phosphorus
- Sodium
- Potassium
- Chloride
- Creatinine * (CTCAE Term: Creatinine increased)
- BUN/Urea Nitrogen
- Albumin
- Total protein
- Aspartate aminotransferase *(CTCAE Term: Aspartate aminotransferase increased)
- Alanine aminotransferase * (CTCAE Term: Alanine aminotransferase increased)
- Lactate dehydrogenase
- Alkaline phosphatase * (CTCAE Term: Alkaline phosphatase increased)
- Total bilirubin * (CTCAE Term: Blood bilirubin increased)
- Carbon dioxide
- Direct bilirubin
- Creatine kinase
- CK-MB (Creatine kinase cardiac isoenzyme)
- Troponin I
- Troponin T

- Amylase (Korean patients only)
- Lipase (Korean patients only)

- TSH
- FT3 (Korean patients only)
- FT4 (Korean patients only)

Coagulation:

- Prothrombin time
- International normalized ratio * (CTCAE Term: INR increased)
- Partial thromboplastin time
- Activated Partial thromboplastin time * (CTCAE Term: Activated partial thromboplastin time prolonged)

Urinalysis:

- Glucose
- Protein
- Blood
- Ketones

All laboratory data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables. In the summary tables the clinical laboratory values will be displayed in conventional units and the laboratory parameters will be 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.

All hematology, chemistry and coagulation parameters will be summarized using descriptive statistics for each treatment group for all time points assessed, including change from baseline for all post-dose assessments.

Shift of hematology tests, coagulation tests, and chemistry tests from baseline CTCAE grade to the worst postbaseline CTCAE grade will be presented based upon laboratory values and not reported adverse event terms. All post-baseline visits, including scheduled or unscheduled visits, will be considered to identify the worst post-baseline value.

The reported results for each parameter with a defined normal range will be classified (‘Low’, ‘Normal’, ‘High’) in relation to the defined normal range limits. If a result is equal to the normal range cut-off value, the result will be considered ‘Normal’. Shift tables from baseline to post-dose assessment time points will be generated for each laboratory parameter with values of Normal, High, and Low used for the shift categories. When calculating the percentage in the shift tables, the denominator is the number of participants with results from both baseline and the analysis visit in each group. Additionally, counts (%) of number participants with values out of normal range and their clinical significance at each scheduled time point will also be presented along with the shift tables.

The urinalysis table will present counts and percentages of normal, abnormal not clinically significant, and abnormal clinically significant for the reported results at baseline and each post-baseline visit for all parameters (categorical descriptive analysis). The microscopic urinalysis data, if reported, will be listed only.

12.3 Vital Signs

Vital signs measurements will be taken at the time points specified in the Schedule of Activities:

- Screening
- C1D1
- C1D15 (CAPOX)/C1D8 (mFOLFOX6) CnD1
- End of Treatment
- Safety Follow-up

The following vital signs measurements will be assessed:

- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Pulse rate (beats/min)
- Respiratory rate (breaths/min)
- Body temperature (ºC)

In addition, weight (kg), height (cm), and body surface area (m^2) will be summarized along with vital sign parameters.

All vital signs data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables. Vital sign data will be summarised by Safety analysis population.

The parameter names that will be used in the outputs will comprise of the test name and the unit of measure, for example, 'Systolic Blood Pressure (mmHg)'. Parameters will be sorted in the order that the measurements were collected in on the Vital Signs eCRF page within the tables and listings.

Vital signs measurements (continuous data) will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit (continuous descriptive analysis).

12.4 12-Lead Electrocardiogram (ECG)

12-lead ECG measurements will be taken at the time points specified in the Schedule of Activities:

- Screening
- C1D1
- CnD1
- End of Treatment
- Safety Follow-up

The following ECG measurements will be assessed:

- Ventricular Rate (bpm)
- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)
- RR Interval (msec)

- Rhythm
- Overall Interpretation

All ECG data collected at scheduled and unscheduled visits will be included in the listings, but only results collected as scheduled visits will be included in the summary tables. ECG data will be summarised by Safety analysis population.

The parameter names that will be used in the outputs will be comprised of the test name and the unit of measure, for example, 'Ventricular Rate (beat/min)'. Within tables and listings parameters will be sorted in the order the measurements were collected on the ECG eCRF page.

ECG measurements will present summary statistics for the results at the baseline and each scheduled post-baseline visit for each of the parameters. In addition, summaries will be presented for the change from baseline values at each scheduled post-baseline visit (continuous descriptive analysis). The summary of Rhythm and ECG overall interpretation (abnormality) will present counts and percentages for the reported results at baseline and each post-baseline visit/time point.

The following QT and QTc categories are defined and will be listed and summarized using frequency counts and percentage:

QT and QTc values:

- ≤450 msec
- >450 and ≤480 msec
- >480 and ≤500 msec
- >500 msec

Change from baseline QT and QTc values:

- ≤30 msec
- >30 and ≤60 msec
- >60 msec

Shift of baseline QT/QTc values to the highest postbaseline QT/QTc values will be presented by gender based on the following categories:

Female QT/QTc at Baseline or Highest Post-Baseline

- ≤470 msec (normal)
- 471-480 msec
- 481-490 msec
- 491-500 msec
- ≥501 msec

Male QT/QTc at Baseline or Highest Post-Baseline

- ≤450 msec (normal)
- 451-460 msec
- 461-470 msec
- 471-480 msec
- ≥481 msec

12.5 Physical Examinations

Physical examination assessments will be conducted at:

- Screening
- C1D1
- End of Treatment
- Safety Follow-up

Any abnormal clinically significant findings in physical examinations post screening will be reported as an AE in Part C. No assessment details are reported in 'Physical Exam' eCRF page. Therefore, only physical examination dates will be listed.

12.6 ECOG Performance Status

By-patient data listings will be created for ECOG performance status for all time points:

- Screening
- C1D1
- CXD1
- End of Treatment
- Safety Follow-up

Patients in each of the ECOG performance status categories will be counted using frequency counts and percentage, by study visit and treatment group.

12.7 Pregnancy Tests

Serum and urine pregnancy test results obtained will be presented in a by-participant data listing. Human chorionic gonadotrophin (hCG) test value, if reported, will be presented in the same data listing.

12.8 Pulmonary Function Tests (Korea only)

Enrolled Korean patients who have a history of radiation pneumonitis will receive Pulmonary Function Tests (PFT) at:

- C1D1
- CXD1
- End of Treatment
- Safety Follow-up

The following lung function parameters will be assessed:

- Absolute FEV_1/FVC Ratio (%)
- $FEF_{25-75\%}$ (L/sec)
- FEV_1 (% predicted)
- FEV_1 absolute value (L)
- FVC (% predicted)
- FVC absolute value (L)
- Overall Interpretation

Lung function parameters (continuous data) observed values and change from baseline values at each scheduled post-baseline visit will be summarized descriptively by treatment group. Overall interpretation and all other data will be listed. Data analysis is only limited to 'All Patients'.

12.9 Ophthalmic Examinations (Korea only)

Enrolled Korean patients will receive eye examination, visual acuity test, and optical coherence tomography (or equivalent diagnostic test) at:

- Screening
- C1D1
- CXD1
- End of Treatment
- Safety Follow-up

Full Ophthalmic Exam parameters include:

- Intraocular Pressures (IOP) (mmHg), Left Eye (OD)
- Intraocular Pressures (IOP) (mmHg), Right Eye (OS)
- Any clinically significant abnormality in one of the eyes:
  - Eyelid
  - Extra-ocular movement
  - Pupil
  - Iris
  - Cornea
  - Inflammation - Anterior Chamber
  - Vitreous body (pre and post-vitrectomy)
  - Retina

Best Corrected Visual Acuity parameters include:

- Best Corrected Visual Acuity Letter Score, Left Eye (OD)
- Best Corrected Visual Acuity Letter Score, Right Eye (OS)

Spectral Domain Optical Coherence Tomography (SD-OCT) parameters include:

- Central Sub-field Thickness (um)
- Any fluid in Intraretinal, Subretinal, or Both

The above reported data will be summarized descriptively by treatment group and listed as well. Data analysis is only limited to ‘All Patients’.

13. CHANGES TO THE PLANNED ANALYSIS

Leap made the decision on 31 January 2025 to terminate the study early based on a recent data analysis suggesting that the experimental treatment will not be more efficacious than its comparator in the primary endpoint of progression-free survival as assessed by the investigators. Therefore, only a subset of the TLFs will be selected from the full list for an abbreviated CSR and will be delivered after the database lock.

14. INTERIM AND FINAL ANALYSIS

14.1 Interim Analyses

Part C is an open label study, and no interim analysis is planned.

A review by the Safety Review Team (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). SRT will 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.

14.2 Final Analysis (End of Study)

The final analysis will be conducted after all patients have completed the study, the clinical database has been locked, the analysis populations have been approved.

The final analysis will be based on the final version of the SAP. Any deviations from the planned analysis will be documented in the CSR.

15. SOFTWARE

- SAS® Version 9.4 or higher (SAS Institute, Cary, North Carolina, USA).

16. TABLES

Table Number	Table Title	Population
	Demographics and Other Baseline Characteristics	
14.1.1.1	Summary of Participant Enrolment and Disposition	ITT
14.1.1.2	Summary of Screen Failure	Enrolled
14.1.2	Summary of Important Protocol Deviations	ITT
14.1.3.1	Summary of Demographics and Baseline Characteristics	ITT
14.1.3.2	Summary of Demographics and Baseline Characteristics	Safety
14.1.4	Summary of Historic Tumor Characteristics	ITT
14.1.5	Summary of Medical and Surgical History/Physical Findings	ITT
14.1.6	Summary of Cancer Diagnosis at Study Entry	ITT
14.1.7.1	Summary of Prior Systemic Cancer Therapies	ITT
14.1.7.2	Summary of Prior Cancer Surgeries	ITT
14.1.7.3	Summary of Prior Radiation Therapies	ITT
	Efficacy, Pharmacokinetics, and Pharmacodynamics	
14.2.1.1.1	Progression-free Survival (PFS): Summary Analysis of Investigator Tumor Assessments	ITT
14.2.1.1.1b	Progression-free Survival (PFS): Summary Analysis of Blinded Independent Central Review (BICR) Tumor Assessments	ITT
14.2.1.1.2	Progression-free Survival (PFS): Summary Analysis of Investigator Tumor Assessments	PP
14.2.1.2	Progression-free Survival (PFS): Subgroup Analysis of Investigator Tumor Assessments	ITT
14.2.1.2b	Progression-free Survival (PFS): Subgroup Analysis of Blinded Independent Central Review (BICR) Tumor Assessments	ITT
14.2.2.1.1	Objective Response Rate (ORR): Summary Analysis of Investigator Tumor Assessments	ITT
14.2.2.1.1b	Objective Response Rate (ORR): Summary Analysis of Blinded Independent Central Review (BICR) Tumor Assessments	ITT
14.2.2.1.2	Objective Response Rate (ORR): Summary Analysis of Investigator Tumor Assessments	PP
14.2.2.2	Objective Response Rate (ORR): Subgroup Analysis of Investigator Tumor Assessments	ITT
14.2.2.2b	Objective Response Rate (ORR): Subgroup Analysis of Blinded Independent Central Review (BICR) Tumor Assessments	ITT
14.2.2.3	Tumor Response (RECIST 1.1) Concordance Analysis between Investigator and Blinded Independent Central Review (BICR) Tumor Assessment	ITT
14.2.3.1.1	Duration of Response (DoR): Summary Analysis of Investigator Tumor Assessments	ITT
14.2.3.1.2	Duration of Response (DoR): Summary Analysis of Investigator Tumor Assessments	PP

Table Number	Table Title	Population
14.2.3.2	Duration of Response (DoR): Subgroup Analysis of Investigator Tumor Assessments	ITT
14.2.4.1.1	Overall Survival (OS): Summary Analysis	ITT
14.2.4.1.2	Overall Survival (OS): Summary Analysis	PP
14.2.4.2	Overall Survival (OS): Subgroup Analysis	ITT
14.2.5	Duration of Complete Response (DoCR): Summary Analysis of Investigator Tumor Assessments	ITT
14.2.6	Duration of Clinical Benefit (DoCB): Summary Analysis of Investigator Tumor Assessments	ITT
14.2.7	Time to Response (TTR): Descriptive Summary Analysis of Investigator Tumor Assessments	ITT
14.2.8	Disease Control Rate (DCR): Summary Analysis of Investigator Tumor Assessments	ITT
14.2.9	Durable Clinical Benefit Rate (DCB): Summary Analysis of Investigator Tumor Assessments	ITT
14.2.10	RECIST Target Lesions: Sum of Diameter of Investigator Tumor Assessments	ITT
14.2.11	Summary of DKK1 RNAscope TPS, Serum DKK1, and PD-L1 CSP (External Data)	ITT
	Safety	
14.3.1.1	Summary of Prior Medications	Safety
14.3.1.2	Summary of Concomitant Medications	Safety
14.3.2.1	Summary of Treatment Exposure: DKN-01	Safety
14.3.2.2	Summary of Treatment Exposure: tislelizumab	Safety
14.3.2.3	Summary of Treatment Exposure: Oxaliplatin	Safety
14.3.2.4	Summary of Treatment Exposure: Leucovorin calcium	Safety
14.3.2.5	Summary of Treatment Exposure: Fluorouracil	Safety
14.3.2.6	Summary of Treatment Exposure: Capecitabine	Safety
14.3.2.7	Summary of Overall Treatment Exposure: All Treatments	Safety
	Adverse Events	
14.3.3.1	Overall Summary of TEAEs	Safety
14.3.3.2	Summary of TEAEs by SOC and PT	Safety
14.3.3.3	Summary of Serious TEAEs by SOC and PT	Safety
14.3.3.4	Summary of Immune Related TEAEs by SOC and PT	Safety
14.3.3.5	Summary of Immune Related TEAEs by SOC, PT and Maximum Severity	Safety
14.3.3.6	Summary of Serious Immune Related TEAEs by SOC and PT	Safety
14.3.3.7	Summary of Infusion Related Reactions (TEAEs) by SOC and PT	Safety

Table Number	Table Title	Population
14.3.3.8	Summary of Infusion Related Reactions (TEAEs) by SOC, PT and Maximum Severity	Safety
14.3.3.9	Summary of TEAEs by SOC, PT and Maximum Severity	Safety
14.3.3.10	Summary of DKN-01 Related TEAEs by SOC, PT and Maximum Severity	Safety
14.3.3.11	Summary of tislelizumab Related TEAEs by SOC, PT and Maximum Severity	Safety
14.3.3.12	Summary of Chemotherapy Regimen (Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) Related TEAEs by SOC, PT and Maximum Severity	Safety
14.3.3.13	Summary of TEAEs Leading to DKN-01 Withdrawal by SOC and PT	Safety
14.3.3.14	Summary of TEAEs Leading to tislelizumab Withdrawal by SOC and PT	Safety
14.3.3.15	Summary of TEAEs Leading to Chemotherapy Regimen (Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) Withdrawal by SOC and PT	Safety
14.3.3.16	Summary of TEAEs Leading to DKN-01 Interrupted by SOC and PT	Safety
14.3.3.17	Summary of TEAEs Leading to tislelizumab Interrupted by SOC and PT	Safety
14.3.3.18	Summary of TEAEs Leading to Chemotherapy Regimen (Oxaliplatin, Leucovorin Calcium, Fluorouracil, and Capecitabine) Interrupted by SOC and PT	Safety
14.3.3.19	Summary of TEAEs leading to Death by SOC and PT	Safety
14.3.3.20	Summary of Most Common TEAEs (Incidence >=10% One or More Treatment Groups) by PT	Safety
	Laboratory Parameters	
14.3.4.1.1	Summary of Hematology	Safety
14.3.4.1.2	Summary of Hematology Shifts from Baseline	Safety
14.3.4.1.3	Summary of Hematology Abnormality	Safety
14.3.4.1.4	Summary of Hematology Toxicity Grade	Safety
14.3.4.1.5	Summary of Hematology Shifts from Baseline to the Worst Post-baseline CTCAE Grade	Safety
14.3.4.2.1	Summary of Chemistry	Safety
14.3.4.2.2	Summary of Chemistry Shifts from Baseline	Safety
14.3.4.2.3	Summary of Chemistry Abnormality	Safety
14.3.4.2.4	Summary of Chemistry Toxicity Grade	Safety
14.3.4.2.5	Summary of Chemistry Shifts from Baseline to the Worst Post-baseline CTCAE Grade	Safety
14.3.4.3.1	Summary of Coagulation	Safety
14.3.4.3.2	Summary of Coagulation Shifts from Baseline	Safety
14.3.4.3.3	Summary of Coagulation Abnormality	Safety
14.3.4.3.4	Summary of Coagulation Toxicity Grade	Safety
14.3.4.3.5	Summary of Coagulation Shifts from Baseline to the Worst Post-baseline CTCAE Grade	Safety

Table Number	Table Title	Population
14.3.4.4	Summary of Urinalysis Abnormality	Safety
	Other Safety	
14.3.5.1	Summary of Vital Signs	Safety
14.3.5.2.1	Summary of 12-Lead ECG	Safety
14.3.5.2.2	Summary of 12-Lead ECG Abnormality	Safety
14.3.5.2.3	Summary of 12-Lead ECG QT and QTc	Safety
14.3.5.2.4	Summary of 12-Lead ECG QT and QTc Shifts from Baseline to the Highest Value Post-baseline	Safety
14.3.5.3	Summary of ECOG Performance Status	Safety
14.3.5.4	Summary of Lung Function Tests (Korean Subjects)	Safety
14.3.5.5.1.1	Summary of Ophthalmic Examinations (Korean Subjects): Intraocular Pressures (IOP)	Safety
14.3.5.5.1.2	Summary of Ophthalmic Examinations (Korean Subjects): Clinically Significant Abnormality	Safety
14.3.5.5.2	Summary of Best Corrected Visual Acuity (BCVA) Letter Score (Korean Subjects)	Safety
14.3.5.5.3	Summary of Spectral Domain Optical Coherence Tomography (SD-OCT) Findings (Korean Subjects)	Safety

17. LISTINGS

Listing Number	Listing Title	Population
	Subject Disposition	
16.2.1.1	Analysis Populations	Enrolled
16.2.1.2	Participant Disposition	Enrolled
16.2.1.3	Randomization	ITT
16.2.1.4	Eligibility Criteria	ITT
	Protocol Deviations	
16.2.2.1	Protocol Deviations	ITT
	Demographic and Other Baseline Data	
16.2.4.1	Demographics and Baseline Characteristics	ITT
16.2.4.2.1	Historic Tumor Characteristics	ITT
16.2.4.2.2	Medical and Surgical History/Physical Findings	ITT
16.2.4.3	Cancer Diagnosis at Study Entry	ITT
16.2.4.4.1	Prior Systemic Cancer Therapy	ITT
16.2.4.4.2	Prior Cancer Surgery	ITT
16.2.4.4.3	Prior Radiation Therapy	ITT
	Treatment Administration	
16.2.5.1	Study Drug Administration - DKN-01	Safety
16.2.5.2	Study Drug Administration - tislelizumab	Safety
16.2.5.3	Study Drug Administration - Oxaliplatin	Safety
16.2.5.4	Study Drug Administration - Leucovorin calcium	Safety
16.2.5.5	Study Drug Administration - IV Fluorouracil	Safety
16.2.5.6	Study Drug Administration - Capecitabine	Safety
	Efficacy and Pharmacodynamics	
16.2.6.1.1	Overall Response Assessment: RECIST v1.1	ITT
16.2.6.1.2	Target Lesions: RECIST v1.1	ITT
16.2.6.1.3	Non-Target Lesions: RECIST v1.1	ITT
16.2.6.1.4	New Lesions - RECIST v1.1	ITT
16.2.6.2	Overall Response: iRECIST	ITT
16.2.6.3	Time to Event Endpoints	ITT
16.2.6.4	Death	ITT
16.2.6.5	DKK1 RNAscope TPS, Serum DKK1, and PD-L1 CSP (External Data)	ITT

Listing Number	Listing Title	Population
	Adverse Events	
16.2.7.1	Adverse Events	Safety
16.2.7.2	Serious Adverse Events	Safety
16.2.7.3	Adverse Events Leading to Treatment Withdrawal	Safety
16.2.7.4	Adverse Events Leading to Study Discontinuation	Safety
16.2.7.5	Immune related Adverse Events (irAEs)	Safety
16.2.7.6	Infusion Related Reactions	Safety
16.2.7.7	Adverse Events Leading to Death	Safety
	Laboratory Parameters	
16.2.8.1	Hematology	Safety
16.2.8.2	Chemistry	Safety
16.2.8.3	Coagulation	Safety
16.2.8.4	Urinalysis	Safety
	Other Safety	
16.2.9.1	Vital Signs	Safety
16.2.9.2	12-Lead ECG	Safety
16.2.9.3	Physical Examination	Safety
16.2.9.4	ECOG Performance Status	Safety
16.2.9.5	Pregnancy Tests	Safety
16.2.9.6	Lung Function Tests (Korean Subjects)	Safety
16.2.9.7	Ophthalmic Examinations (Korean Subjects)	Safety
16.2.9.8	Best Corrected Visual Acuity (Korean Subjects)	Safety
16.2.9.9	Spectral Domain Optical Coherence Tomography (SD-OCT) (Korean Subjects)	Safety
	Prior & Concomitant Medication	
16.2.10.1	Prior Medication	Safety
16.2.10.2	Concomitant Medication	Safety
16.2.11.1	Non-Drug Treatments/Procedures	Safety
16.2.11.2	Radiation Therapy During Treatment Period	Safety
16.2.11.3	Transfusions and Growth Factor	Safety
16.2.12.1	Subsequent Systemic Cancer Therapy	Safety
16.2.12.2	Subsequent Cancer Surgery	Safety
16.2.12.3	Subsequent Radiation Therapy	Safety
16.2.13	Head Imaging	Safety

18. FIGURES

Figure Number	Figure Title	Population
14.2	**Efficacy**	
14.2.1.1	Kaplan-Meier Plot of Progression-free Survival (PFS): Investigator Tumor Assessments	ITT
14.2.1.1b	Kaplan-Meier Plot of Progression-free Survival (PFS): Blinded Independent Central Review (BICR) Tumor Assessments	ITT
14.2.1.2	Forest Plot of Hazard Ratios for Subgroup Analysis of Progression-free Survival (PFS): Investigator Tumor Assessments	ITT
14.2.1.2b	Forest Plot of Hazard Ratios for Subgroup Analysis of Progression-free Survival (PFS): Blinded Independent Central Review (BICR) Tumor Assessments	ITT
14.2.2	Forest Plot of Risk Difference for Subgroup Analysis of Objective Response Rate (ORR): Investigator Tumor Assessments	ITT
14.2.2b	Forest Plot of Risk Difference for Subgroup Analysis of Objective Response Rate (ORR): Blinded Independent Central Review (BICR) Tumor Assessments	ITT
14.2.3	Kaplan-Meier Plot of Duration of Response (DoR): Investigator Tumor Assessments	ITT
14.2.4.1	Kaplan-Meier Plot of Overall Survival (OS)	ITT
14.2.4.2	Forest Plot of Hazard Ratios for Subgroup Analysis of Overall Survival (OS)	ITT
14.2.5	Kaplan-Meier Plot of Duration of Complete Response (DoCR): Investigator Tumor Assessments	ITT
14.2.6	Kaplan-Meier Plot of Duration of Clinical Benefit (DoCB): Investigator Tumor Assessments	ITT
14.2.8.1	Waterfall Plot of Maximum Percentage Decrease from Baseline in Sum of Diameters of Target Lesions: Investigator Tumor Assessments	ITT
14.2.8.2	Spider (Spaghetti) Plot of Maximum Percentage Decrease from Baseline in Sum of Diameters of Target Lesions: Investigator Tumor Assessments	ITT
14.2.9	Swimmer's Plot of Overall Tumor Response: Investigator Tumor Assessments	ITT

19. REFERENCES

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