Phase 1b/2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-HER2 Bispecific Antibody ZW25 in Combination With Chemotherapy With/Without Tislelizumab in Patients With Advanced HER2-positive Breast Cancer or Gastric/Gastroesophageal Junction Adenocarcinoma

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STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-A317-ZW25-101
Study Protocol Title:	Phase 1b/2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-HER2 Bispecific Antibody ZW25 in Combination With Chemotherapy With/Without Tislelizumab in Patients With Advanced HER2-positive Breast Cancer or Gastric/Gastroesophageal Junction Adenocarcinoma
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADA	Antidrug antibody
AE	Adverse Event
BOR	Best overall response
CI	confidence interval
CR	Complete response
DCR	disease control rate
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GEJ	gastroesophageal junction
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
imAE	immune-mediated adverse event
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	Preferred term
Q3W	once every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SOC	System organ class
TEAE	treatment-emergent adverse event

[redacted]

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Protocol BGB-A317-ZW25-101 "Phase 1b/2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-HER2 Bispecific Antibody ZW25 in Combination With Chemotherapy With/Without Tislelizumab in Patients With Advanced HER2-positive Breast Cancer or Gastric/Gastroesophageal Junction Adenocarcinoma". The focus of this SAP is for the three planned analyses (see section 7) as well as the long-term safety analysis specified in the study protocol. The long-term safety analysis mainly includes the AE analysis for patients who entered the long-term extension period.

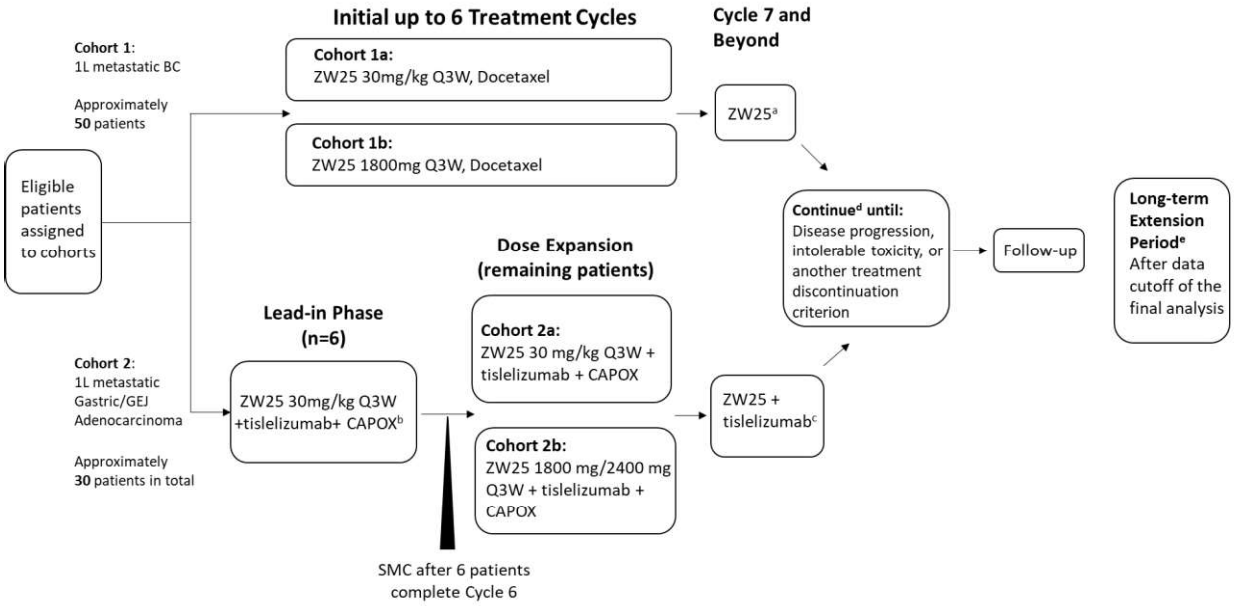
[redacted]

Reference materials for this statistical plan include the protocol amendment BGB-A317-ZW25-101 (version 3.0, dated 26 May 2023). If the protocol or case report forms are amended or updated, then appropriate adjustments to the SAP may be made if changes are related to the planned analyses.

2. STUDY OVERVIEW

This is an open-label, multicenter, Phase 1b/2 study to investigate safety, tolerability, PK and preliminary antitumor activity of ZW25 in combination with chemotherapy with or without tislelizumab in patients with histologically or cytologically confirmed unresectable locally advanced or metastatic human epidermal growth factor receptor (HER2)-positive breast cancer (BC) or gastric/gastroesophageal Junction (GEJ) adenocarcinoma. The study schema is presented in Figure 1.

Figure 1: Study Schema



After being confirmed as eligible, approximately 80 patients will be enrolled into one of the 2 cohorts according to disease type: approximately 50 patients for Cohort 1 (BC) and approximately 30 patients for Cohort 2 (gastric/GEJ adenocarcinoma).

The study will be conducted across approximately 20 sites in Asian countries. This study consists of the 2 cohorts described below.

Patients enrolled under the original protocol and had been assigned to Cohort 1a or 2a will continuously be treated with ZW25 30 mg/kg. Patients enrolled under Protocol Amendment 1.0 or later will be assigned to Cohort 1b or 2b and receive a flat dosing of ZW25.

Cohort 1: patients who have unresectable, locally advanced, recurrent or metastatic HER2-positive (HER2 IHC 3+ or in situ hybridization positive) breast cancer and have not received previous systemic chemotherapy or biologic therapy (including approved or investigational tyrosine kinase/HER inhibitors, checkpoint inhibitors or vaccines) for their advanced or metastatic disease are eligible, and will be treated with ZW25 followed by docetaxel as the first-line therapy. On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity, or another criterion for treatment discontinuation is met. After Cycle 6, continuation of docetaxel treatment is at the discretion of the investigator.

ZW25 will be administered until disease progression, intolerable toxicity, or another criterion for treatment discontinuation is met. Detailed dosing schedule and administration is described below:

- **Cohort 1a:** ZW25 30 mg/kg intravenously (IV); docetaxel 75 mg/m^2 IV Q3W
- **Cohort 1b:** ZW25 1800 mg IV; docetaxel 75 mg/m^2 IV Q3W

Cohort 2: patients who have unresectable, locally advanced, recurrent or metastatic HER2-positive (HER2 IHC 3+ or HER2 IHC 2+ together with in situ hybridization positive) gastric/GEJ adenocarcinoma and who have not received previous systemic therapy for locally

advanced unresectable or metastatic disease are eligible, and will be treated with ZW25, tislelizumab and chemotherapy as the first-line therapy. The chemotherapy regimen will be CAPOX (1000 mg/m^2 capecitabine and 130 mg/m^2 oxaliplatin) and will be administered up to 6 cycles. On or prior to Cycle 6, capecitabine or oxaliplatin should only be discontinued for progressive disease or unacceptable toxicity, or another criterion for treatment discontinuation is met. After Cycle 6, oxaliplatin will be discontinued and continuation of capecitabine as maintenance treatment is at the discretion of the investigator. ZW25 and tislelizumab will be administered until disease progression, intolerable toxicity, or another criterion for treatment discontinuation is met. Detailed dosing schedule and administration of ZW25 and tislelizumab is described below:

- **Cohort 2a:** ZW25 30 mg/kg IV, tislelizumab 200 mg IV, CAPOX (1000 mg/m^2 capecitabine and 130 mg/m^2 oxaliplatin) Q3W
- **Cohort 2b:** ZW25 1800 mg (patient's body weight < 70 kg) or 2400 mg (patient's body weight ≥ 70 kg) IV, tislelizumab 200 mg IV, CAPOX (1000 mg/m^2 capecitabine and 130 mg/m^2 oxaliplatin) Q3W

For **Cohort 2**, a safety lead-in phase is designed, during which 6 patients will be enrolled. After the first 6 patients have completed at least 1 cycle (21 days) of treatment, safety data will be reviewed by SMC to ensure the tolerability before the whole cohort is fully open to enrollment.

If there are no new significant or severe safety signals detected, the enrollment of dose expansion will be expanded up to approximately 30 patients in total for Cohort 2.

The study procedures will occur over a Screening Period, Treatment Period, End of Treatment/Safety Follow-up and Survival Follow-up, and Long-Term Extension Period.

3. STUDY OBJECTIVES

3.1. Primary Objective

- To assess the safety and tolerability of ZW25 in combination with docetaxel in patients with HER2-positive breast cancer, and ZW25 in combination with tislelizumab and chemotherapy in patients with HER2-positive gastric/GEJ adenocarcinoma
- To evaluate the preliminary antitumor activity of ZW25 in combination with docetaxel in patients with HER2-positive breast cancer, and ZW25 in combination with tislelizumab and chemotherapy in patients with HER2-positive gastric/GEJ adenocarcinoma as measured by objective response rate (ORR)

3.2. Secondary Objective

- To further evaluate the preliminary antitumor activity of ZW25 in combination with docetaxel in patients with HER2-positive breast cancer, and ZW25 in combination with tislelizumab and chemotherapy in patients with HER2-positive gastric/GEJ adenocarcinoma as measured by duration of response, time to response, progression free survival (PFS), disease control rate (DCR), overall survival (OS)
- To characterize the PK and immunogenicity of ZW25 in both cohorts

[redacted]

- To evaluate the long-term safety of ZW25 in combination with docetaxel in patients with HER2-positive breast cancer, and ZW25 in combination with tislelizumab and chemotherapy in patients with HER2+ G/GEJC during the long-term extension period

3.3. [redacted]

- [redacted]
- [redacted]

4. STUDY ENDPOINTS

4.1. Primary Endpoints

- AEs and SAEs as characterized by type, frequency, severity (as graded by National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] Version 5.0), timing, seriousness, and relationship to study therapy, discontinuation of investigational product(s) due to toxicity, and changes from baseline in laboratory, electrocardiograms (ECG), echocardiogram or multiple gated acquisition scan (MUGA) and vital signs as needed
- Objective response rate defined as the proportion of patients who had a best overall response of complete response or partial response assessed by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

4.2. Secondary Endpoints

- Duration of response defined as the time from the first determination of an objective response by investigator per RECIST Version 1.1, until the first documentation of progression or death, whichever occurs first
- Time to response defined as the time from the start date of study treatment to the first determination of an objective response by investigator per RECIST Version 1.1
- Progression-free survival defined as the time from the start date of study treatment to the date of the first objectively documented tumor progression assessed by investigator per RECIST Version 1.1, or death, whichever occurs first
- Disease control rate defined as the proportion of patients with best overall response of complete response, partial response, and stable disease by investigator per RECIST Version 1.1
- Overall survival defined as the time from the start date of study drug to the date of death due to any cause
- ZW25 PK and immunogenicity:
    - Serum concentrations of ZW25 as a function of time
    - PK parameters for single (first) dose and multiple doses if data permit

[redacted]

    - Frequency, duration and time of onset of anti-ZW25-antibodies and neutralizing antibodies
- AEs and SAEs during the long-term extension period

4.3. [redacted]

- [redacted]
- [redacted]

5. SAMPLE SIZE CONSIDERATIONS

Approximately 50 patients will be enrolled in Cohort 1 and approximately 30 patients will be enrolled in Cohort 2. Per binomial distribution, for an event of 1% incidence rate, the chance of detecting any safety signal is about 26% to 39% in 30 to 50 patients. The probability of observing a safety event of interest goes up to 79% to 92% in 30 to 50 patients when the underlying rate is 5%. The current sample size is considered adequate for an initial safety evaluation for each combination.

Assume 80% of the patients are efficacy evaluable, approximately 40 patients and 24 patients are expected in Cohort 1 and 2, respectively. If the true ORR is 80%, for Cohort 1, the sample size can estimate the expected proportion with 12% precision with 95% confidence interval. The precision is 16% for the sample size of Cohort 2 under the same assumptions.

6. STATISTICAL METHODS

6.1. Analysis Sets

The Safety Analysis Set includes all patients who received at least 1 dose of any component of study treatment. It will be the primary analysis set for the safety analyses.

The Efficacy Evaluable Analysis Set includes all patients who have received at least 1 dose of the study treatment, had measurable disease at baseline according to RECIST Version 1.1, and had at least 1 postbaseline tumor response assessment unless any clinical PD or death occurred within 10 weeks after the first dose. It will be the primary analysis set for tumor response.

The Per-Protocol Analysis Set (PP) includes all patients in efficacy evaluable analysis set who had the disease defined in inclusion criteria #4 in the protocol. This will be the secondary analysis set for efficacy analysis.

The PK Analysis Set includes all patients who contributed at least 1 quantifiable ZW25 (or tislelizumab) PK sample.

The Immunogenicity Analysis Set includes all patients who received at least 1 dose of ZW25 (or tislelizumab) and for whom both baseline ADA and at least 1 postbaseline ADA results are available.

The LTE Safety Analysis Set includes all patients who received at least 1 dose of any component of study treatment and entered the long-term extension period. This will be the primary analysis set for the safety analysis of patients who entered the long-term extension period.

6.2. Multiplicity Adjustment

Not applicable.

6.3. Data Analysis General Considerations

6.3.1. Definitions and Computations

Study treatments include ZW25, tislelizumab, docetaxel, capecitabine, oxaliplatin.

Study day will be calculated in reference to the date of the first dose of study treatment. For assessments conducted on or after the date of the first dose of study treatment, study day will be calculated as (assessment date – date of first dose of study treatment + 1). For assessments conducted before the date of the first dose of study treatment, study day is calculated as (assessment date – date of first dose of study treatment). There is no study day 0. In the situation where the event date is partial or missing, the date will appear partial or missing in the listings.

Unless otherwise specified, a baseline value is defined as the last non-missing value collected before the first dose of study treatment.

Summary table by cohort is defined as one table for cohort 1 (cohort 1a and cohort 1b combined) and one table for cohort 2 (cohort 2a and cohort 2b combined).

All calculations and analyses will be conducted using SAS® (SAS Institute, Inc., Cary, NC, USA), version 9.4 or higher.

Unless otherwise specified, all analyses are in study period through the data cutoff date of the final analysis (the third planned analysis, see section 7). The analysis for patients who entered the long-term extension period will be specified otherwise.

6.3.2. Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Duration of image-based event endpoints (such as PFS and DOR) will be based on the actual date the radiograph was obtained rather than the associated visit date.

- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.
- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).
- For discrete endpoints, summary statistics will include frequencies and percentages.

6.3.3. Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in this SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures.

By-visit endpoints will be analyzed using observed data unless otherwise specified. For observed data analyses, missing data will not be imputed, and only the observed records will be included.

6.3.4. Data Integrity

Before any pre-specified statistical analysis begins, the integrity of the data should be reviewed to assure fit-for-purpose. The data set for analysis should be an accurate and complete representation of the patients' relevant outcomes from the clinical database. All data should be complete and reviewed up to a pre-specified cutoff date as specified in the Data Extract and Snapshot Plan. Consistency checks and appropriate source data verification should be completed as specified in the Site Monitoring Plan.

6.4. Patient Characteristics

6.4.1. Patient Disposition

The number (percentage) of patients treated, discontinued from study treatment, remained on treatment, discontinued from the study, and remained on study will be summarized by cohort in the Safety Analysis Set. The primary reasons for study treatment discontinuation and study discontinuation, and study follow-up time will be summarized by cohort in the Safety Analysis Set. The primary reason for screen failure will be summarized in all screened patients.

The number (percentage) of patients who entered long-term extension period treated, discontinued from study treatment and discontinued from the study will be summarized by cohort in the LTE Safety Analysis Set. The primary reasons for study treatment discontinuation and study discontinuation, and study follow-up time will be summarized by cohort in the LTE Safety Analysis Set.

6.4.2. Protocol Deviations

Patients with important protocol deviations will be identified and documented before the database lock.Important protocol deviation will be summarized and listed by category and by cohort in the Safety Analysis Set.

In addition, important protocol deviations related to COVID-19 will be summarized by category and by cohort in the Safety Analysis Set.

6.4.3. Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by cohort using descriptive statistics in the Safety Analysis Set, including the following variables:

- Age (continuously and by categories [<65, ≥65 years])
- Sex
- Ethnicity, Race
- Weight, BMI
- ECOG status
- Smoking status (never, current, former)
- Alcohol status (never, current, former)

6.4.4. Disease History

Disease history will be summarized by cohort in the Safety Analysis Set, including the following variables:

- time from initial diagnosis to study entry
- time from advanced/metastatic disease diagnosis to study entry
- disease stage at study entry
- metastatic sites at study entry
- hormone ER/PR responsiveness (only applicable for cohort 1)
- HER2 status from central lab and local lab
- location of primary tumor (only applicable for cohort 2)
- histologic type (Lauren classification, only applicable for cohort 2)
- PD-L1 score (≥5% vs <5%, only applicable for cohort 2), PD-L1 expression is determined by PD-L1 score assessed by tumor area positive score which is defined as the total percentage of the tumor area covered by tumor cells with any membrane staining above background and tumor-associated immune cells with any staining above background using Ventana PD-L1 (SP263) assay.

Please note study entry date refers to the first dose date.

6.4.5. Prior Anticancer Drug Therapies, Surgeries and Radiotherapies

The number and percentage of patients with prior anti-cancer systemic therapies, number of prior regimens, time from end of last therapy to study entry, and type of prior anti-cancer systemic therapy will be summarized by cohort in the Safety Analysis Set. Prior anti-cancer systemic therapy will be coded using the version of World Health Organization Drug Dictionary (WHO DD) drug codes version currently in effect at the time of database lock.

The number and percentage of patients with any prior anti-cancer radiotherapy, treatment intent, irradiated site, treatment setting of prior anti-cancer radiotherapy will be summarized in the Safety Analysis Set.

The number and percentage of patients with any prior anti-cancer surgeries, treatment intent, and time from last surgery to study entry will be summarized in the Safety Analysis Set.

6.4.6. Prior and Concomitant Medications

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

Prior and concomitant medications will be coded using the version of WHO DD drug codes version currently in effect at the time of database lock. They will be further classified to the appropriate ATC code.

The number (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred name by cohort in the Safety Analysis Set.

In addition, concomitant systemic corticosteroids and immunosuppressants received will be summarized in cohort 2 only in the Safety Analysis Set.

6.4.7. Medical History

Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at the time of database lock. The number (percentage) of patients reporting a history of any medical condition will be summarized by cohort, by system organ class and preferred term in the Safety Analysis Set.

6.5. Efficacy Analysis

6.5.1. Primary Efficacy Endpoint

ORR (confirmation required according to RECIST Version 1.1) is the proportion of patients who had a BOR of CR or PR assessed by investigator per RECIST Version 1.1. The two-sided Clopper-Pearson 95% CIs for ORR will be calculated by cohort. ORR will be estimated on Efficacy Evaluable Analysis Set as primary and on Per-Protocol Analysis Set as sensitivity analysis.

A waterfall plot of best percent change in sum of target lesion diameters from baseline per investigator will be provided by cohort with prior anti-HER2 therapy, local lab HER2 status and central lab HER2 status for cohort 1 and with PD-L1 status, local lab HER2 status and central lab HER2 status for cohort 2. The patients in each cohort will be ordered by the percentage, patients with the largest percentage will be presented on the right.

[redacted]

6.5.2. Secondary Efficacy Endpoints

Duration of response (DOR)

Only the subset of patients who show a confirmed complete response or partial response will be included in the DOR analysis. Duration of response is defined as the time from the first determination of an objective response by investigator per RECIST Version 1.1, until the first documentation of progression or death, whichever occurs first. DOR will be analyzed on Efficacy Evaluable Analysis Set as primary and on Per-Protocol Analysis Set as sensitivity analysis.

Data for patients who are alive and who have not experienced disease progression or death at the time of analysis will be censored at the date of the last tumor assessment. If no tumor assessments were performed after the date of the first occurrence of the objective response (CR or PR), DOR will be censored at the date of the first occurrence of the objective response. In addition, all the censoring rules for PFS analysis (Table 1) except No. 1 and 8 should be applied to DOR as well. Median DOR will be estimated using Kaplan-Meier method with corresponding 95% CI estimated using the Brookmeyer and Crowley method (Brookmeyer and Crowley 1982) with log-log transformation (Collett 1994).

Time to response (TTR)

Only the subset of patients who show a confirmed complete response or partial response will be included in the TTR analysis. The mean, SD, median, and range of TTR will be provided. TTR will be analyzed on Efficacy Evaluable Analysis Set as primary and on Per-Protocol Analysis Set as sensitivity analysis.

Progression-free survival (PFS)

Progression-free survival defined as the time from the start date of study treatment to the date of the first objectively documented tumor progression assessed by investigator per RECIST Version 1.1, or death, whichever occurs first. PFS censoring rules are specified in Table 1.

Table 1: Censoring Rules for Progression-free Survival Per RECIST Version 1.1

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline or any post-baseline tumor assessments and without death within 13 weeks from the first dose date	Date of the first dose	Censored
2	Progression documented on scheduled visit or between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cut-off or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cut-off or withdrawal from study	Censored
4	New anticancer treatment started	Date of last adequate radiologic assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD assessment	Date of death	Progressed
6	Death between adequate assessment visits*	Date of death	Progressed
7	Death or progression after more than one missed visit**	Date of last adequate radiologic assessment before missed tumor assessments	Censored
8	No baseline or any post-baseline tumor assessments and died within 13 weeks from the first dose date	Date of death	Progressed

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

** More than one missed visit is defined if the duration between the last tumor assessment and death or PD is longer than D2. The D2 is defined as two times protocol specified interval between tumor assessments (TAs) plus the protocol allowed window around the assessments. Since tumor assessment is scheduled as once every 6 weeks for first 36 weeks and once every 12 weeks afterwards with one-week window, D2 is 13 (6*2+1) weeks in the first 36 weeks and 25 (12*2+1) weeks afterwards.

The priority of the censoring rules is as follows:

1. If the patient had PD or death, the following sequence will be applied:
   - If a patient did not have baseline tumor assessment (No. 1), the patient will be censored on date of the first dose. However, if the patient died within 91 days (6*2+1 weeks) after the first dose and did not receive new anticancer treatment, the date of death will be the PFS event date (not censored).
   - If a patient had new anticancer treatment before PD or death (No. 4), the patient will be censored on the date of the last tumor assessment prior to or on the date of new anticancer treatment.
   - If a patient missed two assessments before PD or death (No. 7), the patient will be censored on the date of the last tumor assessment before PD or death. Note that if a patient is censored by both this criterion and the anticancer treatment criteria, the earliest censoring date will be used.
   - Otherwise, if a subject had an event (No. 2, No. 5, No. 6), the earliest event date will be used.
2. If a patient did not have PD or death, the censoring date will be the earliest censoring date if the patient met multiple censoring criteria (No. 1, No. 3, No. 4, No. 7).

[redacted]

PFS will be analyzed in Efficacy Evaluable Analysis Set as primary and Per-Protocol Analysis Set as sensitivity analysis. Kaplan-Meier method will be used to estimate median and other quartiles of PFS along with its 95% confidence interval (constructed using Brookmeyer and Crowley method (Brookmeyer and Crowley 1982) with log-log transformation (Collett 1994)). Kaplan-Meier survival probabilities for each cohort will be plotted over time. Event free rate at selected timepoints will be estimated with 95% confidence interval using Greenwood formula.

Disease control rate (DCR)
DCR will be analyzed similarly to ORR, and DCR will be estimated on Efficacy Evaluable Analysis Set as primary and on Per-Protocol Analysis Set as sensitivity analysis.

Overall survival (OS)
Overall survival is defined as time from the start date of study treatment to the documented death date for patients who died prior to or on the clinical cutoff date. For patients who are alive by the clinical cutoff date, OS will be censored at the last known alive date. The last known alive date will be defined as either the clinical data cutoff date for patients who are still on treatment, or last available date showing patients alive or cutoff date whichever comes first for other alive patients.

Similar methodologies used to evaluate PFS will be applied to OS analysis except that OS will be analyzed on Safety Analysis Set as primary and Per-Protocol Analysis Set as sensitivity analysis.

6.5.3. Subgroup Analyses

Subgroup analysis of primary endpoint ORR will only be conducted in the Efficacy Evaluable Analysis Set for cohort 2 per PD-L1 score (≥1% vs <1%, ≥5% vs <5%).

A subgroup will not be analyzed if it includes <10% of the Efficacy Evaluable Analysis Set. Within each selected subgroup, ORR and corresponding 95% CI will be calculated.

[redacted]

6.5.5. Post and during-treatment Anti-Cancer Therapy

Post treatment anti-cancer therapy is defined as the anti-cancer therapy started after the last dose of study drug(s).

Separate flags of start date of new anti-cancer therapy for efficacy and safety analyses are derived individually.

- As for efficacy analysis, start date of new anti-cancer therapy will be the earliest date of prohibited anti-cancer therapy taken during treatment, date of the post-treatment systemic anti-cancer therapy and date of other anti-cancer therapy such as post-treatment surgery and radiotherapy as deemed appropriate.
- The start date of new anti-cancer therapy in defining TEAE for safety is always the first date of new systemic anti-cancer therapy taken after the last study treatment.

Tumor response per RECIST or event driven endpoints have not been commonly used for the efficacy evaluation of traditional Chinese medicine. ORR, PFS or OS benefit of Chinese herbal

medicines or Chinese patent medicines has not yet been established. Therefore, they will not be taken into account as new anti-cancer therapy in the efficacy and safety analyses.

Patient listings of post-treatment anti-cancer systemic therapy, radiotherapy, procedure or surgery will be provided.

6.6. Safety Analyses

All safety analyses will be performed by cohort based on the Safety Analysis Set, unless otherwise specified. The incidence of treatment-emergent adverse events (TEAEs, Section 6.6.2) and SAEs will be summarized. Laboratory test results, vital signs, ECG, ECOG and their changes from baseline will be summarized using descriptive statistics.

6.6.1. Extent of Exposure

The following measures of the extent of exposure will be summarized for each component of study treatment:

- Duration of exposure (months):
  - If a patient discontinued or completed treatment, the duration of exposure is defined as (min(cutoff date, death date, last dose date + 20) – first dose date + 1)/30.4375 for all study treatment except Capecitabine; for Capecitabine: the duration of exposure is defined as (min(cutoff date, death date, last dose date + 6) – first dose date + 1)/30.4375.
  - If a patient is under treatment, the duration of exposure is defined as (cutoff date - first dose date+1)/30.4375.
- Number of treatment cycles received: defined as the total number of treatment cycles in which at least one dose of the study treatment is administered.
- Cumulative dose received per patient (mg): defined as the cumulative dose of the study treatment during the treatment period of the study.
- Actual dose intensity (mg/cycle): defined as cumulative dose (mg) received by a patient divided by the duration of exposure (cycle).
- Relative dose intensity (%): defined as the ratio of the actual dose intensity and the planned dose intensity in percentage. Planned dose intensity is defined as the planned dose as defined in the section 3 of protocol by a subject divided by the duration of exposure.

The extent of exposure for patients who entered the long-term extension period will be summarized by cohort on the LTE Safety Analysis Set, similar analysis as above will be conducted.

6.6.2. Adverse Events

AEs will be graded by the investigators using NCI-CTCAE version 5.0. The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA version currently in

effective at the time of database lock lowest level term closest to the verbatim term, along with the linked MedDRA preferred term (PT) and primary system organ class (SOC).

A treatment-emergent adverse event (TEAE) is defined as an AE that had an onset date or a worsening in severity on or after the date of the first dose of study treatment up to 30 days after the last dose (permanent discontinuation of study treatment) or the initiation of new anti-cancer therapy, whichever is earlier. Only those AEs that were treatment emergent will be included in summary tables of TEAE. All AEs, treatment-emergent or otherwise, will be presented in patient data listings. In addition, SAEs for patients with COVID-19 infection will be presented in listing.

An overview table of patients with at least one TEAE will be presented with the following incidence by cohort, if applicable:

- patients with any TEAE
- patient with any grade 3 or above TEAE
- patients with any serious TEAE
- patient with any TEAE leading to death
- patient with any TEAEs leading to permanent discontinuation of any component of study treatment
    - patient with any TEAEs leading to ZW25 discontinuation
    - patient with any TEAEs leading to tislelizumab discontinuation
- patient with any TEAEs leading to treatment modification
- patients with any treatment-related TEAE
    - patients with ZW25-related TEAE
    - patients with tislelizumab-related TEAE
- patients with any treatment-related grade 3 or above TEAE
    - patients with any ZW25-related grade 3 or above TEAE
    - patients with any tislelizumab-related grade 3 or above TEAE
- patients with any serious treatment-related TEAE
    - patients with any serious ZW25-related TEAE
    - patients with any serious tislelizumab-related TEAE
- patient with any treatment-related TEAE leading to death
    - patients with any ZW25-related TEAE leading to death
    - patients with any tislelizumab-related TEAE leading to death
- patient with any treatment-related TEAEs leading to permanent discontinuation of any component of study treatment
    - patient with any treatment-related TEAEs leading to ZW25 discontinuation
    - patient with any treatment-related TEAEs leading to tislelizumab discontinuation

- patient with any treatment-related TEAEs leading to treatment modification
- AESI/Selected AE of ZW25

Treatment-related is defined as related to any component of study treatment.

Treatment-related TEAEs include those events considered by the investigator to be related or with missing assessment of the causal relationship. For patients with multiple occurrences of the same event will be counted only once, and the worst grade per NCI-CTCAE v5.0 will be used.

The incidence of following TEAEs will be reported by SOC, by PT and by cohort, if applicable:

- TEAE by worst grade
- ≥ grade 3 TEAE
- Serious TEAE by worst grade
- Treatment-related TEAE by worst grade
    - ZW25-related TEAE by worst grade
    - Tislelizumab-related TEAE by worst grade
- Serious treatment-related TEAE by worst grade
    - ZW25-related serious TEAE by worst grade
    - Tislelizumab-related serious TEAE by worst grade

The incidence of following TEAEs or imAE will be reported by PT and by cohort, if applicable:

- TEAE leading to ZW25 discontinuation
- TEAE leading to tislelizumab discontinuation
- TEAE leading to death
- TEAE leading to treatment modification
- TEAE leading to ZW25 dose reduction
- Treatment-related TEAE leading to death
    - ZW25-related TEAE leading to death
    - Tislelizumab-related TEAE leading to death
- Treatment-related TEAE leading to ZW25 discontinuation
    - ZW25-related TEAE leading to ZW25 discontinuation
- Treatment-related TEAE leading to tislelizumab discontinuation
    - Tislelizumab-related TEAE leading to tislelizumab discontinuation
- Treatment-related TEAEs leading to treatment modification
    - ZW25-related TEAE leading to treatment modification

- Tislelizumab-related TEAE leading to treatment modification

- Treatment-related TEAEs leading to ZW25 dose reduction
  - ZW25-related TEAE leading to ZW25 dose reduction
- Adverse Event of Special Interest
  - For ZW25 AESI, which are TEAEs with AE start date within 30 days after the last dose of ZW25:
    - ZW25-related infusion related reactions, defined using MedDRA preferred term of 'infusion related reaction' or event identified by the investigator as infusion related reactions and related to ZW25.
    - Potential cardiac events, defined as events meeting the following search criteria:
      - grade 2 or higher adverse events in the Broad Cardiac Failure SMQ or ECHO/MUGA scan results that indicate a post baseline decrease in LVEF of ≥ 10% from pretreatment baseline and a value < 50%.
    - Confirmed cardiac events, defined as the subset of potential cardiac events that have been clinically reviewed and determined to be consistent with cardiac events of absolute decrease in LVEF of ≥ 10% from pretreatment baseline and absolute value < 50%, and/or grade ≥2 heart failure.
    - Non-infectious pulmonary toxicities, defined by the broad interstitial lung disease SMQ.
    - Selected AEs:
      - Treatment-emergent diarrhea: defined using the MedDRA preferred term of "Diarrhoea"
      - Treatment-emergent embryo-fetal toxicity: defined using the modified Pregnancy and neonatal topics SMQ which excludes *the sub SMQ Lactation related topics including neonatal exposure through breast milk (SMQ)*.
  - For Tislelizumab AESI (for cohort 2 only)
    - imAE
    - Tislelizumab-related infusion related reactions, defined using MedDRA preferred term of 'infusion related reaction' or event identified by the investigator as infusion related reactions and related to tislelizumab.

The AE and SAE for patients who entered the long-term extension period will be summarized by cohort on the LTE Safety Analysis Set. An overview of patients with at least one TEAE will be presented with the following incidence, if applicable:

- patients with any TEAE
- patient with any grade 3 or above TEAE

- patients with any serious TEAE
- patient with any TEAE leading to death
- patient with any TEAEs leading to permanent discontinuation of any component of study treatment
- patient with any TEAEs leading to treatment modification
- patients with any treatment-related TEAE
- patients with any treatment-related grade 3 or above TEAE
- patients with any serious treatment-related TEAE
- patient with any treatment-related TEAE leading to death
- patient with any treatment-related TEAEs leading to permanent discontinuation of any component of study treatment
- patient with any treatment-related TEAEs leading to treatment modification

Besides, for patients who entered long-term extension period, the incidence of following TEAEs will be reported by SOC, by PT and by cohort, if applicable:

- TEAE by worst grade
- ≥ grade 3 TEAE
- Serious TEAE by worst grade
- Treatment-related TEAE by worst grade
- Serious treatment-related TEAE by worst grade

Also, for patients who entered long-term extension period, the incidence of following TEAEs will be reported by PT and by cohort, if applicable:

- TEAE leading to permanent discontinuation of any component of study treatment
- Treatment-related TEAE leading to permanent discontinuation of any component of study treatment
- TEAE leading to death
- Treatment-related TEAE leading to death
- TEAE leading to treatment modification
- Treatment-related TEAEs leading to treatment modification
- TEAE leading to ZW25 dose reduction
- Treatment-related TEAEs leading to ZW25 dose reduction

All deaths and cause of death will be summarized, including those occurred during the study treatment period and those reported during the survival follow-up period after treatment discontinuation. For patients who entered long-term extension period, deaths and cause of death will be summarized on the LTE Safety Analysis Set.

6.6.3. Laboratory Values

Laboratory safety tests will be evaluated for selected parameters described in Table 2.

Descriptive summary statistics (n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be summarized by visit for each cohort.

Selected laboratory parameters that are graded in NCI-CTCAE v5.0 will be summarized by shift from baseline NCI-CTCAE grades to maximum post-baseline grades, parameters with NCI-CTCAE grading in both high and low directions will be summarized separately.

Potential Hy's law cases by lab value will be summarized.

Patient data listings of selected laboratory parameters will be provided.

Table 2: Clinical Laboratory Tests

Serum Chemistry	**Hematology**	**Thyroid Function (Cohort 2 only)**
Alanine aminotransferase (ALT)	Hemoglobin	Free Triiodothyronine (FT3)
Aspartate aminotransferase (AST)	White blood cell (WBC) count	Free Thyroxine (FT4)
Creatinine	Neutrophil (Absolute)	Thyroid stimulating hormone (TSH)
Alkaline phosphatase (ALP)	Red blood cell count	
Potassium	Platelet count	
Sodium	Lymphocytes	
Creatine kinase (CK)		
Creatine kinase-cardiac muscle isoenzyme (CK-MB) or Troponin		
Lipase		
Amylase		
Glucose		
Total bilirubin		
Blood urea nitrogen		

6.6.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, body temperature and weight) and changes from baseline will be summarized by visit for each cohort.

6.6.5. Electrocardiograms (ECG)

The number and percentage of patients satisfying the following QTcF conditions at any time post-baseline will be summarized by cohort:

- <450msec, ≥450 and <480msec, ≥480 msec

- < 30 msec increase from baseline, ≥30 msec to ≤ 60 msec increase from baseline, or > 60 msec increase from baseline

6.6.6. Eastern Cooperative Oncology Group (ECOG)

A shift table from baseline to worst post-baseline in ECOG performance score will be summarized.

6.6.7. Echocardiogram/MUGA

The number and percentage of patients satisfying the following left ventricular ejection fraction conditions will be summarized by cohort:

- Minimal LVEF result post-baseline (<50%, ≥50%)
- Minimum post-baseline LVEF result with a decrease of ≥10% from the baseline result
- Criteria 1: Post-baseline LVEF result that is <50% with a decrease of ≥10% from the baseline result
- Criteria 2: Grade ≥2 TEAE that meets the criteria for the broad scope of the cardiac failure SMQ
- Criteria 1 or 2

6.7. Pharmacokinetic Analyses

6.7.1. Pharmacokinetic Analysis of ZW25

PK analyses are planned approximately 12 months after the first dose of last patient. Serial PK samples from up to 28 patients are planned to characterize the PK profiles of ZW25 in targeted patient population. After serial PK collection completion, sparse samples will be collected subsequently in the following cycles, details as below:

- A large set of serial PK samples will be collected in Cycle 1 on timepoints with pre-dose (within 1 hour before ZW25 infusion), 0 hour post-dose (within 15 min after the end of ZW25 infusion), 2 hours, 4 hours (Cycle 1 Day 1, C1D1), 24 hours (Cycle 1 Day 2, C1D2), 96 hours (Cycle 1 Day 5, C1D5), 168 hours (Cycle 1 Day 8, C1D8), 336 hours (Cycle 1 Day 15) and 504 hours (pre-dose of Cycle 2 Day 1, C2D1).
- Another smaller set of serial PK samples will be collected in Cycle 2 on timepoints with pre-dose, 0 hour post-dose (C2D1), 168 hours (C2D8), and 336 hours (C2D15).
- Sparse PK samples will be subsequently collected on timepoints with pre-dose and 0 hour post-dose in the Day 1 of Cycle 5, 9 ,17, 26 ,35, and every 17 cycles thereafter or EOT/safety follow-up visit if feasible.

Except above mentioned 28 serial PK patients, all the other patients will contribute sparse PK samples on the timepoints with pre-dose and 0 hour post-dose in the Day 1 of Cycle 1, 2, 5, 9 ,17, 26 ,35, and every 17 cycles thereafter or EOT/safety follow-up visit if feasible.

For the serial PK analysis set, serum concentration-time data of each patient will be tabulated and graphically presented on linear semi-logarithmic scales. Pharmacokinetic parameters will be

determined using a standard noncompartmental method. A listing of patients excluded from the analysis set and individual data points excluded from the analysis will be provided.

The PK parameters will be derived and summarized with descriptive statistics (N, arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV) % associated to the geometric mean, as appropriate) by nominal timepoint, for all subjects with either serial or sparse sampling data.

PK parameters will include, but are not limited to, the following as allowed by data (Units may differ as need):

- C_{max} (μg/mL): Observed maximum plasma concentration during a sampling interval；
- t_{max} (hour): Observed time to maximum plasma concentration during a sampling interval；
- $t_{½}$ (hour): Terminal elimination half-life, determined from the quotient 0.693/λz；
- CL (L/h): Apparent clearance；
- Vz, the terminal volume of distribution；
- $AUC_{(0\text{-}t)}$ (μg·h/mL): Area under the plasma concentration-time curve from time zero to the last measurable timepoint calculated by log-linear trapezoidal summation；
- $AUC_{0\text{-}tau}$, area under the plasma concentration-time curve during the dosing interval；
- $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time zero to infinity；
- R_o, observed accumulation ratio determined by the ratios of parameters ($AUC_{0\text{-}tau}$ and C_{max}) at steady state and single dose；

Accumulation ratio is defined as the ratio of C_{trough} at steady state (Cycle 5 or Cycle 9) to the C_{trough} after the first dose (Cycle 1). It may be assessed using linear mixed effects models, including Day as the fixed effect and a subject-level random effect.

$$\log(\text{PK parameter}) = \beta_0 + \beta_1 \times \text{Day} + \beta_2 \times \text{Patient} + \varepsilon$$

where Patient is a subject-level random effect. The categorical variable, Day, distinguishes daily C_{trough} on Cycle 1 and C_{trough} at steady state.

For each dose, the estimate of accumulation ratio will be obtained by applying an exponential function on the difference of least square (LS) means of $\log(PK_{Cycle\ 5\ or\ Cycle\ 9})$ and $\log(PK_{Cycle\ 1})$. Similarly, a 95% CI for the accumulation ratio will be obtained by applying the exponential function on the 95% CI for the mean of $\log(PK_{Cycle\ 5\ or\ Cycle\ 9})$ and $\log(PK_{Cycle\ 1})$.

Population PK analyses may be conducted as appropriate, and the results of such analysis may be reported separately from the clinical study report.

6.7.2. Pharmacokinetic Analysis of Tislelizumab

Sparse PK samples for tislelizumab will be collected pre-dose of tislelizumab (within 1 hour before tislelizumab infusion) on Day 2 of Cycle 1, 2, and Day 1 of Cycle 5, 9 and 17, and pdose

(within 15 min after the end of tislelizumab infusion) on Day 2 of Cycle 1 and Day 1 of Cycle 5, and at EOT visit. Serum Concentrations will be summarized with descriptive statistics.

6.8. Immunogenicity Analyses

Human anti-drug antibodies (ADA) to ZW25 and tislelizumab will be assessed during the study as defined in the protocol.

ADA samples for ZW25 should be collected at the timepoint of pre-dose in the Day 1 of Cycle 1, 2, 5, 9 ,17, 26 ,35, and every 17 cycles thereafter or EOT/safety follow-up visit if feasible. For serial PK patients, additional ADA sample at 336 hour of Cycle 1 Day 15 will be needed.

ADA samples for tislelizumab should be collected at the timepoint of pre-dose in the Day 2 of Cycle 1, 2 and Day 1 of Cycle 5, 9 and 17, and at EOT/Safety follow up visit if feasible.

The scope of ADA calculations used for characterizing clinical immunogenicity depends on the incidence and kinetics of detected (ADA). Therefore, not all parameters described below may be derived or additional parameters may be added. The individual immunogenicity results will also be listed. The immunogenicity results will be summarized using descriptive statistics by the number and percentage of subjects who develop detectable ADAs. The incidence of positive and neutralizing ADAs will be reported for ADA-evaluable subjects according to the following definitions:

- ADA-evaluable patient: patients who received at least 1 dose of study drug and for whom both baseline ADA and at least 1 postbaseline ADA results are available.
- Treatment-emergent ADA: The sum of both treatment-boosted and treatment-induced ADA-positive patients. Synonymous with “ADA Incidence”.
- Treatment-induced ADA: ADA-evaluable patients that were ADA-negative at baseline and ADA-positive following administration of study drug.
- Treatment-boosted ADA: Baseline-positive ADA-evaluable patient with significant increases (4-fold or higher) in ADA titer after study drug administration.
- Persistent ADA: Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer; or detected in the last time point.
- Transient ADA: Treatment-induced ADA that is not considered as persistent ADA.
- Neutralizing ADA: patients with positive NAb.

Additional ADA analyses (such as the effect of immunogenicity on PK, efficacy, and safety) may be conducted if deemed necessary and will be described in a separate analysis plan.

7. INTERIM ANALYSES

There are 3 planned analyses for this study. The first analysis is planned after all patients in Cohort 2 have been followed for at least 4 months. The second analysis is planned

after all patients in Cohort 1 have been followed for at least 4 months. The third analysis (the FA) will take place at least 12 months after the first dose of the last patient enrolled in the study, or until study termination or study completion decided by the sponsor, whichever occurs first.

8. CHANGES IN THE PLANNED ANALYSIS

Table 3 summarizes the major changes in the planned analyses from SAP version 1.0 and the statistical section of the study protocol (Protocol Amendment 3.0), including the timing, rational and descriptions of the changes. The changes are all made before database lock.

Table 3: Statistical Analysis Plan Changes

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
2.0	This Version	SAP V1.0	To perform sensitivity analysis on patients in efficacy evaluable analysis set who had no critical protocol deviations	Added the Per-Protocol Analysis Set and changed the sensitivity analysis set for efficacy analysis from Safety Analysis Set to Per-Protocol Analysis Set.
2.0	This Version	Protocol Amendment V3.0	To add analysis for people who entered long-term extension period	1. Added long-term safety evaluation as secondary objective and long-term AEs and SAEs as secondary endpoints. 2. Added the LTE Safety Analysis Set to be the primary analysis set for the safety analysis for patients who entered the long-term extension period. 3. Added analysis for patients who entered the long-term extension period.
2.0	This Version	Protocol Amendment V3.0	"Severe hypersensitivity reactions and flu-like symptoms" was deleted from Adverse Events of Special Interest (AESI)	Deleted "Severe hypersensitivity reactions and flu-like symptoms" in the AESI analysis part.
2.0	This Version	SAP V1.0	To update ZW25 Adverse Event of Special Interest (AESI)	1. Deleted "Cardiac events of symptomatic heart failure", added and defined potential cardiac events and confirmed cardiac events as part of ZW25 AESI. 2. Added and defined selected AEs as part of ZW25 AESI.

SAP version	Approval date	Change made from	Rationale of the change	Description of the change
2.0	This Version	SAP V1.0	To update definition of duration of exposure per Standard Definitions and Derivation Rules of Key Variables (SDD) of IO programs in BeiGene and dosing schedules specified in the protocol.	1. Consider the two different situations of whether the patient has discontinued/completed treatment or is under treatment. 2. For patient who has discontinued/completed treatment, updated the duration of response of Capecitabine from "(date of last dose of study treatment + 8 days – date of first dose of study treatment)/30.4375 with censored by death date and cutoff date" to "(min(cutoff date, death date, last dose date + 6) – first dose date + 1)/30.4375", due to the dosing schedule of Capecitabine.
2.0	This Version	SAP V1.0	To further clarify the details of PK and Immunogenicity analyses.	1. In the PK analyses section, specified sampling details, analysis scope, as well as methods for ZW25 and tislelizumab respectively. 2. In the Immunogenicity analyses section, added details including sample collections, definitions of different sub-populations of ADA-evaluable subjects, etc.
2.0	This Version	SAP V1.0	To clarify calculation methods of actual and planned dose intensity of chemotherapy in this study	Added calculation methods of actual and planned dose intensity for the three chemotherapy agents respectively as Appendix 1.
2.0	This Version	SAP V1.0	To explore the subgroup analysis of more PD-L1 score cutoffs.	Added 1% as PD-L1 score cutoff for subgroup analysis.

9. REFERENCES

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Greenwood M. The Natural Duration of Cancer. Reports on Public health and medical subjects. 1926;33:1-26.

APPENDIX 1. ACTUAL DOSE INTENSITY AND PLANNED DOSE INTENSITY CALCULATION FOR CHEMOTHERAPY

	Actual Dose Intensity (mg/cycle)	Planned Dose Intensity per Cycle
Docetaxel	$\frac{\sum_1^{\#of\ cycles} actual\ dose \times 21}{date\ of\ last\ dose\ up\ to\ cutoff + 21 - first\ dose\ date}$	75 mg/m^2× BSA *
Oxaliplatin	$\frac{\sum_1^{\#of\ cycles} actual\ dose \times 21}{date\ of\ last\ dose\ up\ to\ cutoff + 21 - first\ dose\ date}$	130 mg/m^2× BSA *
Capecitabine	$\frac{\sum_1^{\#of\ cycles} actual\ dose}{k^{**}}$	1000 mg/m^2 × BSA * × 14 × 2

* To derive BSA at each visit is to use baseline weight unless weight change for one visit is at least 10% greater compared to baseline weight. The general principle is to employ the same drug administration rule as the one specified in the protocol.

** $k = \max(\frac{date\ of\ last\ dose\ up\ to\ cutoff+7-first\ dose\ date}{21}, number\ of\ cycles\ in\ last\ dosing\ record)$

The planned dose of chemotherapy is adjusted based on body surface area. The detailed calculation is specified below:

- BSA_i: Body surface area on i^{th} cycle of chemotherapy. BSA_1 is the BSA at baseline.

$$\text{BSA}_i(m^2) = 0.0061 * \text{Height}_1 + 0.0128 * \text{Weight}_i\text{-}0.1529$$

- Weight_i: Body weight (kilogram) on i^{th} cycle of chemotherapy. Weight_1 is the weight at baseline.
  - The planned dose for k^{th} cycle is $\text{BSA}'_\text{i} * \text{standard dose}$, where $\text{BSA}'_\text{i} = \text{BSA}_1$ if $(\text{Weight}_\text{i} - \text{Weight}_1)/\text{Weight}_1 < 10\%$; otherwise, $\text{BSA}'_\text{i} = \text{BSA}_\text{i}$.
  - If body weight on i^{th} cycle of chemotherapy is missing, last available weight value will be used as Weight_i.