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Statistical Analysis Plan

Protocol Title:	Phase 2 Study of ZW25 Plus First-line Combination Chemotherapy in HER2-Expressing Gastrointestinal (GI) Cancers, Including Gastroesophageal Adenocarcinoma (GEA), Biliary Tract Cancer (BTC), and Colorectal Cancer (CRC)
Protocol Number:	ZWI-ZW25-201
Protocol Version:	Amendment 6; 16-Oct-2023
EudraCT Number:	NA
Phase:	2
Investigational Product:	Zanidatamab (ZW25)
US IND Number:	[redacted]
Sponsor:	Jazz Pharmaceuticals Ireland Limited Fifth Floor, Waterloo Exchange Waterloo Road Dublin 4 Dublin, Ireland D04 E5W7
Version - Date:	Final 1.1 – 31Oct2024
Author:	[redacted]

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
λ_z	Terminal elimination rate constant
5-FU	Fluorouracil
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
$AUC_{0-\infty}$	Area under the serum concentration-time curve from zero to infinity
AUC_{0-t}	Area under the serum concentration-time curve from zero to the last measurable concentration
BTC	Biliary Tract Cancer
C_{ave}	Average concentration over dosing interval
CBC	Complete blood count
CL	Serum clearance
C_{max}	Maximum observed serum concentration
C_{min}	Minimum observed serum concentration
CR	Complete response
CRC	Colorectal Cancer
CRF	Case report form
C_{ss}	Trough concentration at steady state
CT	Computed tomography
C_{trough}	Trough concentration
DCO	Data Cutoff
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of Treatment
FDA	Food and Drug Administration
FISH	Fluorescence *in situ* hybridization
FP	5-FU and cisplatin
GEA	Gastroesophageal adenocarcinoma
GEJ	Gastroesophageal junction
HER	Human epidermal growth factor receptor
IHC	Immunohistochemistry
IV	Intravenous
kg	Kilogram
L	Liter

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LVEF	Left ventricular ejection fraction
m	Meter
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	5-FU and leucovorin plus oxaliplatin
mg	Milligrams
MRI	Magnetic resonance imaging
mL	Milliliter
min	Minute
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition scan
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
RBC	Red blood cell
RD	Recommended dosage
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SMC	Safety Monitoring Committee
SMQ	Standardized MedDRA Querie
SOC	System organ class
$t_{½}$	Apparent elimination half-life
t_{max}	Time to maximum observed serum concentration
$t_{max,1}$	Time to maximum observed serum concentration for dose 1
ULN	Upper limit of normal
V_d	Volume of distribution in the terminal elimination phase
WHO	World Health Organization
XELOX	Capecitabine plus oxaliplatin
XP	Capecitabine plus cisplatin
ZW25	Zanidatamab

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Version History

SAP Version	*Date*	*Change*	*Rationale*
Final 1.0	*10Sep2024*	*Not applicable*	*Original version*
Final 1.1	*31Oct2024*	*1.Section 6.4.2: updated the IDI calculation.* *2.Section 5.3: added imputation rule if the month and year are the same as the preceding date of interest.* *3.Section 6.1.7: added Subsequent Systemic Anticancer Therapies will be provided in a listing.*	*Updated based on team discussion*

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3 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods, assumptions, and details of the planned statistical analyses to be performed for Study ZWI-ZW25-201.

4 STUDY DESIGN

4.1 Description

This is a multicenter, global, Phase 2, open-label, first-line, 2-part study to investigate the safety, tolerability, and anti-tumor activity of Zanidatamab (ZW25) plus standard first line combination chemotherapy regimens for selected GI cancers. Eligible subjects include those with unresectable, locally advanced, recurrent, or metastatic HER2-expressing GEA, BTC, or CRC.

Subjects with GEA received the physician's choice of one of 3 globally-recognized, multi-agent, first-line combination chemotherapy treatments:

- XELOX, which consists of capecitabine plus oxaliplatin:

  Three variants of the XELOX and ZW25 combination (XELOX-1, XELOX-2, and XELOX-3) are being tested. The variants differ in the ZW25 regimen.

- FP, which consists of fluorouracil (5-FU) plus cisplatin.

  Two variants of the FP and ZW25 combination (FP-1 and FP-2) are being tested. The variants differ in the ZW25 regimen.

- mFOLFOX6, which consists of 5 FU, leucovorin, and oxaliplatin.

  Two variants of the mFOLFOX6 and ZW25 combination (mFOLFOX6-1 and mFOLFOX6-2) are being tested. The variants differ by the presence (mFOLFOX6-1) or absence (mFOLFOX6-2) of a 5-FU bolus on Days 1 and 15 of each 4-week treatment cycle AND by the ZW25 dose (weight-based vs flat).

Thus, 7 variants of the XELOX, FP, and mFOLFOX6 regimens are being tested in subjects with GEA.

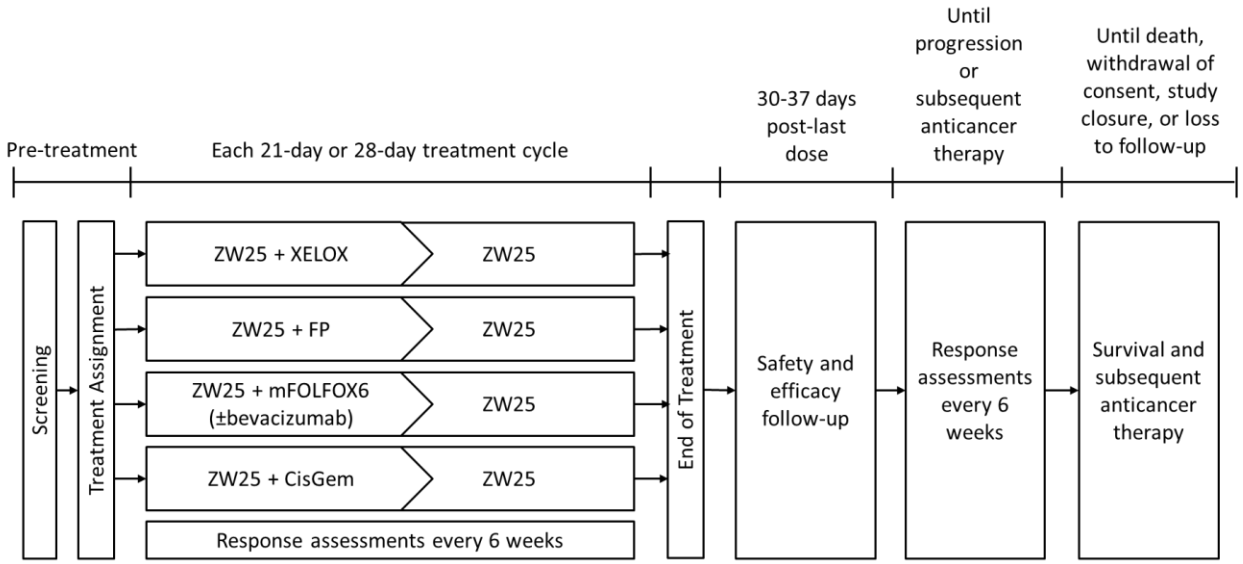
Subjects with BTC receive CisGem, a globally recognized, multi-agent, first-line combination chemotherapy treatment, which consists of cisplatin plus gemcitabine.

Subjects with CRC receive mFOLFOX6-2, a globally recognized, multi-agent, first-line combination chemotherapy treatment. Two variants of mFOLFOX6-2, one with and one without bevacizumab, are being tested in subjects with CRC.

The overall study design is illustrated in Figure 1.

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Figure 1 – Overall Study Design



CT = computed tomography; D = day; FP = fluorouracil (5-FU) plus cisplatin; mFOLFOX6 = 5-FU and leucovorin plus oxaliplatin; MRI = magnetic resonance imaging; ELOX = capecitabine plus oxaliplatin; CisGem = Cisplatin plus Gemcetabine.
Notes: On the days of ZW25 dosing, ZW25 will be administered first. The chemotherapy components will be administered in the usual order per institutional standards. All regimens with the "-1" designation use weight-based dosing (mg/kg) for ZW25. All regimens with the "-2" designation use flat dosing (one dose for subjects < 70 kg and another dose for subjects ≥ 70 kg) for ZW25. The XELOX-3 regimen uses flat dosing (one dose for subjects < 70 kg and another dose for subjects ≥ 70 kg) for ZW25 as well but the ZW25 dosing days are different from those for XELOX-2.

4.1.1 Part 1

Part 1 of the study is a safety and tolerability evaluation of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment for HER2 expressing GEA, BTC, or CRC (physician's choice of XELOX, FP, or mFOLFOX6 for subjects with GEA, CisGem for subjects with BTC, and mFOLFOX6 with or without bevacizumab for subjects with CRC). Part 1 will also be used to establish the recommended dosage for ZW25 when administered with these first-line combination chemotherapy agents. Up to 2 step-down dose levels may be recommended by the Safety Monitoring Committee (SMC) if dose-limiting toxicities (DLTs) related to study treatment are observed. Information on the initial recommended doses and the step-down dosing plan are provided in the sample size determination section of this SAP.

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4.1.2 Part 2

Part 2 of the study will evaluate the potential anti-tumor activity of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment for HER2 expressing GEA, BTC, or CRC.

4.2 Study Objectives and Endpoints

4.2.1 Part 1

Study Objectives and Endpoints	
Primary Objective	**Primary Endpoint**
• To characterize the safety and tolerability of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment for human epidermal growth factor receptor 2 (HER2)-expressing GEA, BTC, or CRC (physician's choice of XELOX, FP, mFOLFOX6 for subjects with GEA; CisGem for subjects with BTC; and mFOLFOX6 with or without bevacizumab for subjects with CRC) • To establish the recommended dose (RD) of ZW25when administered with combination chemotherapy	• Frequency of DLTs • Frequency and severity of adverse events (AEs) • Frequency of serious adverse events (SAEs) and deaths • Frequency and severity of clinical laboratory abnormalities • Frequency of electrocardiogram (ECG) abnormalities • Frequency of LVEF abnormalities • Frequency of dose reductions of ZW25 • Frequency of dose reductions of chemotherapy
Secondary Objectives	**Secondary Endpoints**
• To evaluate the antitumor activity of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment forHER2-expressing GEA, BTC, or CRC	• Objective response rate (ORR) • Disease control rate (DCR) • Duration of response (DOR) • Clinical Benefit Rate (CBR) • Progression-free survival (PFS) • Overall survival (OS)
• To characterize the immunogenicity of ZW25 when administered with combination chemotherapy	• Frequency, duration, and time of onset of anti-drug antibodies (ADAs) and neutralizing antibodies
• To evaluate the PK of ZW25 when administered with combination chemotherapy	• Serum concentrations of ZW25 as a function of time post-dosing • PK parameters for single (first) dose and multiple doses
Exploratory Objectives	**Exploratory Endpoints**
▪ [redacted]	▪ [redacted]

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4.2.2 Part 2

Primary Objective	**Primary Endpoints**
• To evaluate anti-tumor activity of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment for HER2-expressing GEA, BTC, or CRC	• ORR
Secondary Objectives	**Secondary Endpoints**
• To further evaluate the anti-tumor activity of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment for HER2-expressing GEA, BTC, or CRC	• DCR • CBR • DOR • PFS • OS
• To characterize the safety and tolerability of ZW25 when administered with combination chemotherapy	• Frequency and severity of AEs • Frequency of SAEs and deaths • Frequency and severity of clinical laboratory abnormalities • Frequency of ECG abnormalities • Frequency of dose reductions of ZW25 • Frequency of dose reductions of chemotherapy
• To characterize the immunogenicity of ZW25 when administered with combination chemotherapy	• Frequency, duration, and time of onset of ADAs and neutralizing antibodies
• To evaluate the PK of ZW25 when administered with standard first-line combination chemotherapy	• Serum concentrations of ZW25 as a function of time post-dosing • PK parameters for single (first) dose and multiple doses
Exploratory Objectives	**Exploratory Endpoints**
▪ [redacted]	▪ [redacted]

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4.3 Treatment Assignment and Blinding

This is an open-label study to assess the safety profile and preliminary anti-tumor activity of ZW25 plus standard first line combination chemotherapy regimens for selected GI cancers. No blinding or randomization will be performed.

4.4 Statistical Hypotheses

This is a two-part Phase-2 study. No statistical hypotheses will be tested. The primary objectives for Part 1 are to characterize the safety and tolerability of ZW25 and establish recommended dosages (RDs) of ZW25 when administered with physician's choice chemotherapy (XELOX, FP, mFOLFOX6 ±bevacizumab, or CisGem).

The primary objective for Part 2 of the study is to evaluate the antitumor activity of ZW25 combined with physician's choice chemotherapy (XELOX, FP, mFOLFOX6 ± bevacizumab, or CisGem).

4.5 Determination of Sample Size

4.5.1 Part 1

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4.5.2 Part 2

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5 GENERAL STATISTICAL CONSIDERATIONS

Data collected in this study will be presented using summary tables, subject data listings, and figures. Continuous variables will be summarized using descriptive statistics, specifically, the number (n), mean, quartiles, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

5.1 Analysis Sets

All Enrolled

All participants who sign the informed consent form and begin the screening process.

Safety

All subjects in the study who receive any amount of ZW25 and/or combination chemotherapy (XELOX, FP, CisGem, or mFOLFOX6).

Measurable Disease

All subjects in the safety analysis set who had at least one measurable target lesion (per RECIST 1.1) at baseline.

Note: per the study's inclusion/exclusion criteria, participants pass screening in Part 1 may have either measurable or non-measurable disease, while participants in Part 2 will only have measurable disease, therefore the measurable disease and safety analysis sets for Part 2 should contain the same subjects.

Response Evaluable

Response Evaluable includes all subjects in the safety analysis set with measurable disease at baseline and at least 1 evaluable post-baseline disease assessment (per RECIST 1.1) or who discontinued study treatment due to death or unequivocal clinical progression without any post-baseline disease assessment.

Pharmacokinetics

The pharmacokinetic (PK) analysis set will include all subjects who received any amount of zanidatamab and have at least one post-baseline PK assessment. Subjects will be evaluated by the treatment actually received.

Immunogenicity

The immunogenicity analysis set will include all subjects who received any amount of zanidatamab and have both baseline ADA and at least one post-baseline ADA results available.

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5.2 Subgroups

The following subgroups will be evaluated for efficacy for each cancer group (BTC, CRC and GEA) separately.

- Age (< 65 years, ≥ 65 years)
- Sex (Female, Male)
- Race1 (White, non-White)
- Race2 (Asian, non-Asian)
- Geographic region (Asia, EU/North America, Rest of World)
- Primary tumor site: GEA (gastric, GEJ, esophageal), BTC (ICC, ECC, or GBC), CRC (colon vs rectal)
- ECOG performance status (0, 1) from baseline disease characteristics
- HER2 status (IHC3+ and IHC2+/FISH+ VS IHC3+ VS IHC2+/FISH+) per central lab testing.

Subgroups should contain at least 5 subjects per arm in order for an analysis to be performed.

5.3 Handling of Missing Data

5.3.1 General

Subjects with missing values of a variable other than efficacy-related endpoints will be excluded from the analysis of that endpoint except the events list below. If EOS date is missing but death occurred, the death date or imputed death date will be used for EOS date.

5.3.2 Efficacy

Partial or Missing Dates

Partial or missing death dates, tumor assessment dates, dates of last contact, dates of onset of post-study treatment anticancer therapy, and dates used in computing secondary efficacy endpoints will be imputed as follows:

- Missing day only: For partial dates with only the day of the month missing, the day will be imputed as the 1st day of the month for death dates, dates of last contact, dates of onset of post-study treatment anticancer therapy. For tumor assessment date, the day will be imputed as the 1st day of the month if the progression and last day of the month for response or SD. If the month and year are the same as the preceding date of interest, the day will be imputed as the preceding date of interest for death, dates of last contact and tumor assessment date of response or stable disease, and will be imputed as the next day of the preceding date of interest for onset of post-study treatment anti-cancer therapy.
- Missing month and day: Month will not be imputed.

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- Missing month, day, and year: Complete missing will not be imputed.

Missing Post-Baseline Assessments

For RECIST based endpoints, subjects without any post-baseline tumor assessments will be handled as follows:

- For the analysis of PFS, the censoring scheme are described in Table 5.
- Subjects with no evaluable post-baseline response assessments will be considered as Not Evaluable (NE) for best overall response.
- For the analysis of OS, subjects with no post-baseline assessments (death date or last contact date) will be censored at the date of the first dose of study treatment (ZW25 or chemotherapy) .

5.3.3 Safety

Adverse Event Start Dates

For AEs where the date of onset is during or after administration of the first dose of study treatment, missing or partial start dates will be imputed as the earliest possible date that is on or after the date of the first dose of study treatment (ZW25 or chemotherapy). For events occurring prior to the first dose of study treatment, missing or partial dates will not be imputed.

- Missing day only: If the start date and date of first dose share the same month and year, the missing start day will be imputed as the day of first dose. If the start month is after the month of first dose, day will be imputed as the 1st (i.e., 01-MMM-YY).
- Missing month and day: If the start date and date of first dose share the same year, day and month will be imputed as the day and month of first dose. If the start year is after the year of first dose, the month and day will be imputed as January 1st (i.e., 01-JAN-YY).
- Missing month, day, and year: Missing start dates will be imputed as the date of first dose.

Adverse Event End Dates

Missing or partially missing end dates for AE which are known to have resolved will be imputed as follows:

- Missing day only: The day will be imputed as last day of the month (e.g., 31-MMM-YY or 30-MMM-YY). The AE end date is then imputed as the minimum of {last day of the month} and {death date}. If the month and year are the same as the data cutoff date or end of study date month and year, then the data cutoff date or end of study date will be used as the imputed AE end date.

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- Missing month and day: The missing month and missing day will be imputed as December 31. The AE end date is then imputed as the minimum of {Dec 31 of the year}, {death date}, {End of Study date} and {data cutoff date}.
- Missing month, day, and year: The AE end date will be imputed as the minimum of {death date}, {End of Study date} and {data cutoff date}.
- The end dates of ongoing AEs will not be imputed, except in AE duration calculation, which will be imputed as the minimum of death date, End of Study date and data cutoff date.

5.3.4 Pharmacokinetics

Missing values for PK measurements will be listed as missing and excluded from the calculation of summary statistics. Sample concentrations that are below the lower limit of quantification (LLOQ or BQL)will be shown as less than reportable (<LLOQ or BQL) in the individual subject listings and imputed as follows for the purposes of calculating summary statistics and producing graphical summaries:

- If the sample was collected prior to the 1st dose of study drug, then the value will be imputed as zero.
- If the sample was collected after the 1st dose of study drug, then the value will be imputed as the value of the LLOQ or BQL.

Exclusion of PK data will be based on documented errors in dosing, sample labeling, sample handling, deviation from sample collection window, or bioanalysis. Excluded data will be flagged in the listing and will not be used in calculations for any tabulated or graphical summaries. Subjects that were not dosed or were not dosed in accordance with their assigned treatment will be excluded from any tabulated or graphical summaries. Biologically implausible data may also be excluded in the summaries; however, all individual data will be listed and any exclusion, along with the corresponding rationale, will be noted.

5.4 Multicenter Studies

No comparisons among sites will be performed.

5.5 Adjustments for Covariates

No adjustments for covariates will be performed.

5.6 Multiple Comparisons, Multiplicity, and Multiple Testing

No adjustments for multiple comparisons will be applied.

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5.7 Data Conventions, Definitions, and Formulas

The following data conventions will be used for the tables, listings, and figures.

- **Study drug**: Zanidatamab or JZP598 and relevant chemotherapy regimen
- **Baseline value of a study assessment**: The last non-missing observation prior to the first dose of study treatment [ZW25 or chemotherapy], unless otherwise specified. If both a planned assessment and repeat assessment (e.g., retest) meet the above criteria and were collected on the same date and time, the repeat assessment will be used as baseline.
- **Baseline value of an efficacy assessment**: The last value observed prior to the first dose of study treatment [ZW25 or chemotherapy], unless otherwise specified. If both a planned assessment and repeat assessment (e.g., retest) meet the above criteria and were collected on the same date and time, the repeat assessment will be used as baseline.
- **Disease Assessment dates:** In the event, radiographic assessment for a subject occurs over multiple days for a visit, the following convention will be used to determine the date of the disease response assessment:
    - For a response of Progressive Disease (PD), the date of the earliest radiographic scan will be used.
    - For responses other than PD, the date of the latest radiographic scan will be used.
-
- **Study Day of a safety event or assessment**: The difference between the date of the event or assessment and the date of first dose of study treatment [ZW25 or chemotherapy] plus 1 for events or assessments occurring on or after the day of first dose of study treatment [ZW25 or chemotherapy]. For example, if an event occurs on 08JUN2014 and the date of first dose of study treatment [ZW25 or chemotherapy], was 06JUN2014, the study day of the event is 3. For events or assessments occurring before the day of first dose of study treatment [ZW25 or chemotherapy], it will be the difference between the date of the event or assessment and the date of first dose of study treatment [ZW25 or chemotherapy]. For example, if an event occurs on 05JUN2014 and the date of first dose of study treatment [ZW25 or chemotherapy], was 06JUN2014, the study day of the event is -1, which is consistent with the Study Data Tabulation Model (Version 3.2) from Clinical Data Interchange Standards Consortium (CDISC).
- **Study day of an efficacy event or assessment**: The difference between the date of the event or assessment and the date of first dose of study treatment [ZW25 or chemotherapy] plus 1 for all events or assessments occurring on or after the date of first dose of study treatment [ZW25 or chemotherapy]. For events or assessments occurring prior to the date of first dose of study treatment [ZW25 or chemotherapy], it will be the difference between the date of the event or assessment and the date of first dose of study treatment [ZW25 or chemotherapy].
- **Pre-treatment Period**: Period of time prior to first dose of study treatment [ZW25 or chemotherapy], starting with informed consent.

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- **Study Treatment Period**: Period of time that begins on the date of the first dose of study treatment [ZW25 or chemotherapy] through 30 days after the date of the last dose of study treatment [ZW25 or chemotherapy].
- **Post-treatment Follow up Period**: Period of time that begins 1 day after End of Treatment (EOT) and ends at End of Study (EOS).

6 STATISTICAL METHODOLOGY

This study consists of 2 parts. All parts will be summarized together by tumor type as follows: CRC only, BTC only and GEA only. All summaries will be performed overall and separately by ZW25 dose regimen and chemotherapy combination. Additional groupings as appropriate will be presented for HER2 status.

6.1 Trial Details

The following information will be summarized for the safety analysis set including both subjects from part 1 and part 2 unless otherwise specified.

6.1.1 Enrollment

The following study enrolment information will be summarized for all enrolled analysis set:

- Number of screen failures and the percentage relative to the total number of subjects screened.
- Number of subjects treated in part 1, part2 and overall, and the percentage relative to the total number of subjects screened.
- A listing of subjects who failed screening will also be produced.

6.1.2 Analysis Sets Evaluated

- Number and percentage of subjects in each analysis set will be presented.

6.1.3 Subject Disposition

The following disposition information will be summarized in each treatment group and overall.

- Number and percentage of treated [ZW25 or chemotherapy] subjects.
- Number and percentage of subjects who discontinued ZW25 study treatment and the associated reasons for discontinuation.
- Number and percentage of subjects who discontinued each chemotherapy component and the associated reasons for discontinuation.
- Number and percentage of subjects remaining on treatment.

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- Number and percentage of subjects who discontinued from the study and the associated reasons for discontinuation.
- Number and percentage of subjects active in post-treatment survival follow-up.
- Number and percentage of subjects remaining on Study.
- Descriptive statistics for duration of study follow-up defined as the time from the time subject was first treated with study treatment [ZW25 or chemotherapy] to the data cutoff date.

Disposition information will also be provided in the listings.

6.1.4 Protocol Violations and Deviations

Protocol deviations and violations (as defined in the ZW25-201 Monitoring Plan) will be identified by clinical trial team member and by checks of the clinical database. Important deviations and violations will be summarized for each cohort by type of deviation/violation. A listing of protocol deviations will be provided by treatment regimen.

6.1.5 Baseline Characteristics and Disease History

Demographics and baseline characteristics will be summarized using counts and percentages for categorical variables and summary statistics (mean, quartiles, standard deviation, and range) for continuous variables. Characteristics to be summarized include the following:

- Demographic variables:
  - Age at informed consent (< 65 and ≥ 65 years ; < 75 and ≥ 75 years)
  - Sex (Female, Male)
  - Ethnicity (Hispanic, Latino/a or of Spanish Origin, Not Hispanic, Latino/a or of Spanish Origin, Not Reported, Unknown)
  - Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reportable, Unknown)
  - Race group 1 (White, Non-White)
  - Race group 2 (Asian, Non-Asian)
- Physical characteristics: height (cm), weight (kg) and BMI
- ECOG performance status (0, 1, Missing)

Demographics and baseline characteristics will be provided in the listings.

6.1.6 Disease History and Tumor Characteristics:

Disease history and baseline tumor characteristics will be summarized as follows:

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- Primary diagnosis
- Stage at initial diagnosis
- Tumor classification/characteristics
  - HER2 status
    - HER2+: IHC3+, IHC2+/FISH+
    - HER2-: IHC2+/FISH-, IHC1+, IHC0
- Tumor characteristics per RECIST v1.1
  - Measurable disease at baseline (Yes, No)
  - Baseline sum of diameter (mm) per RESIST

Disease history and Medical history will be provided in the listings.

6.1.7 Prior Anticancer Therapy

- Prior radiotherapy
  - Any (Yes, No)
  - Total number of courses
- Prior cancer surgery
  - Any (Yes, No)
  - Total number of surgeries
- Prior systemic cancer regimens (related to study indication)
  - Any (Yes, No)
  - Total number
  - Prior neoadjuvant therapy (Yes, No)
  - Prior adjuvant therapy (Yes, No)

Prior systemic cancer therapies will be coded using the World Health Organization Drug Dictionary (WHODRUG) Version 2024-03 B3 or higher and tabulated by ATC level 4 term and preferred term. Prior surgery and radiotherapies will also be listed. Subsequent Systemic Anticancer Therapies will be provided in a listing.

6.1.8 Concomitant Medications

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODRUG) Version 2024-03 B3 or higher and listed and summarized by ATC level 4 term and preferred term using counts and percentages. Multiple occurrences of the same medication within a subject will be summarized only once.

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6.1.9 Concomitant Procedures

Concomitant procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.0 or higher and listed and summarized by procedure and indication using counts and percentages. Multiple occurrences of the same procedure within a subject will be summarized only once.

6.2 Analysis of Efficacy

Efficacy analyses will be based on the Response Evaluable, Measurable Disease, and Safety analysis sets unless otherwise specified.

The primary efficacy endpoint is confirmed objective response defined as achieving a confirmed best overall response of either complete response (CR) or partial response (PR) per RECIST 1.1. Efficacy will be evaluated by combining data from Part 1 and 2 subjects.

6.2.1 Confirmed Objective Response per Investigator

The primary efficacy analysis will estimate the confirmed objective response rate in HER2-expressing GEA, BTC, or CRC, pooled across the appropriate chemotherapy treatment groups for both the response evaluable and measurable disease analysis sets. Confirmed objective response is defined as achieving a confirmed BOR of CR or PR per RECIST 1.1 (see Table 4 below) which is confirmed at a subsequent visit that occurs at least 28 days after the first CR or PR was observed. The date of the confirmed objective response is the first documented CR or PR (the First Time Point Response in Table 4) that is subsequently confirmed. Subjects whose first confirmed objective response occurs after disease progression or new antitumor therapy will not be counted as a responder. The proportion of subjects with a confirmed objective response and the corresponding two-sided, exact Clopper-Pearson binomial 95% CI will be calculated for the investigator assessments of disease response. Swimmer and waterfall plots will be provided for response evaluable set. Efficacy follow-up period will be used for swimmer plot. If subjects discontinue the treatment, then efficacy follow-up is EOT date – first dose date +30; otherwise, the efficacy follow-up is DCO date – first dose date +1.

Table 4. Determination of Confirmed Overall Response

Overall Response Assessment		Confirmed Response (Best Response) *
First Time Point Response	**Second Time Point Response**	
PD	No further evaluation	PD
NE	PD	PD
CR	PD	SD or PD (1)
PR	PD	SD or PD (1)

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SD	PD	SD or PD (1)
CR	CR	CR
CR	NE	SD or NE (2)
PR	CR	PR
PR	PR	PR
PR	SD (3)	SD
PR	NE	SD or NE (2)
SD	CR	SD
SD	PR	SD
SD	SD	SD
SD	NE	SD or NE (2)
NE	CR	SD
NE	PR	SD
NE	SD	SD
NE	NE	NE

*** A Best Response of SD can only be made after the subject is on-study for a minimum of 5 weeks (35 days) . If the subject is not on-study for this amount of time, any tumor assessment indicating stable disease before five weeks will have a Best Response of NE unless PD is identified. Same criteria of SD will be applied to non-CR/non-PD.**
(1) Best response will be SD if the first TPR is after five weeks on-study.
Otherwise, the best response will be PD.
(2) Best response will be SD if the first TPR is after five weeks on-study.
Otherwise, the best response will be NE.
(3) TPR is SD if the increase from the first to the second assessment does not qualify for PD

6.2.2 Progression-Free Survival (PFS)

Progression-Free survival will be conducted on subjects in the safety population and is defined as the time from the first dose of study treatment (ZW25 and chemotherapy) to the date of documented disease progression (per RECIST v1.1) or death from any cause, whichever occurs first. Subjects who are alive and have not progressed at the time of the analysis will be censored at the time of their last tumor assessment that was a CR, PR, SD, or non-CR/non-PD. Details of the censoring scheme for this endpoint are described in Table 5.

Table 5: Censoring and Event Scheme for PFS

Scenario	Progression/Censor Date	Outcome
No post-baseline tumor assessments and no death	Date of first dose of study treatment	Censored
No radiographic disease progression	Date of last CR, PR, SD, or non-CR/non-PD	Censored
New anticancer treatment started before first PD	Date of last CR, PR, SD, or non-CR/non-PD on or prior to date of new anticancer treatment	Censored

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PD	Date of PD, if response assessment prior to PD was either CR, PR, SD, or non-CR/non-PD	Progressed
	Date of PD, if PD occurred at the 1st response assessment, or PD occurred at the 2nd response assessment with a missing 1st response assessment	Progressed
	Date of last CR, PR, SD, or non-CR/non-PD, or date of first dose if PD occurred after 2 or more consecutive missed and/or NE post-baseline overall response assessments *	Censored
Death before first PD	Death date, if response assessment prior to death is CR, PR, SD, or non-CR/non-PD and death occurred within 2 scheduled response assessment*	Progressed
	Death date, if there is no post-baseline disease assessments and death occurred within the first two scheduled disease assessment	Progressed
	Date of last CR, PR, SD, or non-CR/non-PD, or date of first dose if death occurred after 2 or more consecutive missed and/or NE post-baseline overall response assessments*	Censored

Note: * Two consecutive post-baseline tumor assessments refers to the next two protocol scheduled tumor assessments. Time is measured from the last adequate response assessment date. Subjects will be considered to have missed two consecutive scheduled visits if no scans, scheduled or unscheduled, have occurred within the protocol-mandated disease assessment schedule; this will be within 2*(6 + 1) = 14 weeks (98 days). Note: The scanning schedule is every 6 weeks (42 days).

Kaplan Meier estimates of the PFS curves and quartiles will be calculated for each cohort. Two-sided 95% CIs for the quartiles will be calculated using the Brookmeyer and Crowley method with log-log transformation method (Collett 1994). KM plot for PFS will also be performed.

Additionally, median PFS and the probability of PFS at timepoints from 3 months to the end of the follow-up period will be reported for each cohort. Timepoints of most interest in this descriptive landmark (milestone) analysis are 3, 6, 9, 12 and 18 months. Two sided 95% CIs for the landmark PFS estimates will be calculated for each cohort based on the Greenwood estimator (Greenwood 1926).

6.2.2.1 PFS Subgroup Analyses

For the subgroups described in Section 5.2, Kaplan Meier estimates of the quartiles for PFS will be calculated by cohort for each subgroup level along with their corresponding 95% CI.

Subgroups should contain at least 5 subjects in order for an analysis to be performed.

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6.2.3 Disease Control Rate (DCR)

Disease control is defined as a BOR of SD or confirmed CR or PR per RECIST 1.1. The proportion of subjects who achieve disease control and the corresponding two-sided, exact Clopper-Pearson binomial 95% confidence interval will be estimated.

6.2.4 Clinical Benefit Rate (CBR)

Clinical benefit is defined as achieving SD or non-CR/non-PD for ≥ 24 weeks or a confirmed BOR of CR or PR per RECIST 1.1. The proportion of subjects with clinical benefit and the corresponding two-sided, exact Clopper-Pearson binomial 95% confidence interval will be estimated.

6.2.5 Duration of Response

Duration of response (DOR) is defined as the time from the first documented CR or PR (the First Time Point Response in Table 4) that is subsequently confirmed per RECIST 1.1 at least 28 days later to documented PD or death from any cause, whichever occurs first. Only subjects who achieve a confirmed objective response will be included in the analysis.

DOR will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided using measurable disease analysis sets . The same censoring rules outlined in Table 5 for PFS will be applied to DOR. The median DOR and its two-sided 95% CI will be calculated using the Brookmeyer and Crowley method with log-log transformation method by cohort.

6.2.6 Overall Survival

Overall survival (OS) is defined as the time from the date of first dose of study treatment [ZW25 or chemotherapy]to death due to any cause. Specifically,

OS = Date of death – Date of first dose of study treatment [ZW25 or chemotherapy] + 1

For a subject who is not known to have died at the time of analysis, observation of OS is censored on the date the subject was last known to be alive (i.e., date of last contact with the subject). Subjects lacking data beyond the day of the first dose of study treatment (ZW25 and chemotherapy) will have their survival time censored on the date of first dose of study treatment [ZW25 or chemotherapy] (i.e., OS duration of 1 day). Subjects whose death date or last known alive date is after the data cutoff date will be considered as censored and their last known alive date will be set to the data cutoff date for the analysis. Partial or missing dates of death and dates of last contact will be imputed as described in Section 5.3.2.

The cutoff date will not be used for last contact date, unless the subject was seen or contacted on that date.

Kaplan Meier estimates of the survival curve and quartiles will be calculated in the Safety Population. The 2-sided 95% CIs for the quartiles will be calculated using the Brookmeyer and

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Crowley method with log-log transformation method. Additionally, the probability of survival at timepoints from 3 months to the end of the follow-up period will be reported. Timepoints of most interest in this descriptive landmark (milestone) analysis are 6, 12, and 18 months, estimated using the Kaplan Meier method with two-sided. The 2-sided 95% CIs of OS timepoints will be calculated using the Greenwood estimator.

OS Subgroup Analyses

For the subgroups described in Section 7.2, subgroup analyses may be performed for OS. Analysis methods will match the methods used for subgroup analyses of PFS as detailed in Section 8.2.2.2.

6.3 Exploratory Efficacy Analyses

6.3.1 Biomarkers

[redacted]

6.4 Analysis of Safety

All analyses of safety will be based on the safety analysis set. Safety will be evaluated by combining data from Part 1 and 2 subjects.

6.4.1 Dose Limiting Toxicities

The DLT-evaluation period is the first cycle of treatment for all Part 1 treatment regimens. The number and proportion of subjects experiencing a dose-limiting toxicity in Cycle 1 (as defined in Section 3.1.1.1 of Protocol) will be summarized for Part 1of the study by combination therapy group and by ZW25 dose level if differing doses are provided.

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6.4.2 Extent of Exposure

Zanidatamab and chemotherapy exposure will be summarized using counts and percentages for categorical variables and summary statistics (mean, quartiles, standard deviation, and range) for continuous variables.

The following information will be summarized for each treatment regimen overall, and within each regimen, ZW25 and each chemotherapy component:

- Duration of exposure of study treatment in months defined as [(last date of study treatment - first dose date of study treatment + 1)/ 30.4375
- The number of cycles of study treatment initiated and the number of doses of each treatment component administered for each participant will be categorized as 1, 2, 3, 4, 5, 6, 7, 8, 9 or > 10.
- The number of dose modifications, dose reductions, and dose delays for each participant will be categorized as 0, 1, 2, or ≥ 3. Dose modifications, dose reductions, and dose delays due to an AE will be identified.
- **Total Cumulative Dose**: Total cumulative dose (mg) = sum of all doses (mg) received during the entire treatment duration on or before the data cut-off date. The cumulative dose for all cycles and the cumulative dose for first 6 cycles will be presented.
- **Actual Dose Intensity (ADI)**: ADI is the actual cumulative dose divided by the number of weeks of treatment, for subjects received treatment more than 6 cycles:
    - For ZW25: dosing for all cycles will be used for ADI calculation
    - For all Chemotherapy: only dosing used in the first 6 cycles will be used for ADI calculation

  For ZW25 and Chemotherapy other than capecitabine, the actual dose received for a given dose (mg) will be derived as planned dose (mg) multiplied by the fraction of the infusion received (actual volume/ planned volume). Calculated as:

    - Actual dose received (mg) = planned dose (mg) * (actual volume (ml) / planned volume (ml))

  The actual cumulative dose calculation is listed below:

  - For capecitabine:
    - For the D1 and D15 of each cycle, Planned Daily Dose = Planned Daily Dose/2, because only one dose is given at night of D1 and morning of D15.
    - if Dose Deviation = No, actual cumulative dose = sum of (Planned Daily Dose (mg)* (Stop date – Start date +1))
    - if Dose Deviation = Yes, actual cumulative dose = sum of (Actual Daily Dose (mg)* (Stop date – Start date +1))

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- Sum of two above actual cumulative dose for total actual cumulative dose.

- For 5-fluorouracil: total actual cumulative dose = sum of Actual dose received (mg)
- For 5-fluorouracil Bolus: the total actual cumulative dose = sum of Calculated dose (mg)
- For all other Chemotherapy and ZW25: total actual cumulative dose = sum of Actual dose received (mg)

For calculating ADI, the treatment period is defined for each treatment regimen as follows: (Date of last dose + x days)- (date of first dose), regardless of death status and EOT during this period. The number of weeks of treatment will be calculated to 1 decimal place.

- For ZW25:
  - (Date of last dose + 14 days)- (date of first dose) for Q2W, x=14 days,
  - (Date of last dose + 21 days)- (date of first dose) for Q3W, x=21 days
- For oxaliplatin:
  - (Date of last dose + 21 days) - (date of first dose) for Q3W schedule, x=21 days
  - For Q2W schedule: (date of last dose + 14 days) - (date of first dose), x=14 days
- For capecitabine:
  - If the last dose before the data cut-off date is at Day 1 and (End date-start date <14) of the 21-day cycle: (Date of last dose + 1 day) - (date of first dose), x=1 day
  - If the last dose before the data cut-off date is at Day 1 and (End date-start date >=14) of the 21-day cycle: (Date of last dose + 7 days) - (date of first dose), x=7 days
- For cisplatin:
  - For GEA, (date of last dose + 21 days) - (date of first dose), x= 21 days
  - For BTC, (date of last dose + 7 days) - (date of first dose) if last dose was on Day 1, x= 7 days, or (date of last dose + 14 days) - (date of first dose) if last dose was on Day 8, x=14 days
- For 5-FU:
  - For GEA Q3W:
    - If the last dose before the data cut-off date is at Day 1 and (End date-start date <5) of the 21-day cycle: (Date of last dose + 1 day) - (date of first dose), x =1 day
    - If the last dose before the data cut-off date is at Day 1 and (End date-start date >=5) of the 21-day cycle: (Date of last dose + 17 days) - (date of first dose), x= 17 days
  - For Q2W:
    - For GEA:

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- Bolus, (date of last dose + 14 days) - (date of first dose), x=14 days
- Continuous IV:
  - ✓ If the last dose before the data cut-off date is at Day 1 or D15 and (End date-start date =1) of the 28-day cycle: (Date of last dose + 1 day) - (date of first dose), x=1 day
  - ✓ If the last dose before the data cut-off date is at Day 1 or D15 and (end date – start date > =2) of the 28-day cycle: (Date of last dose + 13 days) - (date of first dose), x=13 days

– For CRC:

- Continuous IV:
  - ✓ If the last dose before the data cut-off date is at Day 1 or D15 and (End date-start date =1) of the 28-day cycle: (Date of last dose + 1 day) - (date of first dose), x=1 day
  - ✓ If the last dose before the data cut-off date is at Day 1 or D15 and (end date – start date >=2) of the 28-day cycle: (Date of last dose + 13 days) - (date of first dose), x=13 days

- For leucovorin:
  - (Date of last dose + 14 days) - (date of first dose), x=14 days
- For gemcitabine:
  - (Date of last dose + 7) days - (date of first dose) if last dose was on Day 1, x= 7 days, or (date of last dose + 14 days) - (date of first dose) if last dose was on Day 8, x=14 days
- For bevacizumab:
  - (date of last dose + 14 days) - (date of first dose), x= 14 days

Intended Dose Intensity (IDI): IDI is the planned cumulative dose as specified in the protocol divided by the planned number of weeks of treatment. The planned cumulative dose is summarized in mg for all study treatment components. Some of the planned dose collected in the CRF were not following the protocol define, so the planned dose derived from weight or BSA will be used for calculation the IDI. The planned cumulative dose by protocol of each chemotherapy agent and ZW-25 is calculated following the steps below:

1. For ZW-25, all cycles will be used for IDI calculation:

- Calculate the duration of study treatment components in days:
  - (Date of last dose + 14 days)- (date of first dose) for Q2W, x=14 days,
  - (Date of last dose + 21 days)- (date of first dose) for Q3W, x=21 days
- Calculate the planned weeks of treatment:
  - Calculate the number of full cycles: I = integer part of (duration in days/21 for Q3W or duration in days/28 for Q2W)

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- Calculate the number of days in the last cycle: R = duration in days - 21*I for Q3W or R = duration in days - 28*I for Q2W
  - ✓ Q3W: if R =0, planned weeks = 3i.
    if R >0, planned weeks = 3 (i+1)
  - ✓ Q2W: if R = 0, planned weeks = 4i
    if 15>R >0, planned weeks = 4 (i+1) – 2
    if R >= 15, planned weeks = 4 (i+1)

- Cumulative planned dose by protocol:
  - For weight based:
    - For C1D1, the planned dose = weight* Dose Regimen of C1D1 (20 or 30 mg/kg)
    - For other visit:
      - ✓ if the weight reduce/increase compare to C1D1 weight is <10%, the planned dose = C1D1 panned dose
      - ✓ if the weight reduce/increase compare to C1D1 weight is >=10%, the planned dose = weight for current cycle* Dose Regimen of C1D1
  - For flat dose:
    - For C1D1, if Q2W and weight < 70, then planned dose =1200, else if weight >= 70 then planned dose =1600; , if Q3W and weight < 70, then planned dose =1800, else if weight >= 70 then planned dose =2400;
    - For other visit:
      - ✓ if the weight reduce/increase compare to C1D1 weight is <10%, the planned dose = C1D1 panned dose
      - ✓ if the weight increase compare to C1D1 weight is >=10% and C1D1 weight < 70 and current weight >=70, then change 1200 to 1600, or change 1800 to 2400 for current visit planned dose.
      - ✓ if the weight decrease compare to C1D1 weight is >=10% and C1D1 weight >= 70 and current weight <70, then change 1600 to 1200, or change 2400 to 1600 for current visit planned dose.
      - ✓ Other visit, planned dose = C1D1 panned dose
  - Cumulative planned dose by protocol for all cycles = sum of planned dose by protocol (mg) for all visits. If the planned dose is missing, the planned dose of day 1 in the previous non-missing cycle will be used.

- IDI of ZW-25 is the planned cumulative dose by protocol divided by number of planned weeks of treatment.

2. For chemotherapy agent, only the first 6 cycles will be used for IDI calculation:

- Cumulative planned dose by protocol:
  - For Chemo except Capecitabine:
    - C1D1 planned dose = C1D1 Calculated Dose
    - Other visit planned dose = C1D1 planned dose * (BSA of current visit / BSA of C1D1)
  - For Capecitabine:
    - C1D1 planned dose = C1D1 planned daily dose

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  - Other visit planned dose = C1D1 planned dose * (BSA of current visit / BSA of C1D1)
- Calculate the duration of study treatment components in days: the date of the last dose before the data cut-off date – Date of Day 1 + x day (the number of days to next dose), x day is same as described in ADI.

- If the treatment duration >=126 days for Q3W or >=168 days for Q2W, the IDI Calculation is based on the first 6 cycles (subjects are intended to receive 6-cycle treatment, regardless which cycle the subjects are actually in).
  - For Q3W, if treatment duration >=126 days, the planned cumulative dose is the sum of planned dose in mg for all visits in the first 6 cycles for all the chemotherapy. The IDI is the planned cumulative dose divided by 18 weeks.
  - For Q2W, if the treatment duration >=168 days for Q2W, the planned cumulative dose is same as above. The IDI is the planned cumulative dose divided by 24 weeks.
- If the treatment duration < 126 days for Q3W or < 168 days for Q2W, the IDI is the planned cumulative dose divided by number of planned weeks of treatment.
  - Calculate the planned cumulative dose and planned weeks of treatment:
    - ✓ Calculate the number of full cycles: I = integer part of (duration in days/21 for Q3W or duration in days/28 for Q2W)
    - ✓ Calculate the number of days in the last cycle: R = duration in days - 21*I for Q3W or R = duration in days - 28*I for Q2W
    - ✓ Calculate the dose in last cycle (D), the planned dose of Day 1 in last cycle will be used for calculate the dose in the last cycle (D). If the planned dose is missing, the planned dose of day 1 in the previous non-missing cycle will be used:
      - Capecitabine, total planned cumulative dose for last cycle: if R =1 then D = Planned Daily Dose in mg/2; if R >= 15 then D = Planned Daily Dose in mg * 14; if 1<R<15 then D = Planned Daily Dose in mg * (R-0.5).
        planned weeks of treatment: if R = 0, planned weeks = 3i
        if 15>R >0, planned weeks = 3i + R/7
        if R >= 15, planned weeks = 3(i+1)
      - 5-fluorouracil continue infusion, total planned cumulative dose for last cycle = sum of Calculated Dose for each record :

        - Q3W: planned cumulative dose for last cycle: if R >= 5, then D = Calculated Dose in mg; if 1≤ R<5 then D =Calculated Dose * R/5 in mg; Calculated Dose in EDC for 5-fluorouracil Q3W is sum of all 5 days doses together.
          planned weeks of treatment: if R =0, planned weeks = 3i.
          if 5>R >0, planned weeks = 3i + R/7
          if R >=5, planned weeks = 3(i+1)
        - Q2W: planned cumulative dose for last cycle: if R >= 16, then D = Calculated Dose *2 in mg; if R=15, then D = Calculated Dose *1.5 in mg; if 2≤ R<15 then D = Calculated Dose *1 in mg; if R=1 then D =

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Calculated Dose *0.5 in mg; Calculated Dose in EDC for 5-fluorouracil Q2W is sum of all 2 days doses together
planned weeks of treatment: if R =0, planned weeks = 4i.
if 2>R >0, planned weeks = 4i + R/7
if 15>R >=2, planned weeks = 4i + 2
if 16>R >=15, planned weeks = 4i + R/7
if R >= 16, planned weeks = 4(i+1)

- All other chemotherapy:
  - Q3W:
    - if cisplatin or gemcitabine in BTC: planned cumulative dose for last cycle: if R <8, then D = the planned does for day 1 of last cycle, if R >= 8, D = 2 * the planned does for day 1 of last cycle.
      planned weeks of treatment: if R = 0, planned weeks = 3i
      if 8>R >0, planned weeks = 3i + 1
      if R >= 8, planned weeks = 3(i+1)
    - if other Chemotherapy: planned cumulative dose for last cycle: D = the planned does for day 1 of last cycle
      planned weeks of treatment: if R =0, planned weeks = 3i.
      if R >0, planned weeks = 3 (i+1)
  - Q2W: planned cumulative dose for last cycle: if R <15, then D = the planned does for day 1 of last cycle, if R >= 15, D = 2 * the planned does for day 1 of last cycle
    planned weeks of treatment: if R = 0, planned weeks = 4i
    if 15>R >0, planned weeks = 4 (i+1) – 2
    if R >= 15, planned weeks = 4 (i+1)

✓ Calculate the planned cumulative dose, use the Day1 dose of each cycle for calculating the cumulated dose for I cycles:
- Capecitabine: sum of 14*I cycle(s) of Planned Daily Dose in mg + D
- 5-fluorouracil: sum of 1*I cycle(s) of the planned dose + D for Q3W
  sum of 2*I cycle(s) of the planned dose + D for Q2W
- Cisplatin or gemcitabine in BTC: sum of 2*I cycle(s) of the planned dose + D
- All other chemotherapy: sum 1* I cycle(s) of the planned dose + D for Q3W
  sum 2* I cycle(s) of the planned dose + D for Q2W

- **Relative Dose Intensity (RDI)**: RDI is the percent of the intended dose intensity over the entire treatment period:
  - ADI/IDI * 100
- Exposure will be categorized by 0 - ≤ 12 weeks, > 12 - ≤ 24 weeks, > 24 - ≤ 48 weeks, and > 48 weeks.
- Relative dose intensity summarized will be categorized as ≤ 75%, > 75%, ≤ 90%, and > 90%.

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- Interrupted infusions and incomplete infusions for each participant will be categorized as 0, 1, 2, or ≥ 3.

The following exposure data will be listed:

Dose reductions, interruptions, and delays, including the reasons for the dose modifications.

Incomplete infusions and interrupted infusions.

Study drug administration details such as actual dose, start and end day and time, batch/lot number of the study drug administered will be listed separately.

6.4.3 Adverse Events

An AE is any untoward medical occurrence in a subject administered a pharmaceutical or investigational product, in this case ZW25 and chemotherapy, which does not necessarily have a causal relationship with these treatments. All AEs will be coded to standard "preferred terms" and system organ classifications (SOC) using MedDRA. Severity will be graded by study investigators using NCI-CTCAE v5.0. All AEs will be coded by the Sponsor to standard preferred terms and system organ classifications (SOC) using MedDRA Version 27.0 or higher.

According to the protocol, the safety reporting period for all AEs and SAEs (regardless of relationship to study drug) is from start of dosing of any study drug on Cycle 1 Day 1 to 30 days after last dose of study drug (ZW25 or chemotherapy) or prior to beginning the next course of anticancer therapy, whichever occurs sooner. However, all study protocol-related AEs are to be recorded from the time of informed consent. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol-mandated procedure. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should be reported to the sponsor.

Definitions

Treatment-emergent adverse events: Treatment-emergent AEs are defined as events with an onset during or after receipt of the first dose of component study treatment (ZW25 or chemotherapy) and up to and within 30 days after the last dose for subjects who discontinued study treatment on or prior to the data cut-off date, or up to the data cutoff date for subjects who are continuing with study treatment.

Treatment-related adverse events: Adverse events assessed by the Investigator as 'related' relationship to each component study treatment (ZW25 or chemotherapy).

The frequency of TEAEs will be summarized in descending frequency by preferred term and SOC using subject counts and percentages. Multiple occurrences of the same AE within a subject will be counted only once at the most severe grade level for the time frame under consideration. For summaries by severity, only the worst grade for an AE will be counted for a particular subject. AEs occurring more than 30 days after the last dose of any component of study treatment will be excluded from summaries but included in data listings.

Summaries

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Summaries to be produced include, chemotherapy related summary will be separated summarized by each chemotherapy reagent:

- Overview of all AEs by subject incidence
- TEAEs by SOC and preferred term
- TEAEs by preferred term
- TEAEs by toxicity grade and preferred term
- Grade 3 or higher TEAEs by SOC and preferred term
- Grade 3 or higher TEAEs by preferred term
- Grade 3 or higher ZW25 and/or any chemotherapy TEAEs by preferred term
- Incidence of TEAEs which resulting in death
- TEAEs that led to discontinuation of study treatment by preferred term
- TEAEs that led to discontinuation of ZW25 by preferred term
- TEAEs that led to discontinuation of any chemotherapy by preferred term
- TEAEs which lead to dose reduction of ZW25 by preferred term
- TEAEs which lead to dose reduction of any chemotherapy by preferred term
- TEAEs which lead to dose delay of ZW25 by preferred term
- TEAEs which lead to dose delay of any chemotherapy by preferred term
- TEAEs which lead to dose interruption of ZW25 by preferred term
- TEAEs which lead to dose interruption of any chemotherapy by preferred term
- TEAEs which lead to dose held of ZW25 by preferred term
- TEAEs which lead to dose held of any chemotherapy by preferred term
- ZW25 and/or any chemotherapy related TEAEs by preferred term
- ZW25 and/or any chemotherapy related grade 3 or higher TEAEs by preferred term

In addition to summary tables, the following listings will be produced.

- All TEAEs
- TEAEs which resulted in death (deaths not related to disease progression)
- TEAEs which lead to discontinuation of study treatment
- TEAEs which lead to dose reduction of study treatment
- TEAEs which lead to dose delay of study treatment
- TEAEs which lead to dose interruption

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- Grade 3 or higher TEAEs

6.4.4 Adverse Events of Special Interest

Adverse events of special interest (AESIs) will be listed and summarized by preferred term using counts and percentages. Multiple occurrences of the same AESI within a subject will be counted only once for the time frame under consideration. For summaries by severity, only the worst grade for an AESI will be counted for a particular subject. Summary statistics (median, quartiles and range) for time to the first onset and the duration of AESIs will also be provided.

AESIs to be summarized include the following:e 3

- **Infusion related reactions (IRR)**: Defined using the MedDRA preferred term of, "Infusion Related Reaction"
- **Non-infectious pulmonary toxicities**: Defined by the Broad Interstitial Lung Disease SMQ.
- **Left ventricular (LV) dysfunction:** Defined as absolute decrease in LVEF of ≥ 10 percentage points from pretreatment baseline and value < 50% by ECHO/MUGA results OR Grade ≥ 2 TEAE that of PT included in Heart Failure Custom Query.

Similar data summaries will be performed for the following select 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, excluding the sub-SMQ Lactation related topics (including neonatal exposure through breast milk).

6.4.5 Serious Adverse Events

Serious TEAE will be summarized by preferred term and SOC using counts and percentages. Multiple occurrences of the same TESAE within a subject will be counted only once for the time frame under consideration. The following summaries of serious TEAE will be produced.

- Incidence by SOC and decreasing frequency of SOC and preferred term in overall
- Incidence by decreasing frequency of preferred term
- Incidence of ZW25 and/or any chemotherapy related SAEs by decreasing frequency of preferred term

In addition to summary tables, listings of SAEs will be produced.

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6.4.6 Death

The frequency of deaths will be summarized using counts and percentages. A table of deaths showing causes of death that occurred ≤ 30 days after last dose of last component of study treatment versus that occurred > 30 days after last dose of last component of study treatment will be produced. By-subject listings of deaths will also be produced.

6.4.7 Clinical Laboratory Results

Summary statistics (mean, median, minimum, maximum, standard deviation) for actual value and change from baseline will be tabulated as appropriate for laboratory results.

Laboratory results were graded using CTCAE v5.0. Laboratory results collected after first dose date to 30 days after last dose date are considered as treatment emergent. Toxicities grades for both low and high are provided in **Table 6**.

Table 6: Toxicity Terms for Laboratory Parameters Graded for both High and Low values

Analyte	Term (high values)	Term (low values)
Calcium	Calcium high	Calcium low
Potassium	Potassium high	Potassium low
Sodium	Sodium high	Sodium low
Hemoglobin	Hemoglobin high	Hemoglobin low
Lymphocyte Count	Lymphocyte count high	Lymphocyte count low
Magnesium	Magnesium high	Magnesium low
WBC	White blood cell count high	White blood cell low

Clinical Laboratory Summaries

- Hematology, coagulation, and biochemistry tests laboratory values at baseline and each post-baseline assessments, along with the change from baseline. The number of participants with missing clinical laboratory values at baseline and each post-baseline assessment will be included. Incidence of Grade ≥ 3 treatment emergent laboratory abnormalities
- Worst post-baseline toxicity grade shift since baseline for treatment emergent laboratory abnormalities

Both the scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

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Abnormal hepatic laboratory values will be identified and flagged for all post-baseline assessments:

- Alanine aminotransferase (ALT) > 5 x Upper Limit of Normal (ULN)
- Aspartate aminotransferase (AST) > 5 x ULN
- AST or ALT > 3 × ULN and ≤ 5 × ULN
- Total bilirubin > 2 × ULN
- For potential Drug-Induced Liver Injury (DILI): AST or ALT

  > 3 × ULN and total bilirubin > 2 × ULN
- Potential for Hy's Law case criteria: AST or ALT > 3 × ULN and total bilirubin > 2 × ULN and Alkaline Phosphatase (ALP) < 2 × ULN.
- ALP > 2 × ULN

Listings of select laboratory results may be produced for all subjects by nominal visit and where appropriate, may include the change from baseline, laboratory toxicity grade, and reference range. Each abnormal value will be flagged to show whether it is a value below or above the reference range.

6.4.8 Cardiac Function

The frequency of ECG abnormalities (e.g., heart rate, PR interval, QRS complex, and QTcF) will be summarized using counts and percentages. In addition, the percentage of subjects with LVEF abnormalities will be summarized.

ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) will be summarized for each scheduled ECG and shifts from baseline will be tabulated.

6.4.8.1 Left Ventricular Ejection Fraction

The following left ventricular ejection fraction (LVEF) endpoints will be summarized using counts and percentages.

- LVEF result at baseline (< 50%, ≥ 50%, No Baseline value)
- Minimum LVEF result post-baseline (< 50%, ≥ 50%, No Post-baseline value)
- Change from baseline for minimum post-baseline LVEF result (Increase or no change, <10% decrease, ≥ 10% decrease)
- Any post-baseline LVEF result that is < 50% with a decrease of ≥ 10% from the baseline result (Criteria 1)

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In addition, a shift table based on the < 50% and ≥ 50% cut-offs will be used to summarize changes of the baseline LVEF values against the lowest on-treatment values.

6.4.8.2 ECGs

Electrocardiogram (ECG) interpretations (e.g., normal or abnormal) will be summarized using counts and percentages at screening, Cycle 1 Day 1, Cycle 4 Day 1, EOT, and 30-day follow-up. On Cycle 1 Day 1 and Cycle 4 Day 1, ECGs will be summarized by predose, at 1 hour after the end of ZW25infusion, and 4 hours after the end of ZW25 infusion. For abnormal ECG the frequency of clinically significant findings will also be summarized using counts and percentages. The following QTc interval endpoints will be summarized using counts and percentages.

- QTc interval increase from baseline (<30 milliseconds, 30–60 milliseconds, and >60 milliseconds) during the treatment period
- QTc interval prolongation <450 msec, 450-480 msec, 480-500 msec and >500 msec during the treatment period

For both endpoints, the worst value for each patient during the treatment period will be summarized.

QTc interval prolongation will be provided in a listing. In addition, summary statistics (mean, quartiles, standard deviation and range) will be used to summarize other ECG outcomes by nominal timepoint.

On Cycle 1 Day 1 and Cycle 4 Day 1, ECGs will be done predose, at 1 hour after the end of ZW25 infusion, and 4 hours after the end of ZW25 infusion.

6.4.9 ECOG Performance Status

ECOG performance status over time will be listed by patient. The baseline status, best status post-baseline, worst status post-baseline, and status at end of treatment will be summarized using counts and percentages.

Shifts from baseline to the best and worst post baseline score may be tabulated.

6.4.10 Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be summarized using descriptive statistics (i.e., mean, quartiles, standard deviation, and range) for minimum and maximum values post baseline.

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6.5 Immunogenicity Analyses

All immunogenicity analyses will be based on the immunogenicity analysis set. Anti-drug antibody (ADA) responses to zanidatamab will be assessed. Subjects developing an ADA response to Zanidatamab will be listed. Subjects 'positive' in Tier 1 (screening assay) and Tier 2 (confirmation assay) will be listed along with their Tier 3 (titration) ADA titers. The presence or absence of anti-zanidatamab neutralizing antibodies will be listed and summarized as well, if available.

For zanidatamab, the occurrence of ADA, time of onset of ADA, duration of ADA detection, will be summarized using counts and percentages by combination therapy group, nominal time point.

- Occurrence of ADA: ADA incidence is the sum of both treatment-induced and treatment boosted ADA-positive subjects as a proportion of the immunogenicity set. When determining post-baseline incidence, subjects are considered to be ADA positive if they are initially ADA negative at baseline and test positive for ADAs following study drug exposure ("treatment-induced ADA response"), or if they are ADA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater than the titer of the baseline sample ("treatment-enhanced ADA response"). Subjects are considered to be ADA negative if they are ADA negative at baseline and all post-baseline samples are negative, or if they are ADA positive at baseline but do not have any post-baseline samples with a titer that is at least 4-fold greater than the titer of the baseline sample ("treatment unaffected").
- Time of onset of ADA: refers to the time period between the first dose date and the first instance of treatment-induced ADA.
- Duration of ADA: Duration of ADA is also monitored and identified as either "transient" (ADA positive result detected at only one post-baseline sampling timepoint [excluding last timepoint] or at 2 or more timepoints during treatment or safety follow-up where the first and last ADA positive samples are separated by a period of <16 weeks, irrespective of any negative samples in between) or "persistent" (ADA positive result detected at the last post-baseline sampling timepoint or at 2 or more timepoints during treatment or safety follow-up where the first and last ADA positive samples are separated by a period ≥16 weeks, irrespective of any negative samples in between.

Titers for confirmed positive ADA will be summarized using descriptive statistics (n, arithmetic mean, geometric mean, median, standard deviation, range, coefficient of variance).

Additional analyses to evaluate the association between development of ADAs and adverse events may also be performed based on immunogenicity results.

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6.6 Pharmacokinetic Analyses

All PK analyses will be performed on the PK analysis set. At least 6 subjects from each combination and at each dose schedule will be assigned to an applicable extensive PK schedule. Further subjects will then be assigned to the sparse PK schedule.

6.6.1 General Considerations

Quantitative variables will be summarized using descriptive statistics, including n, arithmetic mean, SD, coefficient of variation (CV%), median, min, and max. Geometric statistics (mean and SD) will be included for PK concentrations and parameters, where applicable.

All plasma data will be reported and analyzed with the same precision as the source data provided by the bioanalytical laboratory regardless of how many significant figures or decimals the data carry. Derived PK parameters will be rounded for reporting purposes in by-participant listings. The rounded derived PK data will be considered the source data for the calculation of descriptive statistics and the statistical analysis. For most derived PK parameters, 3 significant digits will be used as the standard rounding procedure, with the following exceptions:

- Parameters directly derived from source data (e.g., maximum activity [Cmax]) will be reported and analyzed with the same precision as the source data.

- Parameters derived from actual elapsed sample collection times (e.g., time to maximum activity [tmax]) will be reported with the same precision as the actual elapsed sampling time value of the source data.

For the reporting of descriptive statistics, the arithmetic and geometric means and SDs, will be presented to one digit more precision than the source data. The min, median, and max will be presented to the same precision as the source data. Coefficients of variation will always be reported to 1 decimal place.

6.6.2 Serum Concentrations

Serum concentrations of zanidatamab will be summarized using descriptive statistics (i.e., n, arithmetic mean, geometric mean, median, standard deviation, range, coefficient of variance) by treatment assignment, dose, and Part. Tabulations and graphs such as mean plots will be presented.

6.6.3 Pharmacokinetic Parameters

Serum PK parameters for Zanidatamab will be generated using non-compartmental analysis using Phoenix WinNonlin software (Certara USA, Inc., Princeton, NJ). For each subject, the parameters listed below will be reported when there is sufficient data available to support the accurate estimation of the parameter based on actual sample collection times.

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The following PK parameters will be derived for single dose using extensive PK sampling data after dose 1 for Q2W and Q3W dosing:

- Cmax,1: maximum observed serum concentration for dose 1
- tmax,1: time to maximum observed serum concentration for dose 1
- AUC0-t: area under the serum concentration-time curve from zero to the last measurable concentration for dose 1
- λz: terminal elimination rate constant
- t½: apparent elimination half-life
- AUC0-∞: area under the serum concentration-time curve from zero to infinity for dose 1
- CL: serum clearance
- Vz: volume of distribution in the terminal elimination phase

Elimination parameters will be calculated if data allow to meet standard PK acceptance.

The following PK parameters will be derived for multiple dose using PK sampling data after all doses for subjects in Part 1 and subjects with extensive PK sampling in Part 2 only:

- AUCtau: area under the serum concentration-time curve from zero to the last end of dosing interval for Dose 1
- Cave: average concentration over dosing interval, calculated as AUCtau/tau where tau is the dosing interval, for Dose 1

The following parameters will be derived and summarized for all subjects in all Parts using sparse sampling data.

- RCmin: accumulation index, calculated as Cmin(last dose)/Cmin(first dose)
- Cmin,ss: trough concentration at steady state

The following PK parameters will be determined for optional steady-state extensive sampling after Cycle 4: AUCtau,ss, Cave,ss, Cmin,ss, Cmax,ss, λz, t1/2, and Vz.

For PK parameter calculations, pre-dose samples that are BLQ or missing will be assigned a numerical value of zero. BLQ values embedded between 2 quantifiable data points will be treated as missing when calculating PK parameters. If a BLQ value occurs at the end of the collection interval (after the last quantifiable activity), it will be set to zero. If consecutive BLQ values are followed by quantifiable values in the terminal portion of the concentration curve, these quantified values will be excluded from the PK analysis by setting them to missing. Actual elapsed time from dosing will be used for PK parameter calculations.

6.6.4 Analysis of PK Parameters

The attainment of steady state will be determined by repeated measures analysis of variance (ANOVA) using aggregate assessment of trough concentrations.

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Dose proportionality and effect of type of cancer and/or concomitant chemotherapy may be assessed by appropriate statistical methods based on number of available data. Single dose PK parameters (Cmax, AUC0-∞, CL, etc) as well as multiple dose parameters such as Cmax,1; Cmin,1; and Css may be used in these analyses.

Details can be found in the PK analysis plan, the analysis may only be provided after final DBL.

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Approval

Role	Signature and Date
SAP Developer [redacted] Biostatistician, Biostatistics	[redacted]
SAP Reviewer [redacted] Director, Biostatistics	
SAP Reviewer [redacted] Senior Medical Director, Clinical Development	