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
Phase:	Phase 2
Investigational Product:	ZW25 (zanidatamab, JZP598)
US IND Number:	[redacted]
Sponsor:	Jazz Pharmaceuticals Ireland Limited Fifth Floor, Waterloo Exchange Waterloo Road Dublin 4 Dublin, Ireland D04 E5W7
US Sponsor Representative:	Jazz Pharmaceuticals, Inc 3170 Porter Drive Palo Alto, CA 94304
Medical monitor:	[redacted] MD, MBA Medical Director Jazz Pharmaceuticals Contact information appears in trial site binder (or equivalent)

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PROTOCOL APPROVAL SIGNATURE

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

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

[redacted] MD, MBA,
Medical Director
Jazz Pharmaceuticals

See Document Approval page for eSignature and date of approval

SYNOPSIS

Protocol Number: ZWI-ZW25-201	**Protocol Version:** Amendment 6; 16-OCT-2023
Phase: Phase 2	**Investigational Product:** ZW25 (zanidatamab, JZP598)
Sponsor: Jazz Pharmaceuticals Ireland Limited Fifth Floor, Waterloo Exchange Waterloo Road Dublin 4 Dubin, Ireland D04 E5W7	**US Sponsor Representative:** Jazz Pharmaceuticals, Inc 3170 Porter Drive Palo Alto, CA 94304

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)

Study Objectives and Endpoints

Part 1

Objectives	Endpoints
Primary:	
• 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 ZW25 when administered with combination chemotherapy	• Frequency of dose-limiting toxicities (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 left ventricular ejection fraction (LVEF) abnormalities • Frequency of dose reductions of ZW25 • Frequency of dose reductions of chemotherapy
Secondary:	
• To evaluate the antitumor activity of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment for HER2-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)

• To evaluate the pharmacokinetics (PK) of ZW25 when administered with combination chemotherapy	• Serum concentrations of ZW25 as a function of time post-dosing • ZW25 PK parameters for single (first) dose and multiple doses
Exploratory:	
▪ [redacted]	▪ [redacted]

Part 2

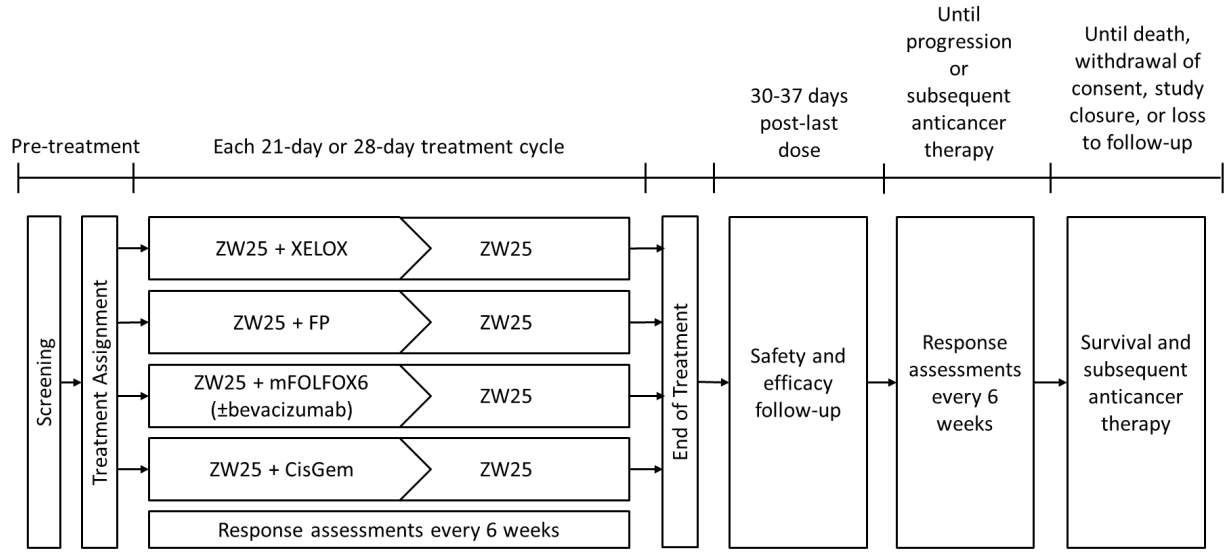
Objectives	**Endpoints**
Primary:	
• To evaluate antitumor activity of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment for HER2-expressing GEA, BTC, or CRC	• ORR
Secondary:	
• To further evaluate the antitumor activity of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment for HER2-expressing GEA, BTC, or CRC	• DCR • DOR • CBR • 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
• 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:	
• [redacted]	▪ [redacted]

Study Design

This is a multicenter, global, Phase 2, open-label, first-line, 2-part study to investigate the safety, tolerability, and antitumor activity of ZW25 plus standard 1st 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. A schematic of the overall study design and overview of study treatments is presented in the figure and table below.

Study Schema



Study Treatments

Indication	Chemotherapy Regimen	Cycle Length	ZW25 Administration		Chemotherapy Administration
			Dosing Days	Dose Calculation	
GEA	XELOX-1[a]	Q3W	D1	Weight-based	• Oxaliplatin D1 • Capecitabine D1-D15[b]
	XELOX-2			Flat	
	XELOX-3		D1, D8	Flat	
	FP-1[a]		D1	Weight-based	• Cisplatin D1 • 5-FU continuous IV infusion on D1-D5
	FP-2			Flat	
	mFOLFOX6-1[a]	Q4W	D1, D15	Weight-based	• Oxaliplatin D1, D15 • Leucovorin D1, D15 • 5-FU bolus D1, D15 • 5-FU continuous IV infusion on D1-D2 and D15-D16
	mFOLFOX6-2			Flat	• Oxaliplatin D1, D15 • Leucovorin D1, D15 • 5-FU continuous IV infusion on D1-D2 and D15-D16
BTC	CisGem	Q3W	D1	Flat	• Cisplatin D1, D8 • Gemcitabine D1, D8
CRC	mFOLFOX6-2	Q4W	D1, D15	Flat	• Oxaliplatin D1, D15 • Leucovorin D1, D15 • 5-FU continuous IV infusion on D1-D2 and D15-D16
	mFOLFOX6-2 with bevacizumab (or biosimilar)			Flat	• Bevacizumab (or biosimilar) D1, D15 • Oxaliplatin D1, D15 • Leucovorin D1, D15 • 5-FU continuous IV infusion on D1-D2 and D15-D16

Abbreviations: 5-FU = 5-fluorouracil; BTC = biliary tract cancer; CisGem = cisplatin and gemcitabine; CRC = colorectal cancer; FP = 5-FU and cisplatin; GEA = gastroesophageal adenocarcinoma; mFOLFOX6 = 5-FU plus oxaliplatin and leucovorin.

[a] Cohort closed to further enrollment

[b] Starting on the evening of Day 1 and continuing through the morning of Day 15

Note: On the days of ZW25 dosing, ZW25 will be administered first. The chemotherapy components will be administered in the usual order per institutional standards.

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

- XELOX, which consists of capecitabine plus oxaliplatin
- FP, which consists of fluorouracil (5-FU) plus cisplatin
- mFOLFOX6, which consists of 5-FU plus oxaliplatin and leucovorin

Seven variants of the XELOX, FP, and mFOLFOX6 regimens that differ primarily by the ZW25 dosing strategy 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, a globally recognized, multi-agent, first-line combination chemotherapy treatment. Two variants of mFOLFOX6, one with and one without bevacizumab (or biosimilar), are being tested in subjects with CRC.

For ZW25 combined with XELOX, FP, or CisGem, each treatment cycle is 21 days; For ZW25 in combination with FOLFOX6 with or without bevacizumab, each treatment cycle is 28 days. Following treatment discontinuation (see Treatment Duration section) and/or disease progression, whichever comes later, subjects will remain on study for survival follow-up during which they will be contacted approximately every 3 months (± 14 days) until death, withdrawal from the study, or study closure, whichever occurs first. Information about subsequent anticancer therapies initiated during follow up will be collected, if available.

The study is conducted in 2 parts. Part 1 of the study will evaluate the safety and tolerability of ZW25 plus standard first-line combination chemotherapy (XELOX, FP, mFOLFOX6 with or without bevacizumab (or biosimilar), or CisGem) and will confirm the RD of ZW25 when administered in combination with each of these multi-agent chemotherapy regimens. Then, Part 2 of the study will evaluate the antitumor activity of ZW25 plus combination chemotherapy in HER2-expressing GEA, BTC and CRC.

All subjects must be able to provide new tissue biopsies or archived tumor biopsies for central review. For both Parts 1 and 2, archival tumor biopsies obtained ≤ 6 months prior to screening may be used; otherwise, new biopsies are required unless archival biopsies > 6 months are approved by the medical monitor.

Subjects with GEA may be eligible to enroll in Part 1 based on local assessment of HER2 status using a United States Food and Drug Administration (US FDA) approved test, but archival tissues must be submitted for retrospective central review after enrollment. If a study site does not have the capacity to use an FDA-approved test, then a biopsy sample must be submitted for prospective central assessement before enrollment in Part 1.

Enrollment of subjects with GEA to Part 2 of the study will be based on prospective central assessment of HER2 status.

Enrollment of subjects with BTC or CRC to Parts 1 and 2 of the study will be based on prospective central assessment of HER2 status.

Part 1: Safety Evaluation

The primary objective of Part 1 is to characterize the safety and tolerability of ZW25 when administered with XELOX (only XELOX-1 was evaluated in Part 1; XELOX-2 and XELOX-3 are only in Part 2), FP, mFOLFOX6 with or without bevacizumab, or CisGem and to confirm the RD of ZW25 with each of these multi-agent chemotherapy regimens. To be eligible for Part 1 of the study, subjects must have a diagnosis of unresectable,

locally advanced, recurrent or metastatic HER2-expressing GEA, BTC, or CRC. Eligibility for Part 1 will be based on central or local assessment of HER2 status for GEA and on central assessment of HER2 status for BTC and CRC.

ZW25 and combination chemotherapy for Part 1 will be administered as described below. For all combination regimens being tested in Part 1, ZW25 will start at the initial recommended dose. Up to 2 step-down dose levels may be recommended by the Safety Monitoring Committee (SMC) if 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 protocol synopsis.

The number of subjects in each cohort in Part 1 is shown in the sample size determination table at the end of the synopsis. The SMC may increase the number of subjects in a cohort within the limits in this table.

Each chemotherapy regimen being studied will advance to Part 2 based on SMC recommendation with the exception of XELOX-2 and XELOX-3 which will be studied only in Part 2. Additional safety data from later cycles may be considered when confirming the RD of ZW25 with each of the combination chemotherapy regimens. The regimens to be tested in Part 2 are shown in the sample size determination table at the end of this synopsis.

Part 2: Antitumor Activity Evaluation

The primary objective of Part 2 of the study is to evaluate the potential antitumor activity of first-line treatment with ZW25 in combination with XELOX, FP, mFOLFOX6 with or without bevacizumab (or biosimilar), or CisGem in subjects with a diagnosis of HER2-expressing unresectable, locally advanced, recurrent or metastatic GEA, BTC, or CRC. Eligibility for Part 2 will be determined based on central assessment of HER2 status.

Enrollment for Part 2 will begin once an RD has been confirmed for at least one regimen in Part 1. However, subjects may only begin treatment in Part 2 with a regimen for which the RD has been identified. Because drug exposure ($C_{max,}$ AUC_{0-t}) for ZW25 in XELOX-1 is similar to or exceeds the predicted exposures for ZW25 doses planned for XELOX-2 and XELOX-3, the RDs for ZW25 in combination with XELOX-2 and XELOX-3 are considered established as safe by the RD for ZW25 in combination with XELOX-1. Therefore, XELOX-2 and XELOX-3 will be evaluated directly in Part 2 (i.e., not first in Part 1). Because expected ZW25 exposures for the initial ZW25 doses tested in FP-1 and FP-2 are nearly identical, Part 1 safety data for these Cohorts (2A and 2.1A) will be grouped together for determination of the ZW25 RD (flat dose) in combination with FP for Part 2. The RD for ZW25 in combination with mFOLFOX6-2 will be determined separately for GEA and CRC cohorts in Part 1 due to the potential for differential ZW25 exposure in different disease states. Similarly, the mFOLFOX6-2 with bevacizumab or bevacizumab biosimilar CRC cohort will also have a separate RD, as the addition of bevacizumab may alter the safety profile of ZW25.

ZW25 and combination chemotherapy for Part 1 will be administered as described below. For each combination regimen, ZW25 will be administered at the RD confirmed in Part 1 of the study. The treatment and blood collection schedules, treatment cycle duration, and imaging evaluation intervals for subjects in the various combination regimens are the same as in Part 1. Subjects must undergo at least one response assessment to be considered response evaluable.

If possible, an additional optional tumor biopsy may be obtained at the time of disease progression from an accessible site to allow for assessment of changes in HER2 expression and of other [redacted]

Study Population

Subjects must meet all of the enrollment criteria to be eligible for this study. All eligibility criteria are applicable to both parts of the study unless otherwise specified. Eligiblity criteria may not be waived by the investigator and are subject to review in the event of a Good Clinical Practice audit and/or health regulatory authority inspection.

Inclusion Criteria

1. Disease diagnosis:

a. Part 1:

   i) GEA: Unresectable, locally advanced, recurrent or metastatic HER2-expressing GEA (IHC 3+ or 2+ with or without gene amplification based upon local or central assessment using an FDA approved HER2 test for GEA)

   ii) BTC: Unresectable, locally advanced, recurrent or metastatic HER2-expressing BTC (including intrahepatic cholangiocarcinoma [ICC], extrahepatic cholangiocarcinoma [ECC], or gallbladder cancer [GBC]) (IHC 3+ with or without gene amplification; or IHC 0, 1+ or 2+ with gene amplification, based upon central assessment)

   iii) CRC: Unresectable, locally advanced, recurrent or metastatic HER2-expressing CRC (IHC 3+ with or without gene amplification; or IHC 0, 1+ or 2+ with gene amplification, based upon central assessment). Subjects' tumors will be required to be extended RAS (KRAS and NRAS) and BRAF wild-type based upon local or central assessment. If local assessment is used for eligibility, central confirmation is required (Exception: If the "FoundationOne CDx" test is used to perform this testing locally, the BRAF, KRAS, and NRAS results can be used to confirm eligibility for the study and no central testing will be required. Submit formal report of results for Sponsor review.)

b. Part 2:

   i) GEA: Unresectable, locally advanced, recurrent or metastatic HER2-expressing GEA (IHC 3+, or IHC 2+ and FISH+ by central assessment)

   ii) BTC: Same as Part 1

   iii) CRC: Same as Part 1

2. Able to provide a new formalin-fixed, paraffin-embedded tumor sample or archival tumor tissues (≤ 6 months) for evaluation of HER2 status and disease pathology prior to enrollment. Note that fine needle aspirates (FNAs; cytology samples) and biopsies from sites of bone metastases are not acceptable. Medical monitor approval for use of archival tissue > 6 months is necessary if a new biopsy is not feasible and more recent archival tumor material (≤ 6 months) is not available
3. Tumor measurements as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1:
   a. Part 1: Measurable or non-measurable disease
   b. Part 2: Measurable disease
4. Male or female, ≥ 18 years of age at the time of signing informed consent
5. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1
6. Adequate hepatic function, as follows:
   a. Aspartate aminotransferase (AST) ≤ 2.5 x the upper limit of normal (ULN) per institutional values (if liver metastases are present, ≤ 5 x ULN)
   b. Alanine aminotransferase (ALT) ≤ 2.5 x ULN per institutional values (if liver metastases are present, ≤ 5 x ULN)
   c. Total bilirubin ≤ 1.5 x ULN per institutional values (for Gilbert's Syndrome, total bilirubin ≤ 2.5 x ULN per institutional values)
7. Adequate renal function (serum creatinine ≤ 1.5 x ULN or calculated glomerular filtration rate ≥ 50 mL/min)
8. Hematological function, as follows:
   a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

b. Platelet count > 100 x 10^9/L (not requiring transfusion support)

c. Hemoglobin ≥ 9 g/dL (subjects with chronic anemia supported by intermittent red blood cell [RBC] transfusions are eligible)

d. Activated partial thromboplastin time (aPTT) < 1.5 x ULN except for subjects receiving therapeutic anti-coagulation who can enroll with approval of the medical monitor

9. Adequate cardiac left ventricular function, as defined by a LVEF ≥ institutional standard of normal

10. For subjects of childbearing potential, willingness to use 2 methods of birth control with a failure rate of less than 1% per year during the study and for 12 months (14 months if on a cisplatin-containing regimen) after the last dose of study treatment. These include, but are not limited to, established use of oral, implanted, or injected hormonal contraceptives; placement of intra-uterine device or intra-uterine system; or use of barrier methods such as condom or diaphragm together with a spermicide product.

11. Female subjects must agree not to breastfeed or donate ova starting at screening and throughout the study period, and for at least 12 months (14 months if on a cisplatin-containing regimen) after the final study drug administration

12. Male subjects must not donate sperm starting at screening and throughout the study period, and for at least 12 months after the final study drug administration

13. Signed informed consent prior to any study procedures (Note: After a subject consents to pre-screening, tumor samples may be sent to the central laboratory for analysis/review of HER2 status before the subject signs informed consent for all other study procedures)

Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Prior treatment with a HER2-targeted agent

2. Prior systemic anticancer therapy (including investigational products) except prior adjuvant/neoadjuvant therapy, which must be completed at least 6 months prior to first study treatment dosing. For subjects with BTC and CRC the following additional exceptions apply:

   a. BTC: subjects may have started therapy for advanced disease but may not have received more than one cycle of any standard gemcitabine-based chemotherapy regimen. Such cases require approval of the medical monitor.

   b. CRC: subjects may have started therapy for advanced disease but may not have received more than one cycle of 5-FU-based chemotherapy (<1 month of therapy). Such cases require approval of the medical monitor.

3. Subjects with CRC may not receive mFOLFOX6-2 with bevacizumab (or biosimilar) if they have any of the following contraindications to bevacizumab:

   a. History of thromboembolic disease within 6 months prior to enrollment

   b. History of stroke or transient ischemic attack

   c. History of significant proteinuria or urine protein to urine creatinine (UPC) ratio of >1

   d. Any history of a serious bleeding event

   e. Hemoptysis, hematochezia, or melena within 6 months prior to enrollment

   f. Unhealed surgical wounds, ulcers, or bone fractures

   g. History of bowel perforation or fistula within 6 months prior to enrollment

   h. History of intestinal obstruction, unless addressed by surgery

4. Palliative radiotherapy is allowed if completed at least 2 weeks prior to first study treatment dosing
5. Total lifetime anthracycline load exceeding 360 mg/m^2 adriamycin or equivalent
6. Use of corticosteroids administered at doses equivalent to > 15 mg per day of prednisone within 2 weeks of first study treatment dosing, unless otherwise approved by the medical monitor
7. Major surgery within 28 days before first study treatment dosing
8. Untreated known brain metastases (subjects with treated brain metastases who are off steroids, off antiseizure medications, and stable for at least 1 month at the time of screening are eligible)
9. Clinically significant cardiac disease, such as ventricular arrhythmia requiring therapy, uncontrolled hypertension or any history of symptomatic congestive heart failure (CHF). Subjects with known myocardial infarction or unstable angina within 6 months prior to randomization are also excluded. Previous anticancer therapy-related CHF must have been ≤ Grade 1 per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0) at the time of occurrence and must have completely resolved.
10. QTc Fridericia (QTcF) > 470 ms. For subjects with longer QTcF on initial electrocardiogram (ECG), follow-up ECG may be performed in triplicate to determine eligibility
11. Ongoing, clinically significant toxicity (Grade 2 or higher, per NCI-CTCAE v5.0) associated with prior cancer therapies, with the exception of alopecia
12. Acute or chronic uncontrolled renal disease, pancreatitis, or liver disease (with exception of subjects with Gilbert's Syndrome, asymptomatic gall stones, liver metastases, or stable chronic liver disease per investigator assessment)
13. Peripheral neuropathy > Grade 1 per NCI-CTCAE v5.0
14. Clinically significant interstitial lung disease
15. History of life-threatening hypersensitivity to monoclonal antibodies or to recombinant proteins or excipients in drug formulation
16. Known hypersensitivity to any components of combination chemotherapy, such that none of the chemotherapeutic regimens can be chosen
17. Prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen
18. Active hepatitis B or hepatitis C infection or infection with human Immunodeficiency Virus (HIV)-1 or HIV-2 (Exception: subjects with well-controlled HIV [e.g., CD4 > 350/mm^3 and undetectable viral load] are eligible)
19. Pregnant or breastfeeding women
20. History of noncompliance with medical regimens

Number of Subjects

Part 1:

GEA: Approximately 31 to 103 DLT-evaluable subjects

BTC: Approximately 6 to 42 DLT-evaluable subjects

CRC: Approximately 6 to 84 DLT-evaluable subjects

Part 2:

GEA: Approximately 43 evaluable subjects

BTC: Approximately 30 evaluable subjects

CRC: Approximately 60 evaluable subjects

Study Centers

Approximately 25 centers

Test Product, Dose, and Mode of Administration

ZW25 (investigational agent):

Part 1:

- ZW25 dose in XELOX-1 and FP-1
  - ZW25: 30 mg/kg IV Q3W; Day 1 of each 21-day cycle. Up to 2 step-down dose level(s) may be evaluated if recommended by the SMC and approved by the sponsor.
- ZW25 dose in FP-2 and CisGem
  - ZW25: 1800 mg (subjects < 70 kg) or 2400 mg (subjects ≥ 70 kg) IV Q3W; Day 1 of each 21-day cycle. Up to 2 step-down dose level(s) may be evaluated if recommended by the SMC and approved by the sponsor.
- ZW25 dose in mFOLFOX6-1 in GEA
  - ZW25: 20 mg/kg IV Q2W; Days 1 and 15 of each 28-day cycle. Up to 2 step-down dose levels to 15 and/or 10 mg/kg Q2W or an intermediate dose level of ZW25 may be evaluated if recommended by the SMC and approved by the sponsor.
- ZW25 dose in mFOLFOX6-2 in GEA and in mFOLFOX6-2 with or without bevacizumab (or biosimilar) in CRC
  - ZW25: 1200 mg (subjects < 70 kg) or 1600 mg (subjects ≥ 70 kg) IV Q2W; Days 1 and 15 of each 28-day cycle. Up to 2 step-down dose levels of ZW25 may be evaluated if recommended by the SMC and approved by the sponsor.

Part 2: RDs of ZW25 as confirmed in Part 1 of the study for each of the combination chemotherapy regimens.

- One RD (flat dose) is expected for ZW25 combined with FP-2, one RD (flat dose) is expected for ZW25 combined with mFOLFOX6-2 for GEA, one RD (flat dose) is expected for ZW25 combined with mFOLFOX6-2 for CRC, one RD (flat dose) is expected for ZW25 combined with mFOLFOX6-2 plus bevacizumab (or biosimilar) for CRC and one RD (flat dose) is expected for ZW25 combined with CisGem.
- An RD of 30 mg/kg IV Q3W has been established for ZW25 combined with XELOX-1 and is being used in Part 2. The ZW25 exposure (Cmax, AUC0-t) from this dose is similar to or exceeds that predicted for two additional ZW25 doses that the sponsor would like to test in combination with XELOX. Therefore, the following two ZW25 doses will be tested directly in Part 2 (i.e., without first going through Part 1):
  - ZW25 dose in XELOX-2: 1800 mg (subjects < 70 kg) or 2400 mg (subjects ≥ 70 kg) IV Q3W on Day 1 of each 21-day cycle.
  - ZW25 dose in XELOX-3: 900 mg (subjects < 70 kg) or 1200 mg (subjects ≥ 70 kg) IV on Days 1 and 8 of each 21-day cycle.

Combination chemotherapy Dose, and Mode of Administration

XELOX-1, XELOX-2, and XELOX-3 (combination chemotherapy):

○ Chemotherapy dose in XELOX-1, XELOX-2, and XELOX-3

Parts 1 and 2:

- Capecitabine 1000 mg/m^2 per oral (PO) bid (total daily dose of 2000 mg/m^2) starting on the evening of Day 1 and continuing through the morning of Day 15 of each 21-day cycle plus oxaliplatin 130 mg/m^2 IV Q3W on Day 1 of each 21-day cycle

FP-1 and FP-2 (combination chemotherapy):

○ Chemotherapy dose in FP-1 and FP-2

Parts 1 and 2:

- 5-FU 800 mg/m^2/day continuous IV infusion on Days 1–5 for a total of 4,000 mg/m^2 over 120 hours of each 21-day cycle plus cisplatin 80 mg/m^2 IV Q3W on Day 1 of each 21-day cycle

mFOLFOX6-1 (combination chemotherapy):

○ Chemotherapy dose in mFOLFOX6-1

Parts 1 and 2:

- 5-FU 400 mg/m^2 IV bolus, leucovorin 400 mg/m^2 IV, and oxaliplatin 85 mg/m^2 IV Q2W on Days 1 and 15 of each 28-day cycle
- 5-FU 1200 mg/m^2/day continuous IV infusion on Days 1-2 and 15-16 for a total of 2400 mg/m^2 over 48 hours Q2W on Day 1 and Day 15 of each 28-day cycle

***mFOLFOX6-2 (combination chemotherapy)*:**

○ Chemotherapy dose in mFOLFOX6-2

Parts 1 and 2:

- Oxaliplatin 85 mg/m^2 IV and leucovorin 400 mg/m^2 IV Q2W on Days 1 and 15 of each 28-day cycle
- 5-FU 1,200 mg/m^2/day continuous IV infusion on Days 1-2 and 15-16 for a total of 2400 mg/m^2 over 48 hours Q2W on Day 1 and Day 15 of each 28-day cycle

***mFOLFOX6-2/bevacizumab (combination chemotherapy)*:**

○ Chemotherapy dose in mFOLFOX6-2/bevacizumab (or biosimilar)

Parts 1 and 2:

- Oxaliplatin 85 mg/m^2 IV and leucovorin 400 mg/m^2 IV Q2W on Days 1 and 15 of each 28-day cycle
- 5-FU 1,200 mg/m^2/day continuous IV infusion on Days 1-2 and 15-16 for a total of 2400 mg/m^2 over 48 hours Q2W on Day 1 and Day 15 of each 28-day cycle
- Bevacizumab (or biosimilar) 5mg/kg IV on Day 1 and Day 15 of each 28-day cycle

***CisGem (combination chemotherapy)*:**

○ Chemotherapy dose in CisGem

Parts 1 and 2:

- Cisplatin 25 mg/m^2 IV on Days 1 and 8 of each 21-day cycle
- Gemcitabine 1,000 mg/m^2 IV on Days 1 and 8 of each 21-day cycle

Required Premedication

Immediately prior to dosing with ZW25, all subjects must receive prophylactic treatment with acetaminophen, diphenhydramine, and corticosteroid to prevent or minimize infusion reactions.

In addition, all subjects must receive prophylactic treatment with loperamide with the first cycle of chemotherapy, starting on Day 1 and continuing for at least 7 days, to prevent or minimize diarrhea.

Other additional premedications are recommended for each of the combination chemotherapy regimens per the prescribing information for the chemotherapeutic component.

Treatment Duration

For both parts of the study, subjects may continue on ZW25 until evidence of clinical disease progression, radiographically-confirmed disease progression as defined by RECIST version 1.1, unacceptable toxicity, investigator decision, consent withdrawal, start of a subsequent anticancer therapy, or study termination by the sponsor. Also, if a subject has not taken ZW25 for more than 4 weeks, he/she will be withdrawn from study treatment unless approval is obtained from the medical monitor to continue on study treatment.

Combination chemotherapy may be administered for the following durations:

- During the first 6 cycles: Discontinue chemotherapy only for evidence of clinical disease progression, radiographically-confirmed disease progression as defined by RECIST version 1.1, unacceptable toxicity, consent withdrawal, start of a subsequent anticancer therapy, or study termination by the sponsor.
- After Cycle 6, continuation of some or all components of combination chemotherapy is at the discretion of the investigator and the subject.

For both parts of the study, for subjects receiving FP or CisGem regimens, if any component of the combination chemotherapy is discontinued due to toxicity unrelated to ZW25, subjects may continue to receive the other component(s) of the combination chemotherapy regimen with ZW25.

For both parts of the study, for subjects receiving XELOX or mFOLFOX6 regimens, if oxaliplatin is discontinued due to toxicity unrelated to ZW25, subjects may continue to receive capecitabine (in XELOX) or 5-FU (in mFOLFOX6) with ZW25. However, if capecitabine or 5-FU is discontinued due to toxicity unrelated to ZW25, oxaliplatin should also be discontinued.

For both parts of the study, for subjects receiving the mFOLFOX6+bevacizumab (or biosimilar) regimen, if oxaliplatin is discontinued due to toxicity unrelated to ZW25, subjects may continue to receive 5-FU and bevacizumab with ZW25. However, if 5-FU is discontinued due to toxicity unrelated to ZW25, oxaliplatin should also be discontinued. Furthermore, if both oxaliplatin and 5-FU are discontinued, bevacizumab (or biosmiliar) should also be discontinued.

If, in the opinion of the investigator, all components of the combination chemotherapy regimen should be discontinued due to toxicity unrelated to ZW25, a subject may continue to receive treatment with ZW25 monotherapy. Subjects may not continue on combination chemotherapy alone on study if ZW25 is discontinued; however, subjects who discontinue treatment with ZW25 in either part of the study for any reason should enter long-term follow-up for survival.

Safety Assessments

Subject safety will be monitored at predetermined time points in both parts of the study by recording the type, frequency, and severity of AEs graded using NCI-CTCAE v5.0, including SAEs and deaths, clinical laboratory values (including hematology, coagulation, serum chemistry, and urinalysis), physical examination, vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature), body weight, ECOG performance status, 12-lead ECG, and echocardiogram or multiple gated acquisition scan (MUGA). AEs will be collected from the start of dosing of any study drug on Cycle 1 Day 1 through 30 days after last dose of study drug or prior to beginning the next course of anticancer therapy, whichever occurs sooner. Study protocol-related AEs will be collected from the time of informed consent. Treatment-emergent adverse events of special interest (AESIs) are infusion-related reactions, absolute decrease in LVEF of ≥ 16 percentage points from pre-treatment baseline or LVEF decrease below institutional lower limit of normal and ≥ 10 percentage points from pre-treatment baseline, and grade ≥ 2 heart failure (see Section 7.2.4 if institution does not define lower limit of normal). AESIs and SAEs should continue to be followed until resolution or return to baseline or study closure. The DLT-evaluation period is the first cycle of treatment for all Part 1 treatment regimens (i.e., 21 days for the XELOX, FP, and CisGem regimens but 28 days for the mFOLFOX6 regimens). Safety and study conduct will be monitored throughout the study by the SMC.

Efficacy Assessments

In both Parts 1 and 2 of the study, regardless of treatment regimen or disease diagnosis, computed tomography (CT) and/or magnetic resonance imaging (MRI) scans will be performed for tumor restaging every 6 weeks timed from Cycle 1 Day 1 during treatment and will be assessed according to RECIST version 1.1.

Pharmacokinetic and Immunogenicity Assessments

Serum concentrations of ZW25 will be measured as a function of time post-dosing. PK parameters to be estimated include the following: 1) for single (first) dose: C_{max}, t_{max}, AUC_{0-t}, λ_z, $t_{1/2}$, $AUC_{0-\infty}$, CL, V_z 2) for multiple doses: AUC_{tau}, C_{ave} for Dose 1, C_{max} and C_{min} (trough) for following doses, accumulation index, fluctuation ratio, C_{ss}, and attainment of steady state, and 3) for steady-state dosing: $AUC_{tau,ss}$, $C_{ave,ss}$, $C_{min,ss}$, $C_{max,ss}$, λ_z, $t_{1/2}$, and V_z. Sample collection at steady-state is optional, and steady-state PK parameters will only be estimated if sufficient data are collected. ADAs to ZW25 and possibly neutralizing antibodies will be measured, including frequency, time of onset, and duration of immunogenicity response.

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

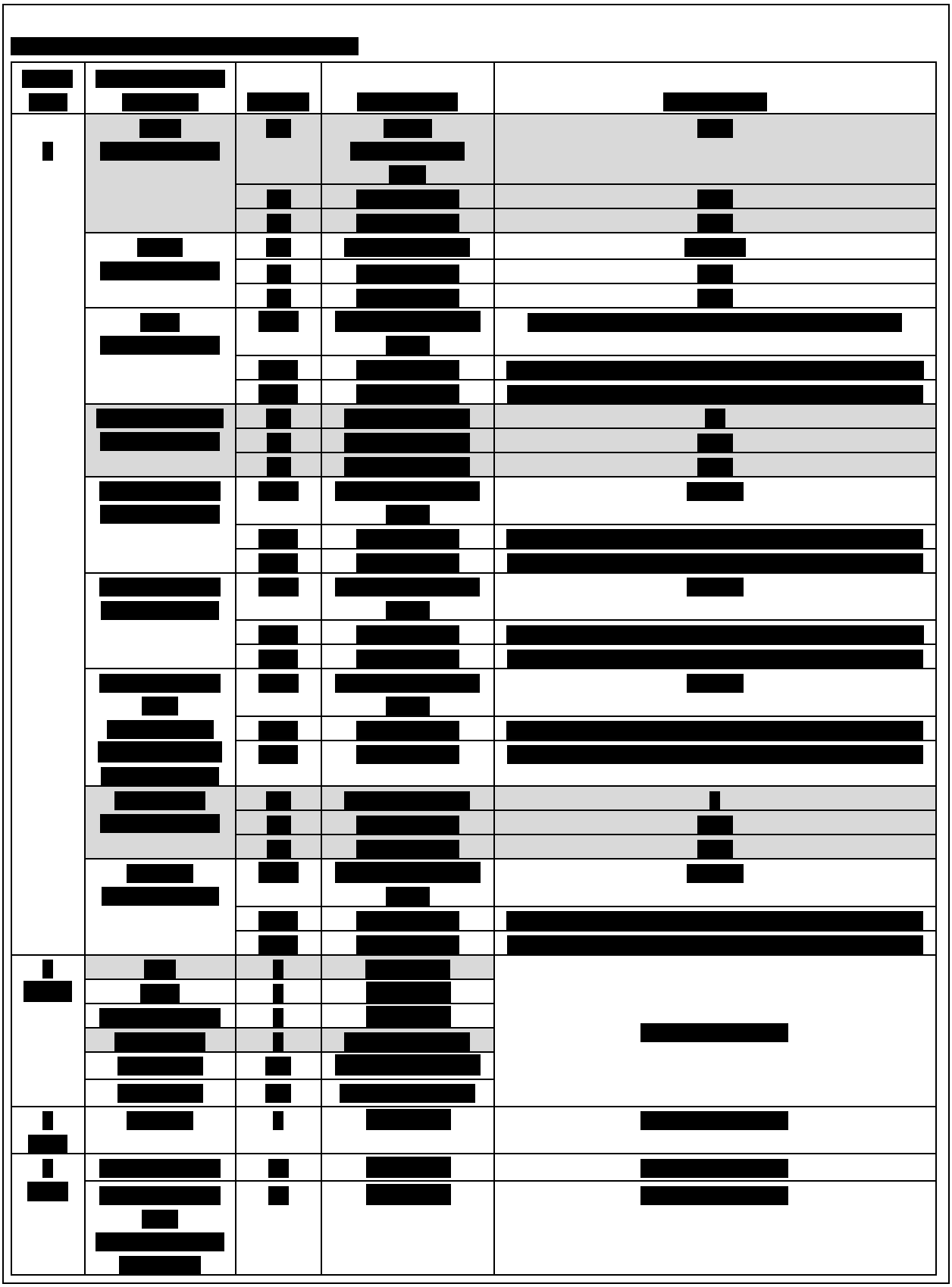
Statistical Analysis

Summaries of subject disposition, demographics, disease characteristics, safety, disease response, and exposure to each study drug will be provided. Analysis of safety and efficacy will be descriptive. Point estimates and corresponding 95% confidence intervals (95% CIs) will be calculated for disease response endpoints. In addition, the PK parameters of ZW25 will be estimated and summarized with descriptive statistics.

For the GEA cohorts in Part 2, the different chemotherapeutic combinations have similar predicted efficacy, and all subjects will be pooled into a single group for statistical analysis, regardless of combination received. The approximate sample size for the GEA cohort in Part 2 of the study is ■ evaluable subjects.

For the BTC cohort in Part 2, a single combination chemotherapy will be studied. The approximate sample size for the BTC cohort in Part 2 is 30 evaluable subjects.

For the CRC cohorts in Part 2, combination chemotherapy with or without bevacizumab may have different efficacy and each cohort will be evaluated separately. The approximate sample size for each CRC cohort in Part 2 is 30 evaluable subjects.



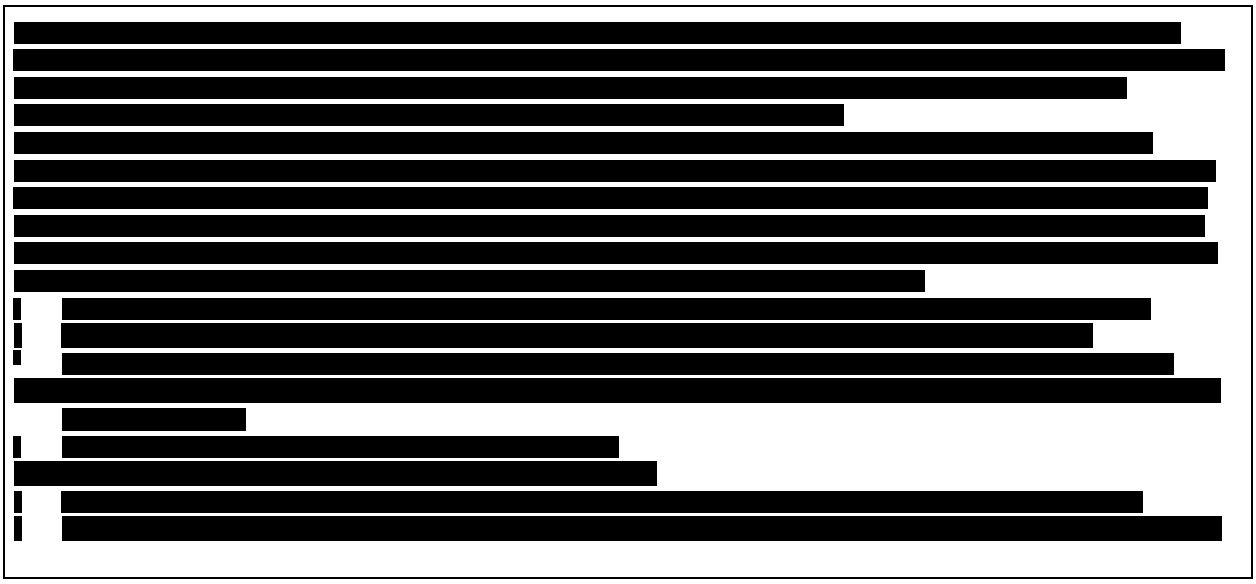


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LIST OF ABBREVIATIONS

λ_z	Terminal elimination rate constant
5-FU	Fluorouracil
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase (SGPT)
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AJCC	American Joint Committee on Cancer
aPTT	Activated partial thromboplastin time
ARDS	Adult respiratory distress syndrome
ASCO	American Society of Clinical Oncology
ASCP	American Society for Clinical Pathology
AST	Aspartate aminotransferase (SGOT)
ATE	Arterial thromboembolic event
$AUC_{0-\infty}$	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
AUC_{tau}	Area under the serum concentration-time curve during a dosage interval
Bid	Twice a day
B_{max}	Maximum binding capacity
BRAF	B-Raf proto-oncogene, serine/threonine kinase
BTC	Biliary tract cancer
BUN	Blood urea nitrogen
CAP	College of American Pathologists
C_{ave}	Average concentration over dosing interval
CBC	Complete blood count
CBR	Clinical benefit rate
CA 19-9	Carbohydrate antigen 19-9
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CisGem	Cisplatin plus gemcitabine
CL	Serum clearance
CLS	Capillary leak syndrome
CNS	Central nervous system
C_{max}	Maximum observed serum concentration
$C_{max,1}$	Maximum observed serum concentration for dose 1
C_{min}	Minimum observed serum concentration
CR	Complete response
CRC	Colorectal cancer
CrCL	Creatinine clearance by Cockcroft/Gault formula
CRF	Case report form
CRO	Contract Research Organization

$C_{min,ss}$	Trough concentration at steady state
CT	Computed tomography
CTC	Circulating tumor cells
ctDNA	Circulating tumor DNA
CTLA4	Cytotoxic T-lymphocyte associated protein 4
C_{trough}	Trough concentration
DCR	Disease control rate
dL	Deciliter
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DYPD	Dihydropyrimidine dehydrogenase
ECC	Extrahepatic cholaniocarcinoma
ECD	Extracellular domain
ECD2	Dimerization domain
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EOT	End of Treatment
EU	European Union
Fab	Fragment antigen-binding
Fc	Fragment crystallizable
FDA	Food and Drug Administration
FISH	Fluorescence *in situ* hybridization
FP	5-FU and cisplatin
GBC	Gall bladder cancer
GEA	Gastroesophageal adenocarcinoma
GCP	Good Clinical Practice
GEJ	Gastroesophageal junction
GFR	Glomerular filtration rate
GI	gastrointestinal
GLP	Good Laboratory Practice
H_0	Null hypothesis
Ha	Alternative hypothesis
HER	Human epidermal growth factor receptor
hIgG	Human immunoglobulin G
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell cancer
HR	Hazard ratio
HUS	Hemolytic uremic syndrome
IB	Investigator's Brochure
ICC	Intrahepatic cholangiocarcinoma
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IHC	Immunohistochemistry

INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ISH	In situ hybridization
IV	Intravenous
Kg	Kilogram
KRAS	KRAS proto-oncogene, GTPase
L	Liter
LVEF	Left ventricular ejection fraction
M	meter
MAPK	Mitogen-activated protein kinase
MCH	Mean cell hemoglobin
mCRC	Metastatic colorectal cancer
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	5-FU plus oxaliplatin and leucovorin
Mg	milligrams
MRI	Magnetic resonance imaging
mL	milliliter
Min	Minute
MSI	Microsatellite instability
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MUGA	Multiple gated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRAS	NRAS proto-oncogene, GTPase
NS	Normal saline
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PO	By mouth
PPE	Palmar/plantar erythema
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
QTcF	QT interval corrected according to Fridericia’s method
QW	Once weekly
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q6W	Every 6 weeks
RAS	RAS type GTPase family
RBC	Red blood cell

R_{Cmin}	Accumulation index
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiotherapy
SAE	Serious adverse event
SAP	Statistical analysis plan
scFv	Single-chain variable fragment
SD	Stable disease
SMC	Safety Monitoring Committee
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Apparent elimination half-life
T-DM1	Ado-trastuzumab emtansine
TEAE	Treatment-emergent adverse event
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
UPC	Urine protein to creatinine
US	United States
V_z	Volume of distribution in the terminal elimination phase
VEGFR2	Vascular endothelial growth factor receptor 2
VOD	Veno-Occlusive disease
VTE	Venous thromboembolic event
WHO	World Health Organization
XELOX	Capecitabine plus oxaliplatin
XP	Capecitabine plus cisplatin

1. INTRODUCTION

1.1. HER2

Human epidermal growth factor receptor 2 (HER2) is a member of the epidermal growth factor receptor (EGFR/ErbB) family comprising 4 structurally related receptors: HER1 (EGFR), HER2, HER3, and HER4. HER receptors are normally activated by binding to specific ligands, resulting in a conformational change that allows formation of receptor homodimers and heterodimers. Receptor dimerization triggers autophosphorylation of specific tyrosine residues and activation of intracellular signaling pathways. Over-expression and amplification drive tumorigenesis through the creation of spontaneous receptor homodimers or heterodimers with other ErbB family members, resulting in activated oncogenic downstream signaling such as phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK), which in turn promote cellular proliferation, survival and angiogenesis (Moasser 2007). HER2 is involved in the pathogenesis and outcomes of several types of cancer (Gravalos 2008) and agents targeting the HER2 receptor have clear clinical activity in breast cancer and gastric/gastroesophageal junction (GEJ) cancers, where they are Food and Drug Administration (FDA) approved for HER2-expressing disease (Bang 2010; Slamon 2001). Many other solid tumors show HER2 protein over-expression and/or HER2 gene amplification, including biliary tract cancer, colorectal cancer, non-small cell lung cancer, uterine cancer and bladder cancer (Meric-Bernstam 2019b) and it is anticipated that HER2-targeted therapies will have meaningful clinical activity outside of breast cancer and gastric/GEJ cancers.

1.2. Gastroesophageal Adenocarcinoma (GEA)

Gastroesophageal adenocarcinomas (GEAs), cancers that originate from the esophagus, GEJ, and stomach, continue to be a major cause of morbidity and mortality worldwide. According to the World Health Organization (WHO), International Agency for Research on Cancer, gastric cancer is globally the fifth most common malignancy, and the third leading cause of cancer deaths. Esophageal cancer is the seventh most common cancer worldwide and the sixth leading cause of cancer deaths. GEAs are approximately 20 times more prevalent in Eastern Asia than in North America (WHO 2018a; WHO 2018b).

1.2.1. HER2 Expression in GEA

As noted above, HER2 is involved in the pathogenesis of GEA. On average, 20% of GEAs are classified as HER2-expressing and this may be associated with poorer prognosis than non-HER2-expressing disease (Abrahao-Machado 2016; Creemers 2018; Gowryshankar 2014; Plum 2019; Yan 2015). HER2 expression is typically determined by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH), although several other methodologies are available. Per the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines, HER2 expression levels may be classified as 0, 1+, 2+ or 3+ by IHC depending upon the extent and pattern of staining, while HER2 gene amplification determined by FISH is classified as either positive or negative (Bartley 2017). To be classified as HER2-positive, GEAs must be either IHC 3+, or IHC 2+ with FISH-positivity.

1.2.2. Standard of Care Therapies for Advanced or Metastatic GEA

Metastatic GEA is generally incurable. While treatment can lead to improvements in progression-free survival (PFS) and overall survival (OS) the goals of therapy are primarily palliative. With first-line combination chemotherapy (usually a fluoropyrimidine and platinum agent), median OS is generally less than 1 year (Charalampakis 2018; Ghosn 2016; Ter Veer 2016). For patients with HER2-positive disease, the addition of trastuzumab, an anti-HER2 antibody, to standard first-line chemotherapy leads to improved outcomes compared with chemotherapy alone. Trastuzumab combined with chemotherapy (capecitabine or 5-fluorouracil [5-FU] in combination with cisplatin) was approved in 2010 by the Food and Drug Administration (FDA) for previously untreated patients with HER2-overexpressing metastatic GEAs arising from the stomach and/or GEJ. Approval was based on the ToGA Study, a Phase 3, randomized trial in 594 subjects, which showed that addition of trastuzumab to standard chemotherapy significantly improved OS compared with chemotherapy alone (median OS of 14 versus 11 months) (Bang 2010). Although this study did not include patients with GEAs arising from the esophagus, its results led to trastuzumab being incorporated into the National Comprehensive Cancer Network (NCCN) guidelines for treatment of these patients.

For patients who progress following first-line therapy, ramucirumab, a monoclonal antibody targeting vascular endothelial growth factor receptor 2 (VEGFR2), with or without paclitaxel has been approved in the United States (US) and the European Union (EU) as second-line therapy (CYRAMZA®). Immune checkpoint inhibitors, including agents targeting the programmed cell death-1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway have also shown promising activity in patients with GEA. In 2017, the anti-PD-1 antibody pembrolizumab received accelerated FDA approval for patients with PD-L1-expressing GEAs arising in the stomach and/or GEJ who had progressed after 2 or more lines of chemotherapy, and/or HER2-targeted therapy (KEYTRUDA®). Most recently, the antibody drug conjugate trastuzumab deruxtecan was approved in Japan for the treatment of HER2-positive gastric cancer that has progressed after chemotherapy.

Other than trastuzumab, trastuzumab deruxtecan, ramucirumab, and immunotherapies, targeted agents have not been approved for the treatment of GEA. Bevacizumab, epidermal growth factor receptor (EGFR) inhibitors, and c-MET inhibitors have all failed to show benefit in large Phase 3 trials, as have T-DM1, lapatinib, and the combination of pertuzumab and trastuzumab in HER2-high patients (Ghosn 2016; Tabernero 2018; Thuss-Patience 2017). Further development of additional HER2-targeted therapies is ongoing and remains a high-priority unmet medical need.

1.3. Biliary Tract Cancers

Biliary tract cancers (BTCs), including gallbladder cancer (GBC) and cholangiocarcinoma (CC) (both intrahepatic cholangiocarcinoma [ICC] and extrahepatic cholangiocarcinoma [ECC]), are poor prognosis malignancies that account for approximately 3% of all adult cancers (Valle 2017). The incidence and mortality rates of BTCs are increasing, mostly due to a rise in the incidence of ICC. Patients with resectable BTC are primarily treated with curative-intent surgery, but relapse rates are high. Unfortunately, approximately 65% of patients with BTC are diagnosed with non-resectable, and therefore incurable, disease. The 5-year survival rate is approximately

5% to 15% for all patients; the estimated 5-year survival rate varies by stage of disease: 50% for American Joint Committee on Cancer (AJCC) Stage I, 30% for Stage II, 10% for Stage III, and 0% for Stage IV (Valle 2017).

1.3.1. HER2 Expression in BTC

Several molecular alterations have been identified as potential drivers of BTC, including IDH1/2, FGFR2, BRAF, and HER2. In the case of HER2, preclinical models suggest HER2-expression leads to more aggressive disease and that HER2-targeted therapies may be effective (Kiguchi 2001; Nam 2016; Treekitkarnmongkol 2010). A systematic literature review and meta-analysis of published data suggests the prevalence of HER2 overexpression in BTC is ~25% (Galdy 2017), but this can differ by both intensity of staining and subtype. When only studies that defined HER2 overexpression as the presence of moderate/strong staining were considered, the mean prevalence of HER2 overexpression was highest for GBC (~20%), followed by ECC (~15%), and ICC (~5%). Studies evaluating HER2 amplification by FISH give similar results. However, the optimal combination of IHC and/or ISH results that define HER2-positive BTC remains to be defined.

1.3.2. Standard of Care Therapies for Advanced or Metastatic BTC

Unresectable or metastatic BTC has a poor prognosis, with median survival of approximately one year. The most active cytotoxic chemotherapeutics for advanced BTCs are gemcitabine- and platinum containing regimens (Eckel 2007; Tsavaris 2004). The current standard of care in the first-line setting was established by the ABC-02 Study, where cisplatin combined with gemcitabine (CisGem) improved overall survival (OS) and progression-free survival (PFS) compared to gemcitabine alone in advanced or metastatic BTC (median OS with CisGem was 11.7 months) (Valle 2010). These results were replicated in a randomized Phase 2 trial conducted in Japan (the BT22 Study) (median OS with CisGem was 11.2 months) (Okusaka 2010). In the second-line setting, the ABC-06 Study showed a modest benefit for mFOLFOX compared to active symptom control (median OS with mFOLFOX was 6.2 months vs. 5.3 months with active symptom control) (Lamarca 2019). Other than the ABC-06 trial, there are no other published randomized data in the second-line and later BTC setting.

Given the lack of highly effective cytotoxic chemotherapy treatments for advanced or metastatic BTC, there has been much interest in using targeted drugs for specific molecularly-defined BTC subpopulations. It is estimated that 50% of BTCs will have a potentially targetable molecular alteration, with the most common being IDH1/2 mutations, FGFR2 activating gene fusions, HER2 amplifications, and BRAF mutations. Targeted therapies are being developed and tested for each of these alterations, and the FGFR inhibitor pemigatinib was granted accelerated FDA approval in 2020 for patients whose tumors have FGFR2 fusions (Abou-Alfa 2020; PEMAZYRE™ 2020).

As noted above, approximately 25% of BTCs are HER2-expressing and HER2 targeted therapies have been tested in BTC. Lapatinib has been evaluated in both the first- and second-line setting but showed no significant evidence of antitumor activity in unselected populations of subjects with advanced BTC (Peck 2012; Ramanathan 2009). However, in a separate case series of 9

GBC and 5 CC subjects treated with HER2-targeted therapies (primarily trastuzumab, but also lapatinib, or pertuzumab) alone (n = 4) or with concurrent chemotherapy (n = 10), 4/9 GBC subjects (44.4%) had partial responses (PRs) and 1/9 GBC subject (11.1%) had a complete response (CR), equating to an ORR of 55.6% (Javle 2015). An additional 3 GBC subjects had stable disease (SD). The duration of response (DOR) ranged from 8 to 168 weeks (median 40 weeks). All 5 GBC subjects with objective responses had HER2 overexpression or amplification. Finally, the MyPathway trial studied pertuzumab and trastuzumab in a small cohort of patients with HER2-positive BTC and showed promising clinical activity, with an ORR of 29% (Hainsworth 2018). The clinical benefit of HER2-targeted agents may therefore be associated with HER2 amplification or over-expression, and a biomarker-based strategy is needed to select patients for HER2-directed therapies. Further development of additional HER2-targeted therapies is a high-priority unmet medical need.

1.4. Colorectal Cancers

Cancers of the colon and rectum (colorectal cancer or CRC) are common, with approximately 150,000 new cases per year in the USA and 1.8 million new cases worldwide. The majority of CRCs present at a localized or locoregional stage and are cured with surgery alone or with surgery followed by post-operative chemotherapy. However, approximately 20% of all CRC patients present with metastatic disease that is considered incurable with currently available therapies. Despite significant progress in the treatment of metastatic CRC (mCRC), including the development of effective multiagent chemotherapy regimens, novel biologic therapies, and expansion of treatments for oligometastatic disease, only one third of patients are alive two years after diagnosis of mCRC and only 15% are alive 5 years after diagnosis of mCRC. Molecular features of mCRC can guide both prognosis and therapy. Treatment guidelines suggest testing all metastatic tumors for microsatellite instability (MSI), extended RAS mutations, and BRAF mutation. Microsatellite instability (MSI), most commonly seen with Lynch syndrome but also present in sporadic tumors, is an indication for treatment with immunotherapy, which leads to extended survival in some patients. However, MSI is present in only ~7% of patients with mCRC. Mutations in RAS genes, seen in approximately 60% of patients, on the other hand, predict shorter survival, in part because these tumors do not respond to anti-EGFR targeted therapies. Finally, BRAF mutations, seen in ~10% of patients, predict aggressive disease biology with limited treatment options. Despite recent advances in targeted therapy for BRAF mutant cancers, survival of this molecular subtype is well below average for mCRC (Afrăsânie 2019).

1.4.1. HER2 Expression in CRC

HER2 expression is rare in CRC. It is estimated that 3-4% of all mCRC cancer samples show HER2-positivity. However, HER2-positivity is almost exclusively seen in RAS/BRAF wild type disease; HER2-positive disease within these RAS/BRAF wild type patients is estimated at 5-8%. For this reason, HER2 testing is generally recommended only in those patients who are known to be RAS/BRAF wild type. Standardized pathological criteria for HER2 expression were published in 2016 and can be used in clinical practice. This system, which is similar to that used for GEA, uses a combination of IHC and FISH (Valtorta 2015). Most clinical trials for HER2-positive mCRC are following these published criteria.

1.4.2. Standard of Care Therapies for Advanced or Metastatic CRC

The standard of care for the majority of patients with mCRC is multiagent chemotherapy in combination with biologic therapies. Fluoropyrimidines (fluorouracil (5-FU) or capecitabine) in combination with irinotecan and/or oxaliplatin are used in early lines of therapy. The anti-VEGFR antibody bevacizumab is typically added to these chemotherapy backbones to improve outcomes. Alternative biologic therapies target the EGFR pathway (the anti-EGFR antibodies cetuximab or panitumumab) and can be added to these chemotherapy backbones, but have minimal to no efficacy in right sided tumors and in tumors with RAS or BRAF mutations. In patients with RAS/BRAF wild type disease, anti-EGFR antibodies can be used in later lines of therapy if not used in the first line setting. Two agents with modest clinical activity, regorafenib and trifluridine/tipiracil, are reserved for late-line treatment.

While the above recommendations apply to most patients, several other molecularly defined subgroups are treated differently. Approximately 5% of patients with mCRC show deficient mismatch repair leading to microsatellite unstable tumors. These tumors are highly responsive to immunotherapeutic agents including anti-PD-1, anti-PD-L1, and anti-CTLA4 antibodies (Ganesh 2019). Another important molecular subset is BRAF mutant tumors, which have a poor prognosis with standard chemotherapy/biologic combinations, with short durations of disease control even with aggressive multi-agent regimens such as FOLFOXIRI with bevacizumab. However, promising data with BRAF inhibitors in combination with EGFR antibodies has recently been reported for this subgroup (Kopetz 2019).

While HER2 has long been recognized as a potential driver of CRC, the rarity of HER2 alterations in mCRC has compromised drug development and there remains limited data on the use of HER2-targeted therapies in HER2-positive mCRC. Two recent studies, the HERACLES trial and the MyPathway basket trial, demonstrated preliminary evidence of clinical benefit of HER2-targeted treatments in later lines of therapy for HER2-expressing mCRC, albeit in small numbers of patients (Meric-Bernstam 2019a; Sartore-Bianchi 2016). Both studies use the criteria in Section 1.4.1 to define HER2 positivity. Both trials were single arm studies and both tested dual HER2 blockade after at least one line of systemic therapy. In HERACLES, the combination of trastuzumab and lapatinib led to a disease control rate of 59%, modified PFS of 21 weeks and modified OS of 26 weeks. In the MyPathway trial, the combination of trastuzumab and pertuzumab led to similar results in the subset of patients with RAS wild type disease. Patients with RAS mutant disease did not appear to respond to HER2-targeted therapy in the MyPathway trial, suggesting that future trials should enroll only those patients with RAS wild type disease. While this data is promising, there is limited experience with HER2-targeted therapies in combination with standard chemotherapy or in the first line setting, and there is no approved treatment for HER2-expressing mCRC. Thus, this remains an unmet clinical need.

1.5. ZW25

ZW25 is a humanized, bispecific, IgG1-like antibody directed against the juxtamembrane extracellular domain (ECD4) and the dimerization domain (ECD2) of HER2, the same domains targeted by trastuzumab and pertuzumab, respectively. The structure of ZW25 drives unique mechanisms of action relative to trastuzumab, including increased binding to HER2 across

different expression levels (low to high), formation of receptor clusters, and increased receptor internalization resulting in greater down regulation. ZW25 also inhibits growth factor dependent and independent tumor cell proliferation as well as potently activating antibody-dependent cellular cytotoxicity. ZW25 therefore has the potential to have improved clinical activity compared with available HER2-targeted therapies across a range of HER2-expressing cancers, including in GEA, BTC, and CRC.

In preclinical models, ZW25 shows anticancer activity both as monotherapy and in combination with chemotherapy, where additive to synergistic effects were seen across various HER2-expressing cancer cell lines in vitro. ZW25 has also shown encouraging antitumor activity in clinical studies of subjects with heavily pre-treated HER2-expressing cancers, both as monotherapy (breast cancer, GEA, BTC, and CRC) and in combination with chemotherapy (breast cancer and GEA). ZW25 was generally well-tolerated, with the most common adverse events including diarrhea, infusion-related reactions, and fatigue.

A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human subjects is provided in the ZW25 Investigator's Brochure (IB).

1.5.1. Rationale for First-Line Treatment With ZW25 Plus Combination Chemotherapy in GEA, BTC, and CRC

HER2-expressing metastatic GEA, CRC and BTC are incurable cancers associated with poor prognosis and limited treatment options; there is a single HER2-targeted therapy approved for GEA and no HER2-targeted therapies approved for either CRC or BTC. ZW25 as a single agent and in combination with chemotherapy shows clinical activity in subjects with HER2-expressing GEA, and ZW25 as a single-agent shows clinical activity in subjects with HER2-expressing CRC and BTC. Furthermore, experience to date shows ZW25 to have an acceptable safety profile, both as a single agent and in combination with chemotherapy. Thus, ZW25 has the potential to provide clinical benefit to subjects with a range of HER2-expressing malignancies. This trial will evaluate the safety and preliminary antitumor activity of ZW25 combined with selected chemotherapy regimens in the first-line treatment of HER2-expressing GEA, CRC, and BTC.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Part 1 Objectives and Endpoints

Objectives	Endpoints
Primary:	
• 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 ZW25 when administered with combination chemotherapy	• Frequency of DLTs • Frequency and severity of 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:	
• To evaluate the antitumor activity of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment for HER2-expressing GEA, BTC, or CRC	• ORR • DCR • DOR • Clinical Benefit Rate (CBR) • PFS • OS
• 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 pharmacokinetics (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:	
• [redacted]	• [redacted]

2.2. Part 2 Objectives and Endpoints

Objectives	Endpoints
Primary:	
• To evaluate antitumor activity of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment for HER2-expressing GEA, BTC, or CRC	• ORR
Secondary:	
• To further evaluate the antitumor activity of ZW25 when administered with combination chemotherapy in subjects receiving first-line treatment for HER2-expressing GEA, BTC, or CRC	• DCR • DOR • Clinical Benefit Rate (CBR) • 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 in combination 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:	
• [redacted]	• [redacted]

3. INVESTIGATIONAL PLAN

3.1. Summary of Study Design

This is a multicenter, global, Phase 2, open-label, first-line, 2-part study to investigate the safety, tolerability, and antitumor activity of ZW25 plus standard 1st 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. A schematic of the overall study design is presented in Figure 1 and an overview of study treatments is presented in Table 1.

Figure 1: Overall Study Design

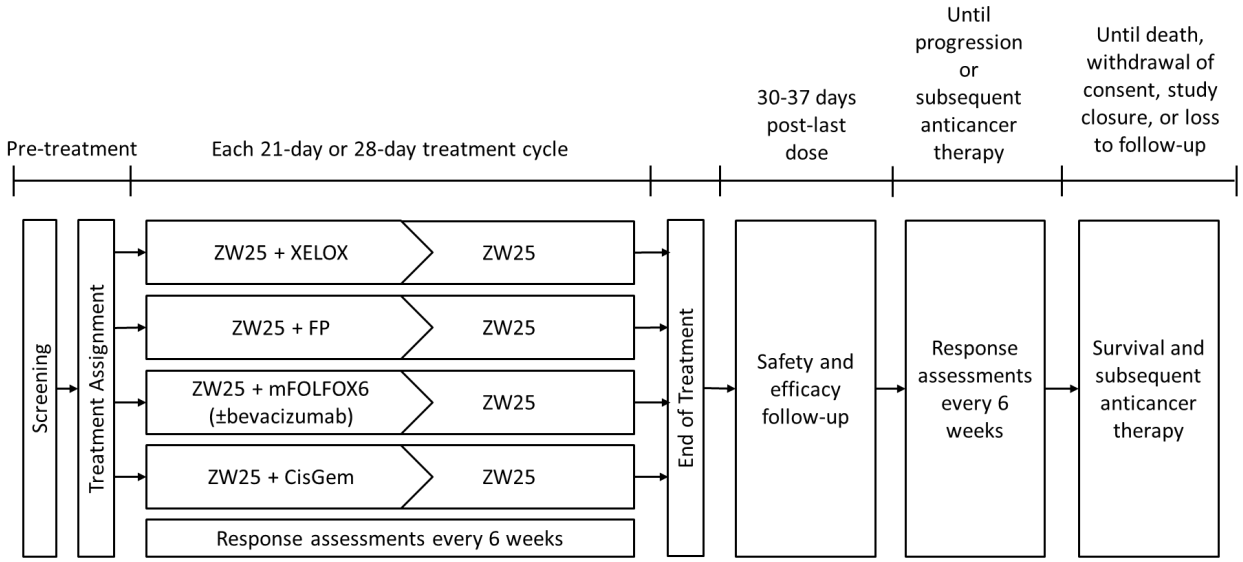


Table 1: Overview of Study Treatments

Indication	Chemotherapy Regimen	Cycle Length	ZW25 Administration		Chemotherapy Administration
			Dosing Days	Dose Calculation	
GEA	XELOX-1[a]	Q3W	D1	Weight-based	• Oxaliplatin D1 • Capecitabine D1-D15[b]
	XELOX-2			Flat	
	XELOX-3		D1, D8	Flat	
	FP-1[a]		D1	Weight-based	• Cisplatin D1 • 5-FU continuous IV infusion on D1-D5
	FP-2			Flat	
	mFOLFOX6-1[a]	Q4W	D1, D15	Weight-based	• Oxaliplatin D1, D15 • Leucovorin D1, D15 • 5-FU bolus D1, D15 • 5-FU continuous IV infusion on D1-D2 and D15-D16
	mFOLFOX6-2			Flat	• Oxaliplatin D1, D15 • Leucovorin D1, D15 • 5-FU continuous IV infusion on D1-D2 and D15-D16
BTC	CisGem	Q3W	D1	Flat	• Cisplatin D1, D8

					• Gemcitabine D1, D8
CRC	mFOLFOX6-2	Q4W	D1, D15	Flat	• Oxaliplatin D1, D15 • Leucovorin D1, D15 • 5-FU continuous IV infusion on D1-D2 and D15-D16
	mFOLFOX6-2 with bevacizumab or biosimilar			Flat	• Bevacizumab (or biosimilar) D1, D15 • Oxaliplatin D1, D15 • Leucovorin D1, D15 • 5-FU continuous IV infusion on D1-D2 and D15-D16

Abbreviations: 5-FU = 5-fluorouracil; BTC = biliary tract cancer; CisGem = cisplatin and gemcitabine; CRC = colorectal cancer; FP = 5-FU and cisplatin; GEA = gastroesophageal adenocarcinoma; mFOLFOX6 = 5-FU plus oxaliplatin and leucovorin.

[a] Cohort closed to further enrollment

[b] Starting on the evening of Day 1 and continuing through the morning of Day 15

Note: On the days of ZW25 dosing, ZW25 will be administered first. The chemotherapy components will be administered in the usual order per institutional standards.

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

- XELOX, which consists of capecitabine plus oxaliplatin
- FP, which consists of fluorouracil (5-FU) plus cisplatin
- mFOLFOX6, which consists of 5-FU plus oxaliplatin and leucovorin

Seven variants of the XELOX, FP, and mFOLFOX6 regimens that differ primarily by the ZW25 dosing strategy 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, a globally recognized, multi-agent, first-line combination chemotherapy treatment. Two variants of mFOLFOX6, one with and one without the anti-VEGF monoclonal antibody bevacizumab (or bevacizumab biosimilar), are being tested in subjects with CRC.

Detailed descriptions of each chemotherapeutic regimen are provided in Section 5.

The study is conducted in 2 parts. Part 1 of the study will evaluate the safety and tolerability of ZW25 plus standard first-line combination chemotherapy (XELOX, FP, mFOLFOX6 with or without bevacizumab [or biosimilar], or CisGem) and will confirm the RD of ZW25 when administered in combination with each of these multi-agent chemotherapy regimens (Section 3.1.1). Then, Part 2 of the study will evaluate the antitumor activity of ZW25 plus combination chemotherapy in HER2-expressing GEA, BTC and CRC (Section 3.1.2).

All subjects must be able to provide new tissue biopsies or archived tumor biopsies for central assessment. For both Parts 1 and 2, archival tumor biopsies obtained ≤ 6 months prior to screening may be used; otherwise, new biopsies are required unless archival biopsies > 6 months are approved by the medical monitor. Subjects with GEA may be eligible to enroll in Part 1 based on local assessment of HER2 status using a United States Food and Drug Administration

(US FDA) approved test, but archival tissues must be submitted for retrospective central review after enrollment. The two FDA-approved tests for assessment of gastric cancer HER2 status are the Hercept test (IHC) and the Dako HER2 FISH pharmDx (FISH) test. Status should be assessed using the College of American Pathologists/American Society for Clinical Pathology/American Society of Clinical Oncology guideline for HER2 testing and clinical decision making in GEA (Bartley 2017). If a study site does not have the capacity to use the FDA-approved tests, then a biopsy sample must be submitted for prospective central review before enrollment in Part 1. Enrollment of subjects with GEA to Part 2 of the study will be based on prospective central assessment of HER2 status. Enrollment of subjects with BTC or CRC to Parts 1 and 2 of the study will be based on prospective assessment of HER2 status by central assessment.

For ZW25 combined with XELOX, FP, or CisGem, each treatment cycle is 21 days; For ZW25 in combination with FOLFOX6 with or without bevacizumab (or biosimilar), each treatment cycle is 28 days. Assessment schedules for each combination treatment are presented in Appendix A (XELOX-1 and XELOX-2), Appendix B (XELOX-3), Appendix C (FP-1 and FP-2), Appendix D (mFOLFOX6-1 and mFOLFOX6-2), and Appendix E (CisGem). In both parts of the study, immunogenicity response will be assessed by detection of ADAs. The serum PK profile of ZW25 when administered with first-line combination chemotherapy, including drug concentration at each time point and derived PK parameters, will also be determined. PK sampling timepoints are presented in Appendix F (extensive sampling for ZW25 plus any XELOX, FP, or CisGem regimen), Appendix G (extensive sampling for ZW25+mFOLFOX6), Appendix H (sparse sampling for ZW25 plus any XELOX, FP, or CisGem regimen), and Appendix I (sparse sampling for ZW25+mFOLFOX6). For all regimens, at least 6 subjects from each combination and at each dose schedule will be assigned to an applicable extensive PK schedule. Further subjects will be then be assigned to the sparse PK schedule.

Regardless of the treatment regimen and in both Parts 1 and 2, computed tomography (CT) and/or magnetic resonance imaging (MRI) scans will be performed for tumor restaging every 6 weeks timed from Cycle 1 Day 1 during treatment and will be assessed according to the revised RECIST guideline version 1.1 (Eisenhauer 2009).

Subject safety will be monitored at predetermined time points in both study parts by recording the type, frequency, and severity of AEs graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 (v5.0), including SAEs and deaths, clinical laboratory values (including hematology, coagulation, serum chemistry, and urinalysis), physical examination, vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature), body weight, Eastern Cooperative Oncology Group (ECOG) performance status, 12-lead ECG, and echocardiogram or multiple gated acquisition scan (MUGA). Study protocol-related AEs will be collected from the time of informed consent. All AEs will be collected from the start of dosing of any study drug on Cycle 1 Day 1 through 30 days after last dose of study drug or prior to beginning the next course of anticancer therapy, whichever occurs sooner. Treatment-emergent adverse events of special interest (AESIs) should continue to be followed until resolution or return to baseline or study closure and include

infusion-related reactions, absolute decrease of ≥ 16 percentage points from pretreatment baseline or LVEF decrease below institutional lower limit of normal and ≥ 10 percentage points from pretreatment baseline, and grade ≥ 2 heart failure (see Section 7.2.4 if institution does not define lower limit of normal).

Safety and study conduct will be monitored throughout the study by the SMC, consisting of the study investigators and the sponsor responsible medical expert. The SMC will meet every 2 weeks (Q2W) while any treatment regimen producing data that will be used to determine a RD remains in Part 1, a minimum of once per quarter after all treatment regimens are either declared not for use in Part 2 (i.e., SMC decided that a ZW25 RD will not be established) or in Part 2 (i.e., ZW25 RD for Part 2 established), and on an ad hoc basis as needed.

For both parts of the study, subjects may continue on ZW25 until evidence of clinical disease progression, radiographically-confirmed disease progression as defined by RECIST 1.1, unacceptable toxicity, investigator decision, consent withdrawal, start of a subsequent anticancer therapy, or study termination by the sponsor. Clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers, or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes.

For both parts of the study, for subjects receiving XELOX or mFOLFOX6 regimens, if oxaliplatin is discontinued due to toxicity unrelated to ZW25, subjects may continue to receive capecitabine (in XELOX) or 5-FU (in mFOLFOX6) with ZW25. However, if capecitabine or 5-FU is discontinued due to toxicity unrelated to ZW25, oxaliplatin should also be discontinued.

For both parts of the study, for subjects receiving the mFOLFOX6+bevacizumab (or bevacizumab biosimilar) regimen, if oxaliplatin is discontinued due to toxicity unrelated to ZW25, subjects may continue to receive 5-FU and bevacizumab with ZW25. However, if 5-FU is discontinued due to toxicity unrelated to ZW25, oxaliplatin should also be discontinued. Furthermore, if both oxaliplatin and 5-FU are discontinued, bevacizumab should also be discontinued.

If in the opinion of the investigator, all components of the combination chemotherapy should be discontinued due to toxicity unrelated to ZW25, a subject may continue to receive treatment with ZW25 monotherapy. Subjects may not continue on combination chemotherapy alone on study if ZW25 is discontinued; however, subjects who discontinue treatment with ZW25 in either part of the study for any reason should enter long-term follow-up for survival.

Following treatment discontinuation and/or disease progression, whichever occurs later, subjects will subsequently remain on study for survival follow-up during which subjects will be contacted approximately every 3 months (± 14 days) until death, withdrawal from the study, or study closure, whichever occurs first. Information about subsequent anticancer therapies initiated during follow-up will be collected, if available.

3.1.1. Part 1: Safety Evaluation

The primary objective of Part 1 is to characterize the safety and tolerability of ZW25 when administered with XELOX (only XELOX-1 was evaluated in Part 1; XELOX-2 and XELOX-3

are only in Part 2), FP, mFOLFOX6 with or without bevacizumab (or biosimilar), or CisGem and to confirm the RD of ZW25 with each of these multi-agent chemotherapy regimens. To be eligible for Part 1 of the study, subjects must have a diagnosis of unresectable, locally advanced, recurrent or metastatic HER2-expressing GEA, BTC, or CRC. Eligibility will be determined based on local (institutional) review of disease pathology. Subjects with GEA may be eligible to enroll in Part 1 based on local assessment of HER2 status using a United States Food and Drug Administration (US FDA) approved test, but archival tissues must be submitted for retrospective central review after enrollment. If the local assessment cannot be based on an FDA approved HER2 test for GEA, then central assessment using such a test is required before a subject can be enrolled. Enrollment of subjects with BTC and CRC will be based on central assessment of HER2 status.

For all combination regimens being tested in Part 1, ZW25 will be administered IV at the initial recommended dose. For all regimens, up to 2 step-down dose levels (not less than 50% initial recommended dose for flat doses) may be recommended by the SMC and approved by the sponsor if DLTs related to study treatment are seen. Detailed information on the initial recommended doses and step-down doses are provided in Section 8.2. The DLT-evaluation period will be the first cycle of treatment (i.e., 21 days for XELOX, FP, and CisGem regimens; and 28 days for the mFOLFOX6 regimens)

The number of subjects in each Part 1 regimen/dose level is described in Table 30. The SMC may decide if more than 6 subjects (up to specified limits) may be enrolled in a given dose level to better characterize the safety profile in a combination regimen. Approximately 43 to 229 DLT-evaluable subjects are expected to be enrolled in Part 1.

Prior to dosing with ZW25, all subjects must receive prophylactic treatment with acetaminophen, diphenhydramine, and corticosteroid for infusion reactions (Section 5.1.10.1). All subjects receiving ZW25 in combination with chemotherapy require mandatory anti-diarrheal prophylaxis during Cycle 1 of treatment as described in Section 5.1.10.1. Additional premedications are recommended for each of the combination chemotherapy regimens per the prescribing information for the chemotherapeutic component (Sections 5.2.6.1, 5.3.6.1, 5.4.7.1, and Section 5.5.6.1).

The RDs of ZW25 when combined with each chemotherapeutic regimen will be confirmed based on DLT evaluation as described in Section 3.1.1.1.

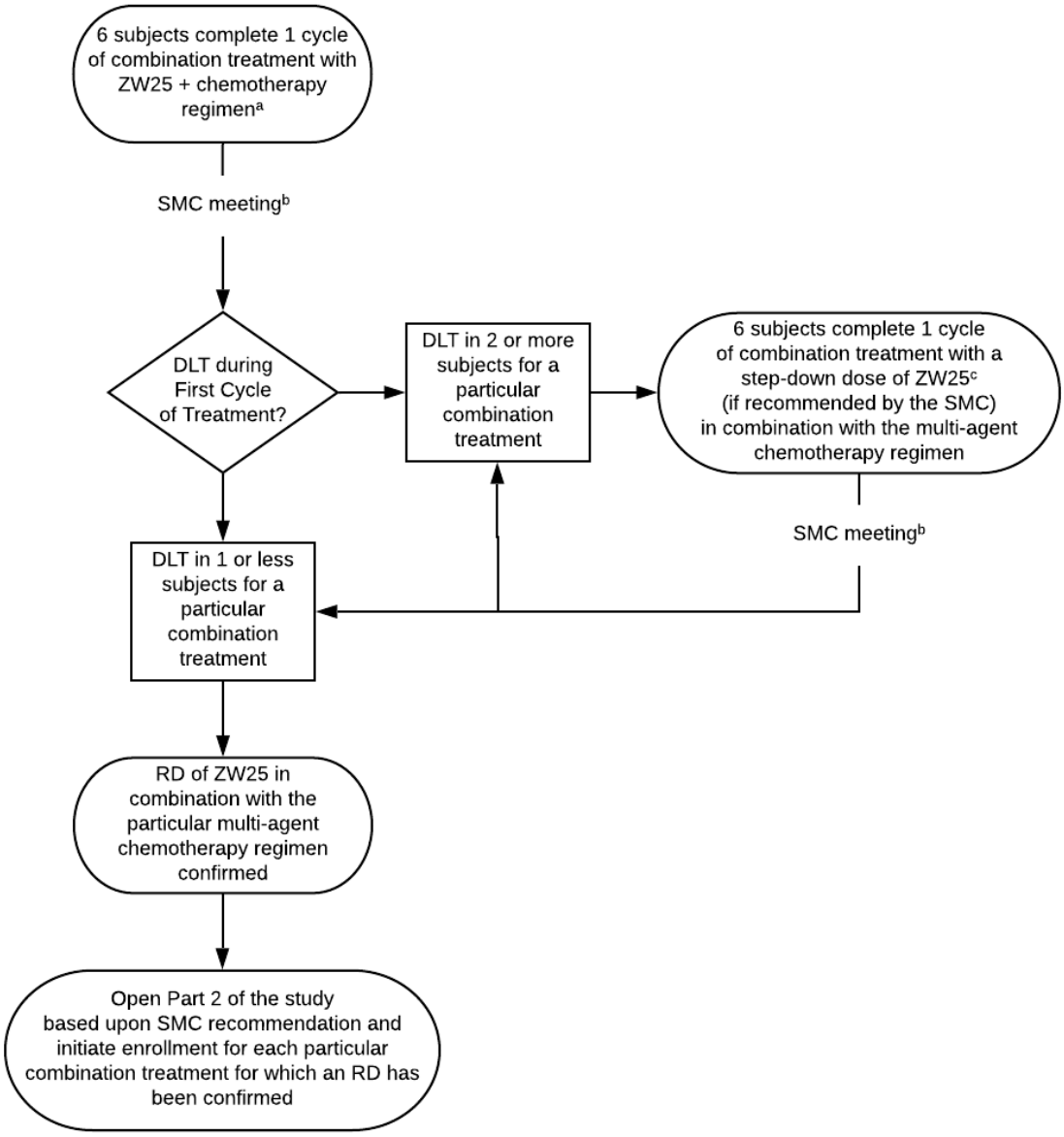
3.1.1.1. Dose-Limiting Toxicity Evaluation and Determination of Recommended Dose (Part 1 only)

For all treatment regimens, the DLT-evaluation period will be the first cycle of treatment (i.e., 21 days for the XELOX, FP, and CisGem regimens and 28 days for the mFOLFOX regimens).

In each of the treatment combinations, the treatment regimen will be considered not tolerated if ≥ 2 of 6 subjects experience a DLT. DLTs include AEs considered to be related to study treatment, including the evaluated dose level of ZW25, any component or combination of the

components of a chemotherapy regimen, or the combination of ZW25 plus a chemotherapy regimen using the definition in the NCI-CTCAE v5.0. If 2 or more subjects experience a DLT related to ZW25, a lower dose of ZW25 may be evaluated for that treatment regimen if recommended by the SMC. For all regimens, the dose of ZW25 is allowed to be de-escalated to a maximum of 2 step-down doses (not less than 50% initial recommended dose for flat doses) as recommended by the SMC and approved by the sponsor. At a reduced dose level, if 1 or fewer of the 6 subjects experience a DLT, then the RD of ZW25 may be confirmed for that reduced dose level in that combination regimen. When necessary, more than 6 subjects (within the limits specified in Table 30) may be enrolled in a given dose level to better characterize the safety profile in a combination regimen. The study will advance to Part 2 based on SMC recommendation. The DLT evaluation schema is presented in Figure 2. Additional safety data from later cycles may be considered when confirming the RDs of ZW25.

Figure 2: DLT Evaluation Schema (Part 1 Only)



[a] The DLT evaluation period is the first treatment cycle in all regimens, regardless of cycle length. Cycle length is 21 days for all XELOX, FP, and CisGem regimens, and 28 days for all mFOLFOX6 regimens.

[b] The SMC will meet every 2 weeks while any regimen that may produce data relevant to producing a RD for Part 2 is still in Part 1.

[c] Step-down dose levels of ZW25 as recommended by the SMC and approved by the Sponsor.

A subject will be considered DLT evaluable if he or she has received at least one dose of ZW25 plus chemotherapy. In the event that a subject receives only a partial dose due to reasons that do not meet DLT criteria, a minimum exposure of 75% of planned dose is required in order for that

subject to be evaluable for DLT. However, if the reason for not receiving 75% or more of the planned dose is a DLT, a subject will still be considered evaluable. To account for potential discontinuations prior to being evaluable for DLT (for example, progressive disease [PD] or subject preference), enrollment of replacement subjects will be allowed to permit assessment of ZW25 RD and DLTs (Section 8.2).

Events for which there is an alternative clinical explanation (e.g., clearly related to an intercurrent illness or disease progression) will not be considered DLTs. The relationship of Aes to each component of the study treatment will be determined by the investigator.

Non-Hematologic DLT Criteria

Any non-hematologic AE ≥ Grade 3 in severity is considered a DLT, with the following **exceptions**:

- Grade 3 fatigue lasting ≤ 3 days
- Grade 3 diarrhea, nausea, or vomiting that resolves to ≤ Grade 1 or baseline within 3 days with adequate supportive care
- Grade 3 rash without maximal use of corticosteroids
- Infusion reaction ≤ Grade 3 related to ZW25, or an infusion reaction of any grade related to any component of chemotherapy (for management of infusion reactions, see Section 5.1.5)

Grade 3 or 4 symptomatic laboratory abnormalities or those that require medical treatment are DLTs if not corrected within 72 hours of onset.

Concomitant ≥ Grade 3 ALT/AST and ≥ Grade 2 bilirubin increases (Hy's Law) will be considered DLTs (FDA 2009).

Any toxicities that are related to study treatment that do not resolve to ≤ Grade 1 or baseline within 2 weeks may be considered a DLT based upon review by the study SMC.

Greater than a 2-week delay in the start of Cycle 2 due to unresolved toxicity clearly related to study treatment will be considered a DLT.

Hematologic DLT Criteria

The following hematologic Aes are considered DLTs:

- Absolute neutrophil count (ANC) of Grade 3 or 4 with fever (fever must be present for the Grade 3 or 4 ANC to be considered a DLT, and is defined as a temperature of ≥ 38.5°C)
- ANC of < 500/μL for > 7 days
- Grade 3 thrombocytopenia associated with significant bleeding
- Grade 4 thrombocytopenia
- Grade 4 anemia

Cardiac DLT Criteria

The following cardiac Aes are considered DLTs:

- LVEF below institutional limits and absolute decrease ≥ 10 percentage points below pre-treatment baseline
- ≥ Grade 2 (symptomatic) heart failure

The first DLT will result in withholding of treatment until recovery of the ejection fraction to prior levels. For the management of left ventricular dysfunction, see Section 5.1.4.

Also, if a subject has not taken ZW25 for more than 4 weeks, he/she will be withdrawn from study treatment unless approval is obtained from the medical monitor to continue on study treatment.

Other

An AE will be considered to be a DLT if a ZW25 dose reduction is needed due to toxicity during the DLT period.

3.1.2. Part 2: Antitumor Activity Evaluation

The primary objective of Part 2 of the study is to evaluate the potential antitumor activity of first-line treatment with ZW25 in combination with XELOX, FP, mFOLFOX6 with or without bevacizumab (or bevacizumab biosimilar), or CisGem in subjects with a diagnosis of HER2-expressing unresectable, locally advanced, recurrent or metastatic GEA, BTC, or CRC. Eligibility for Part 2 will be determined based on central assessment of HER2 status.

Enrollment for Part 2 will begin once a RD has been confirmed for at least one regimen in Part 1. However, subjects may only begin treatment in Part 2 with a regimen for which the RD has been identified. For each combination regimen, ZW25 will be administered at the RD confirmed in Part 1 of the study. The treatment and blood collection schedules, treatment cycle duration and imaging evaluation intervals for subjects are the same as in Part 1. Subjects must undergo at least one response assessment to be considered response evaluable.

If possible, an additional optional tumor biopsy may be obtained at the time of disease progression from an accessible site to allow for assessment of changes in HER2 expression as well as the presence of other [redacted].

3.2. Safety Monitoring Committee

[redacted]

[redacted]

3.3. Discussion and Rationale for Study Design

Although ZW25 has been evaluated in other settings, its tolerability when administered as first-line therapy in combination with standard chemotherapeutic regimens in advanced or metastatic GEA, BTC, and CRC has not been established. Part 1 is designed to address the question of whether the single-agent RDs of ZW25 are tolerable when combined with standard first-line regimens. The starting ZW25 doses and schedules were selected based on clinical and nonclinical safety, PK and modeling data and to complement chemotherapy dosing schedules (see Investigator's Brochure for additional details). The modifications to the ZW25 doses/schedules in the XELOX-2, XELOX-3, FP-2, and mFOLFOX6-2 regimens (all opened by Protocol Amendment 4) compared with XELOX-1, FP-1, and mFOLFOX6-1 regimens (all closed to new subjects before or by Protocol Amendment 4) are based on population PK and exposure-response analyses using interim data from Phase 1 Study ZWI-ZW25-101 (see the ZW25 Investigator's Brochure for details). The change from weight-based to flat ZW25 doses/regimens are designed to simplify dosing and to reduce the amount of drug wastage while maintaining safety, PK, and efficacy. The flat ZW25 dosing on Days 1 and 8 of a 21-day treatment cycle (XELOX-3) is designed to reduce C_{max}, maintain AUC_{tau}, and achieve higher $C_{min,1}$ and $C_{min,ss}$ values compared with an equivalent total dose administered once every 21 days (XELOX-2).

For subjects with GEA, standard-of-care first-line chemotherapy regimens include mFOLFOX6, XELOX, and FP. In the US, mFOLFOX6 is most commonly used, whereas in the rest of the world, XELOX and FP are more commonly used. For subjects with BTC and CRC, the CisGem and mFOLFOX6 (with or without bevacizumab or biosimilar) regimens, respectively, are established worldwide standard-of-care first-line chemotherapy regimens. Because the toxicity profiles of these various chemotherapeutic regimens are different, their safety profiles can potentially be different when combined with ZW25. Therefore, Part 1 of this study is designed to evaluate the safety and tolerability of each specific chemotherapeutic regimen in combination with ZW25 within each specific disease group.

Data gathered from the first GEA cohort receiving the mFOLFOX6-1 plus ZW25 regimen in Part 1 revealed multiple episodes of Grade 2 and Grade 3 diarrhea during the first treatment cycle leading to dose modifications in subsequent cycles. Based on these findings, the SMC felt the initial recommended dose of ZW25 in combination with mFOLFOX6-1 was not tolerated in subjects with GEA and that the mFOLFOX6-1 regimen should not proceed to Part 2. Instead, the mFOLFOX6-2 plus ZW25 regimen, which omits the 5-FU bolus dose on Days 1 and 15 from the original mFOLFOX6-1 regimen, will be tested in Part 1 (elimination of the 5-FU bolus dose on Days 1 and 15 is a standard dose modification used to decrease diarrhea associated with mFOLFOX6). Given the toxicity seen with mFOLFOX6-1 plus ZW25 in the GEA cohort, the Part 1 CRC cohorts will receive mFOLFOX6-2 plus ZW25, as well. Furthermore, because bevacizumab (or biosimilar) can potentiate the toxicities of chemotherapy in subjects with CRC, safety of mFOLFOX6-2 plus ZW25 without bevacizumab (cohort 3.2) will be established prior to opening enrollment to mFOLFOX6-2 plus ZW25 with bevacizumab (cohort 3.3).

After the RDs of ZW25 in combination with each of the chemotherapeutic regimens are established in Part 1, Part 2 will evaluate the preliminary antitumor activity of ZW25 combined with each of the first-line chemotherapy regimens. Although different first-line chemotherapies are used in different parts of the world to treat GEA, to date there are no known meaningful differences in their antitumor efficacies (Al-Batran 2008; Hwang 2017; Kang 2017) and it is reasonable to combine them for analysis. Thus, overall combined efficacy measures, including an overall combined ORR, will be based upon the entire Part 2 study population for subjects with GEA. For subjects with CRC, efficacy of ZW25 in combination with mFOLFOX6-2 with bevacizumab (or biosimilar) will be evaluated independently from ZW25 plus mFOLFOX6-2 without bevacizumab. For additional details regarding the statistical analyses, See Section 8.4.

3.3.1. Method of Assigning Subjects to Treatment Groups

In Part 1, investigators may enroll an eligible subject into any chemotherapy combination based upon their local treatment practices, as long as the combination is open for enrollment.

In Part 2, while investigators may enroll an eligible subject into any chemotherapy combination that is open for enrollment, the sponsor may prioritize enrollment to certain cohorts. Such prioritization will be communicated to investigators at regular SMC calls or through other communications.

3.3.2. Blinding and Randomization

This is an open-label study. No blinding or randomization will be performed.

4. SELECTION OF STUDY POPULATION

4.1. Eligibility Criteria

Subjects must meet all of the enrollment criteria to be eligible for this study. All eligibility criteria are applicable to both parts of the study unless otherwise specified. Eligibilty criteria may not be waived by the investigator and are subject to review in the event of a Good Clinical Practice (GCP) audit and/or health regulatory authority inspection.

4.1.1. Inclusion Criteria

1. Disease diagnosis:
    a. Part 1:
        i) GEA: Unresectable, locally advanced, recurrent or metastatic HER2-expressing GEA (IHC 3+ or 2+ with or without gene amplification based upon local or central assessment using an FDA-approved HER2 test for GEA)
        ii) BTC: Unresectable, locally advanced, recurrent or metastatic HER2-expressing BTC (including ICC, ECC, or GBC) (IHC 3+ with or without gene amplification; or IHC 0, 1+ or 2+ with gene amplification, based upon central assessment)
        iii) CRC: Unresectable, locally advanced, recurrent or metastatic HER2-expressing CRC (IHC 3+ with or without gene amplification; or IHC 0, 1+ or 2+ with gene amplification, based upon central assessment). Subjects' tumors will be required to be extended RAS (KRAS and NRAS) and BRAF wild-type based upon local or central assessment. If local assessment is used for eligibility, central confirmation is required (Exception: If the "FoundationOne CDx" test is used to perform this tesing locally, the BRAF, KRAS, and NRAS results can be used to confirm eligibility for the study and no central testing will be required. Submit formal report of results for Sponsor review).
    b. Part 2:
        i) GEA: Unresectable, locally advanced, recurrent or metastatic HER2-expressing GEA (IHC 3+, or IHC 2+ and FISH+ by central assessment)
        ii) BTC: Same as Part 1

iii) CRC: Same as Part 1

2. Able to provide a new formalin-fixed, paraffin-embedded tumor sample or archival tumor tissues (≤ 6 months) for evaluation of HER2 status and disease pathology prior to enrollment. Note that fine needle aspirates (FNAs; cytology samples) and biopsies from sites of bone metastases are not acceptable. Medical monitor approval for use of archival tissue > 6 months is necessary if a new biopsy is not feasible and more recent archival tumor material (≤ 6 months) is not available
3. Tumor measurements as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (see Appendix K):
   a. Part 1: Measurable or non-measurable disease
   b. Part 2: Measurable disease
4. Male or female, ≥ 18 years of age at the time of signing informed consent
5. An Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0 or 1
6. Adequate hepatic function, as follows:
   a. Aspartate aminotransferase (AST) ≤ 2.5 x the upper limit of normal (ULN) per institutional values (if liver metastases are present, ≤ 5 x ULN)
   b. Alanine aminotransferase (ALT) ≤ 2.5 x ULN per institutional values (if liver metastases are present, ≤ 5 x ULN)
   c. Total bilirubin ≤ 1.5 x ULN per institutional values (for Gilbert's Syndrome, total bilirubin ≤ 2.5 x ULN per institutional values)
7. Adequate renal function (serum creatinine ≤ 1.5 x ULN or calculated glomerular filtration rate (GFR) ≥ 50 mL/min)
8. Hematological function, as follows:
   a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   b. Platelet count > 100 x 10^9/L (not requiring transfusion support)
   c. Hemoglobin ≥ 9 g/dL (subjects with chronic anemia supported by intermittent red blood cell [RBC] transfusions are eligible)
   d. Activated partial thromboplastin time (aPTT) < 1.5 x ULN except for subjects receiving therapeutic anti-coagulation who can enroll with approval of the medical monitor
9. Adequate cardiac left ventricular function, as defined by a LVEF ≥ institutional standard of normal
10. For subjects of childbearing potential (see Section 4.2), willingness to use 2 methods of birth control with a failure rate of less than 1% per year during the study and for 12 months (14 months if on a cisplatin-containing regimen) after the last dose of study treatment. These include, but are not limited to, established use of oral, implanted, or injected hormonal contraceptives; placement of intra-uterine device or intra-uterine system; or use of barrier methods such as condom or diaphragm together with a spermicide product.

11. Female subjects must agree not to breastfeed or donate ova starting at screening and throughout the study period, and for at least 12 months (14 months if on a cisplatin-containing regimen) after the final study drug administration
12. Male subjects must not donate sperm starting at screening and throughout the study period, and for at least 12 months after the final study drug administration
13. Signed informed consent prior to any study procedures (Note: After a subject consents to pre-screening, tumor samples may be sent to the central laboratory for analysis/review of HER2 status before the subject signs informed consent for all other study procedures)

4.1.2. Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criteria are applicable:

1. Prior treatment with a HER2-targeted agent
2. Prior systemic anticancer therapy (including investigational products) except prior adjuvant/neoadjuvant therapy, which must be completed at least 6 months prior to first study treatment dosing. For subjects with BTC and CRC the following additional exceptions apply:
    a. BTC: subjects may have started therapy for advanced disease but may not have received more than one cycle of any standard gemcitabine-based chemotherapy regimen. Such cases require approval of the medical monitor.
    b. CRC: subjects may have started therapy for advanced disease but may not have received more than one cycle of 5-FU-based chemotherapy (<1 month of therapy). Such cases require approval of the medical monitor.
3. Subjects with CRC may not receive mFOLFOX6-2 with bevacizumab (or biosimilar) if they have any of the following contraindications to bevacizumab (or biosimilar):
    a. History of thromboembolic disease within 6 months prior to enrollment
    b. History of stroke or transient ischemic attack
    c. History of significant proteinuria or urine protein to urine creatinine (UPC) ratio of >1
    d. Any history of a serious bleeding event
    e. Hemoptysis, hematochezia, or melena within 6 months prior to enrollment
    f. Unhealed surgical wounds, ulcers, or bone fractures
    g. History of bowel perforation or fistula within 6 months prior to enrollment
    h. History of intestinal obstruction, unless addressed by surgery
4. Palliative radiotherapy is allowed if completed at least 2 weeks prior to first study treatment dosing
5. Total lifetime anthracycline load exceeding 360 mg/m^2 adriamycin or equivalent
6. Use of corticosteroids administered at doses equivalent to > 15 mg per day of prednisone within 2 weeks of first study treatment dosing, unless otherwise approved by the medical monitor

7. Major surgery within 28 days before first study treatment dosing
8. Untreated known brain metastases (subjects with treated brain metastases who are off steroids, off antiseizure medications, and stable for at least 1 month at the time of screening are eligible)
9. Clinically significant cardiac disease, such as ventricular arrhythmia requiring therapy, uncontrolled hypertension or any history of symptomatic congestive heart failure (CHF). Subjects with known myocardial infarction or unstable angina within 6 months prior to randomization are also excluded. Previous anticancer therapy-related CHF must have been ≤ Grade 1 per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0) at the time of occurrence and must have completely resolved.
10. QTc Fridericia (QTcF) > 470 ms. For subjects with longer QTcF on initial electrocardiogram (ECG), follow-up ECG may be performed in triplicate to determine eligibility
11. Ongoing, clinically significant toxicity (Grade 2 or higher, per NCI-CTCAE v5.0) associated with prior cancer therapies, with the exception of alopecia
12. Acute or chronic uncontrolled renal disease, pancreatitis, or liver disease (with exception of subjects with Gilbert's Syndrome, asymptomatic gall stones, liver metastases, or stable chronic liver disease per investigator assessment)
13. Peripheral neuropathy > Grade 1 per NCI-CTCAE v5.0
14. Clinically significant interstitial lung disease
15. History of life-threatening hypersensitivity to monoclonal antibodies or to recombinant proteins or excipients in drug formulation
16. Known hypersensitivity to any components of combination chemotherapy, such that none of the chemotherapeutic regimens can be chosen
17. Prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of the investigational regimen
18. Active hepatitis B or hepatitis C infection or infection with human Immunodeficiency Virus (HIV)-1 or HIV-2 (Exception: subjects with well-controlled HIV [e.g., CD4 > 350/mm^3 and undetectable viral load] are eligible)
19. Pregnant or breastfeeding women
20. History of noncompliance to medical regimens

4.2. Childbearing Potential and Pregnancy

A person of childbearing potential is anyone

- Born female who has experienced menarche and who has not undergone surgical sterilization (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy) or has not completed menopause. Menopause is defined clinically as 12 months of amenorrhea in a person over age 45 years in the absence of other biological, physiological, or pharmacological causes.

- Born male who has testes and who has not undergone surgical sterilization (e.g., vasectomy followed by a clinical test proving that the procedure was effective).

According to the inclusion and exclusion criteria, pregnant or breastfeeding subjects cannot be included in the study, and adequate contraceptive measures should be taken to prevent female subjects of childbearing potential or female partners of male subjects (either of childbearing potential) from getting pregnant during study participation and for at least 12 months (14 months if on a cisplatin-containing regimen and a female of childbearing potential) after the last dose of study treatment (ZW25 or any chemotherapy component). Subjects will be instructed that known or suspected pregnancy occurring from the time of signing informed consent through 12 months (14 months if on a cisplatin-containing regimen and a female of childbearing potential) following the last study treatment administration (ZW25 or any chemotherapy component), regardless of when the pregnancy was confirmed, should be reported to the investigator. If a female subject is pregnant, the investigator will immediately discontinue the subject from the study. Upon discontinuation, only those procedures that would not expose the subject to undue risk will be performed.

In the event that a female subject or female partner of a male subject is found to be pregnant after inclusion in the study, the pregnancy will be followed to resolution with subject/partner consent, and the status of mother and child will be reported to the sponsor after delivery. Only report pregnancies that occur in a male subject's partner if the estimated date of conception is after the male subject's first study drug dose and within 12 months after his last dose.

All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 6 months.

Details of the pregnancy will be recorded on the withdrawal page of the case report form (CRF), and a Pregnancy Report Form will be completed and reported to the sponsor's Drug Safety Department using the contact information on the Pregnancy Report Form. Abortion, whether therapeutic, or spontaneous, should be reported as an SAE (Section 7.2.2).

4.3. Removal of Subjects From Therapy or Assessment

Jazz Pharmaceuticals or their designee must be notified if a subject is withdrawn from study treatment (any part) or from the study. The reason(s) for withdrawal must be documented in the subject's medical records and CRF.

4.3.1. Treatment Discontinuation

For both parts of the study, for subjects receiving FP or CisGem regimens, if any component of the combination chemotherapy is discontinued due to toxicity unrelated to ZW25, subjects may continue to receive the other component(s) of the combination chemotherapy regimen with ZW25.

For both parts of the study, for subjects receiving XELOX or mFOLFOX6 regimens, if oxaliplatin is discontinued due to toxicity unrelated to ZW25, subjects may continue to receive

capecitabine (in XELOX) or 5-FU (in mFOLFOX6) with ZW25. However, if capecitabine or 5-FU is discontinued due to toxicity unrelated to ZW25, oxaliplatin should also be discontinued.

For both parts of the study, for subjects receiving the mFOLFOX6+bevacizumab (or biosimilar) regimen, if oxaliplatin is discontinued due to toxicity unrelated to ZW25, subjects may continue to receive 5-FU and bevacizumab (or biosimilar) with ZW25. However, if 5-FU is discontinued due to toxicity unrelated to ZW25, oxaliplatin should also be discontinued. Furthermore, if both oxaliplatin and 5-FU are discontinued, bevacizumab (or biosimilar) should also be discontinued.

If in the opinion of the investigator, all components of the combination chemotherapy should be discontinued due to toxicity unrelated to ZW25, a subject may continue to receive treatment with ZW25 monotherapy. Subjects may not continue on combination chemotherapy alone on study if ZW25 is discontinued; however, subjects who discontinue treatment with ZW25 in either part of the study for any reason should enter long-term follow-up for survival.

Study treatment may be discontinued for any of the following reasons:

- Adverse event (AE)
- Death
- Lost to follow-up
- Withdrawal of consent
- Physician decision (non-AE, non-progressive disease)
- Pregnancy
- Progressive disease (either radiographic or clinical progression)
- Protocol violation
- Study termination by sponsor
- Other, non-AE

Clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers, or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes.

Also, if a subject has not taken ZW25 for more than 4 weeks, he/she will be withdrawn from study treatment unless approval is obtained from the medical monitor to continue on study treatment.

At a minimum, all efforts should be made for subjects to complete the End of Treatment (EOT) visit (Section 6.10) and the safety follow-up visit (Section 6.11). Subjects who discontinue from study treatment will remain on study and be followed for disease progression (if disease progression was not the reason for study treatment discontinuation) and survival unless they withdraw consent or the sponsor closes the study (Sections 6.12 and 6.13).

4.3.2. Study Discontinuation

Subjects may discontinue/withdraw from the study for any of the following reasons:

- Adverse event (AE)
- Death
- Lost to follow-up
- Withdrawal of consent
- Physician decision (non-AE, non-progressive disease)
- Pregnancy
- Progressive disease (either radiographic or clinical progression)
- Protocol violation
- Study termination by sponsor
- Other, non-AE

5. TREATMENTS

5.1. Investigational Study Drug (ZW25)

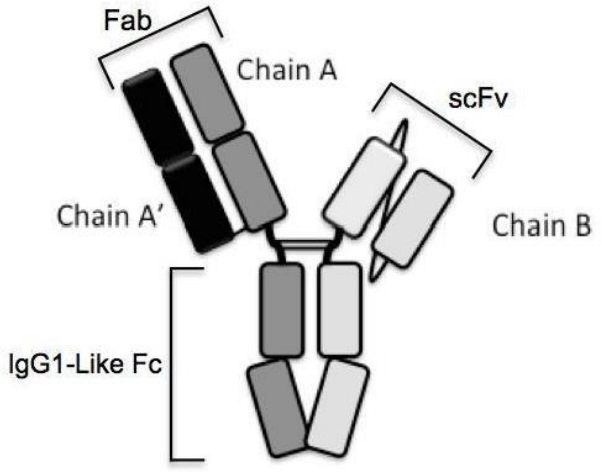
Detailed information describing the preparation, administration, and storage of ZW25 is located in the Pharmacy Manual. Study drug must be diluted as instructed in the Pharmacy Manual prior to administration.

Note: On the days of ZW25 dosing, ZW25 will be administered first. The chemotherapy components will be administered in the usual order per institutional standards.

5.1.1. Description

ZW25 is a humanized bispecific antibody recognizing 2 non-overlapping epitopes of the ECD of the human HER2 antigen. A schematic representation of ZW25 is shown in Figure 3. The IgG1-like fragment crystallizable (Fc) region of ZW25 [redacted] that impart preferential pairing to generate a heterodimeric molecule and correspondingly disfavor formation of homodimers. Chain A is otherwise a normal IgG1 heavy chain and forms a fragment antigen-binding arm of antibody (Fab) through pairing with IgG Kappa light Chain A. Chain A binds to ECD2 of HER2. Chain B has an IgG1-like hinge, CH2 and CH3 domains but contains a single-chain variable fragment (scFv) antibody rather than a Fab arm. Chain B binds to ECD4 of HER2. In place of the CH1 domain it has a VL domain, an unstructured 20 amino acid linker of glycine and serine residues, followed by a VH domain to form an scFv antibody variable domain. ZW25 is being developed as a treatment for locally advanced (unresectable) and/or metastatic HER2-expressing cancers.

Figure 3: Structure of ZW25



5.1.2. Dose and Administration

Dosing for ZW25 will be given as follows:

- Part 1:
  - ZW25 dose in XELOX-1 and FP-1

    ZW25: 30 mg/kg IV Q3W (initial recommended dose per the SMC based on results from Study ZWI-ZW25-101); Day 1 of each 21-day cycle. Up to 2 step-down dose levels may be evaluated if recommended by the SMC and approved by the sponsor.

  - ZW25 dose in FP-2 and CisGem

    ZW25: 1800 mg (subjects < 70 kg) or 2400 mg (subjects ≥ 70 kg) IV Q3W; Day 1 of each 21-day cycle. Up to 2 step-down dose levels may be evaluated if recommended by the SMC and approved by the sponsor.

  - ZW25 dose in mFOLFOX6-1 in GEA

    ZW25: 20 mg/kg IV Q2W; Days 1 and 15 of each 28-day cycle. Up to 2 step-down dose levels to 15 and/or 10 mg/kg Q2W or an intermediate dose level of ZW25 may be evaluated if recommended by the SMC and approved by the sponsor.

  - ZW25 dose in mFOLFOX6-2 in GEA and in mFOLFOX6-2 with or without bevacizumab (or biosimilar) in CRC

    ZW25: 1200 mg (subjects < 70 kg) or 1600 mg (subjects ≥ 70 kg) IV Q2W; Days 1 and 15 of each 28-day cycle. Up to 2 step-down dose levels of ZW25 may be evaluated if recommended by the SMC and approved by the sponsor.

- Part 2: RDs of ZW25 as confirmed in Part 1 of the study for each of the combination chemotherapy regimens.
  - One RD (flat dose) is expected for ZW25 combined with FP-2, one RD (flat dose) is expected for ZW25 combined with mFOLFOX6-2 for GEA, one RD (flat dose) is expected for ZW25 combined with mFOLFOX6-2 for CRC, one RD (flat dose) is expected for ZW25 combined with mFOLFOX6-2 plus bevacizumab (or biosimilar) for CRC and one RD (flat dose) is expected for ZW25 combined with CisGem.
  - An RD of 30 mg/kg IV Q3W has been established for ZW25 combined with XELOX-1 and is being used in Part 2. The ZW25 exposure (C_{max}, AUC_{0-t}) from this dose is similar to or exceeds that predicted for two additional ZW25 flat doses that the sponsor would like to test in combination with XELOX. Therefore, the following two ZW25 flat doses will be tested directly in Part 2 (i.e., without first going through Part 1):

    ZW25 dose in XELOX-2: 1800 mg (subjects < 70 kg) or 2400 mg (subjects ≥ 70 kg) IV Q3W on Day 1 of each 21-day cycle.

    ZW25 dose in XELOX-3: 900 mg (subjects < 70 kg) or 1200 mg (subjects ≥ 70 kg) IV on Days 1 and 8 of each 21 day cycle.

For weight based dosing, doses will be adjusted only for subjects who experience a ≥ 10% change in weight from baseline.

For flat dosing, doses will be adjusted only for subjects who experience a ≥ 10% change in weight from baseline AND cross the 70 kg threshold in either direction.

Subject weight must be measured at the time points described in the schedules of assessments. Other dose adjustments for changes in body weight are permitted per institutional standards. Detailed instructions for dose preparation are provided in the Pharmacy Manual.

ZW25 should be administered prior to any component of the combination chemotherapy regimen. Please refer to the Pharmacy Manual for infusion times. All subjects should receive prophylactic treatment for infusion reactions prior to ZW25 dosing as outlined in Section 5.1.10.1. Subjects who experience a Grade 1 or Grade 2 infusion reaction may resume infusion of drug at a reduced infusion rate (30% through 50% slower than initial rate).

5.1.3. Dose Modifications

Subjects who experience an event that meets the criteria for DLT (defined in Section 3.1.1.1) at any time on study may continue at a reduced dose once the toxicity has returned to Grade 1 or baseline with approval of the medical monitor. If a DLT is observed at the reduced dose, the dose of ZW25 administered to that individual subject should be further reduced but [redacted].

For Part 2 of the study, dose modifications for ZW25-associated toxicity are presented in Table 2 below. Dose decreases or delays for other reasons may be permitted with approval from the

medical monitor. The reason for dose decrease or delay must be recorded, and the sponsor must be notified (for dose delays) or pre-approve the change (for dose reductions). [redacted]

Both ZW25 and chemotherapy can contribute to diarrhea and other toxicities listed in Table 2. In general, side effects associated with ZW25 in combination with chemotherapy improve with dose adjustment of the chemotherapy components and no dose adjustment of ZW25 is required. If there is a question as to whether the chemotherapy or ZW25 is the primary cause of the observed toxicity or if the chemotherapy is suspected to be primary cause of the toxicity, chemotherapy dose reductions should occur before ZW25 dose reduction (see Section 5.2.3, Section 5.3.3, Section 5.4.3, and Section 5.5.3 for further guidance). If dose adjustment of chemotherapy fails to alleviate symptoms, ZW25 dose reductions should then be considered.

Any and all ZW25 dose reductions for individual subjects must be discussed with and pre-approved by the sponsor's medical monitor.

Table 2: Recommended Management and Potential Dose Modifications for ZW25-Associated Toxicity

Adverse Event Related to ZW25	Grade	Action for ZW25
Nausea and/or vomiting	Grade 1/2	• Suggest a 5HT3 receptor antagonist until resolution of symptoms. • No dose modification of ZW25 is required. • For breakthrough nausea or vomiting, consider adding olanzapine 5 or 10 mg daily for three days. For subjects already receiving olanzapine, prochlorperazine may be used.
	Grade 3	• Suggest a 5HT3 receptor antagonist plus a glucocorticoid (e. g., dexamethasone); consider adding a NK-1 receptor antagonist to a 5HT3 receptor antagonist and glucocorticoids if the latter combination is not sufficient for symptom relief. Treatment until resolution of symptoms to ≤ Grade 1. • Hold ZW25 until severity ≤ Grade 1 or pretreatment level, then resume ZW25 at the same dose level
Vomiting	Grade 4	• Suggest a 5HT3 receptor antagonist plus a glucocorticoid (e. g., dexamethasone); consider adding a NK-1 receptor antagonist to a 5HT3 receptor antagonist and glucocorticoids if the latter combination is not sufficient for symptom relief. Treatment until resolution of symptoms to ≤ Grade 1. • Hold ZW25 until severity ≤ Grade 1 or pretreatment level. • For Grade 4 vomiting that improves to ≤ Grade 2 within 72 hours with supportive management, resume at the same dose level. • For Grade 4 vomiting lasting longer than 72 hours, permanently discontinue ZW25. • For recurrent Grade 4 vomiting, permanently discontinue ZW25.

Adverse Event Related to ZW25	Grade	Action for ZW25
Diarrhea[a]	Grade 1/2	• Oral hydration with fluid that contains water, salt and glucose, such as broth or Gatorade. • Suggest loperamide 4 mg PO followed by 2 mg Q4H or with each loose stool until no diarrhea. • No dose modification of ZW25 is required.
	Grade 3	• Aggressive fluid hydration and clear liquid diet. • Loperamide 4 mg PO followed by 4 mg Q2H until resolution of diarrhea; consider Lomotil alternating with loperamide and/or octreotide 100 or 150 mcg subcutaneously Q8H for subjects with persistent diarrhea despite 48 hours of loperamide. If subjects are refractory to loperamide, Lomotil, and octreotide, gastroenterology should be consulted. • Hold ZW25 until severity ≤ Grade 1 or pretreatment level. • When symptoms improve to ≤ Grade 1 or pretreatment level, resume ZW25 at the same dose level or consider dose reduction after discussion with the medical monitor. • For recurrent Grade 3 symptoms despite maximum use of loperamide, Lomotil, and octreotide, ZW25 dose reduction is mandatory. • For recurrent Grade 3 diarrhea lasting longer than 72 hr despite dose reduction of ZW25 and maximum use of loperamide, Lomotil, and octreotide, or non-compliance with maximum antidiarrheal therapy, permanently discontinue ZW25.
	Grade 4	• Aggressive fluid hydration and clear liquid diet. • Loperamide 4 mg PO followed by 4 mg Q2H until resolution of diarrhea; consider Lomotil alternating with loperamide and/or octreotide 100 or 150 mcg subcutaneously Q8H for subjects with persistent diarrhea despite 48 hours of loperamide. If subjects are refractory to loperamide, Lomotil, and octreotide, gastroenterology should be consulted. • Hold ZW25 until severity ≤ Grade 1 or pretreatment level. • For Grade 4 diarrhea that improves to ≤ Grade 2 within 72 hours with supportive management, resume upon improvement to ≤ Grade 1 or pretreatment level. ZW25 dose reduction is mandatory. • For Grade 4 diarrhea lasting longer than 72 hours, permanently discontinue ZW25. • For recurrent Grade 4 diarrhea, permanently discontinue ZW25.
Rash	Grade 1/2	• Suggest topical steroid as needed. • No dose modification of ZW25 is required.

Adverse Event Related to ZW25	Grade	Action for ZW25
	Grade 3	• Suggest initation of topical steroid; if response insufficient, consider oral corticosteroids. Suggest wound care for skin erosions and ulcerations and to prevent infection. • Suggest analgesics for pain control if necessary. • If not limiting self-care activities and not associated with infection requiring systemic antibiotics, follow guidelines for Grades 1–2 severity. • If limiting self-care activities or associated with infection requiring systemic antibiotics, hold ZW25 until severity ≤ Grade 1 or pretreatment level, then resume at the same dose. • For recurrence of Grade 3 symptoms limiting self-care activities or associated with infection requiring systemic antibiotics, despite optimal management with topical and/or oral corticosteroids, dose reduction is mandatory.
	Grade 4	• Permanently discontinue ZW25.
Other ZW25-related Aes (other than IRR)[b]	Grade 1/2	• No dose modification of ZW25 is required
	Grade 3	• Hold ZW25 until severity ≤ Grade 1 or pretreatment level. • When symptoms improve to ≤ Grade 1 or pretreatment level, resume ZW25 at the same dose level.
	Grade 4	• Grade 4 electrolyte imbalances/laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset (e.g., Grade 4 hyponatremia) do not require ZW25 discontinuation. • For other Grade 4 Aes, permanently discontinue ZW25.

AE = adverse event; PO = by mouth; Q2H = every 2 hours; Q4H = every 4 hours; Q8H = every 8 hours.

[a] For further guidance regarding diarrhea, including required anti-diarrheal prophylaxis, see Section 5.1.6. For further guidance on modifications to chemotherapy dosing due to diarrhea, see Table 11, Table 19, and Table 25.

[b] Guidance for management of infusion-related reactions is provided in Section 5.1.5.

5.1.4. Management of Left Ventricular Dysfunction

Management of left ventricular dysfunction, regardless of relationship to study drug, is described in Table 3 below.

Table 3: Management of Left Ventricular Dysfunction

Left Ventricular Dysfunction (Regardless of Causality)	Action for ZW25
• Absolute decrease in LVEF of ≥ 16 percentage points from pre-treatment baseline, or • LVEF below institutional limits of normal and absolute decrease of ≥ 10 percentage points below pretreatment baseline. If an institution does not define a normal range for LVEF, AESI is defined as an absolute decrease in LVEF of ≥ 10 percentage points from pretreatment baseline and absolute value < 50%.	• Suspend dosing for at least 4 weeks • Repeat LVEF assessment within 4 weeks • Dosing may be resumed within 4 to 8 weeks if LVEF returns to normal limits and the absolute decrease is ≤ 15 percentage points from baseline; otherwise, permanently discontinue
• Grade ≥ 2 (symptomatic) heart failure	• Hold ZW25. Referral to a cardiologist is recommended. If symptomatic heart failure is confirmed, permanently discontinue.

LVEF = left ventricular ejection fraction

5.1.5. Management of Infusion Reactions

Required premedication as prophylaxis for potential ZW25-related infusion reactions are described in Section 5.1.10.1.

The symptoms of infusion-related reactions include fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Subjects should be closely monitored for such reactions. Immediate access to an Intensive Care Unit or equivalent environment and appropriate medical therapy (including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen) must be available to treat infusion-related reactions. Management of ZW25-related infusion reactions are based on the grade of symptoms as outlined in Table 4.

Table 4: Treatment Modifications for Symptoms of Infusion-related Reactions Due to ZW25

NCI-CTCAE Grade	Treatment Modification for ZW25
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Closely monitor for any worsening. Institute medical management as described in the text following this table. Subsequent infusions should be given at the reduced infusion rate. Consider additional premedications (e.g., H2 blockers) for subsequent infusions.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reaction has resolved or decreased to Grade 1 in severity. Closely monitor for any worsening. Institute medical management as described in the text following this table. Subsequent infusions should be given at the reduced infusion rate. Consider additional premedications (e.g., H2 blockers) for subsequent infusions.
Grade 3 – severe Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.	Immediately stop the infusion. Institute medical management as described in the text following this table. Consider additional premedications (e.g., H2 blockers) for subsequent infusions. For recurrent G3, permanently discontinue.
Grade 4 – life threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Institute medical management as described in the text following this table. The subject should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

Once the ZW25 infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it may only be increased for subsequent infusions with medical monitor approval; premedication for subsequent infusions must be administered per Section 5.1.10.1 and may be supplemented per institutional standards. If the subject has a second infusion-related reaction (≥ Grade 3) on the slower infusion rate, the infusion should be discontinued and the subject should be withdrawn from ZW25 treatment.

NCI-CTCAE Grade 1 or 2 infusion reaction: Proper medical management should be instituted, as indicated per the type of reaction. This includes but is not limited to an antihistamine (e.g., diphenhydramine or equivalent), antipyretic (e.g., acetaminophen or equivalent), and, if considered indicated, oral (PO) or IV glucocorticoids, bronchodilators, and oxygen.

NCI-CTCAE Grade 3 or 4 infusion reaction: Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This includes but is not limited to PO or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, and oxygen.

If feasible, blood samples for evaluation of PK and/or ADA should be drawn during or as soon as possible after an infusion reaction.

5.1.6. Management of Diarrhea

Required prophylaxis for diarrhea associated with ZW25 in combination with chemotherapy is described in Section 5.1.10.1 .

Diarrhea is a common and sometimes severe side effect of ZW25 given in combination with chemotherapy. Subjects should be counseled on diarrhea prevention, including avoidance of lactose-containing products, assuring adequate fluid intake of 2 liters of clear liquids per day, eating small frequent meals, and eating a low-fat diet. Subjects should also be counseled on diarrhea management and should have a supply of anti-diarrhea medication (loperamide and atropine/diphenoxylate) at the time of the first dose with study drug.

Subjects with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Any subjects who develop ≥ grade 2 diarrhea during any treatment cycle may require dose modifications of chemotherapy and/or ZW25 in subsequent cycles (see Table 2, Section 5.2.3, Section 5.3.3, Section 5.4.3, and Section 5.5.3). As noted in Section 5.1.3, dose adjustment(s) of chemotherapy components should occur first. If diarrhea is not improved with dose adjustment(s) of chemotherapy, ZW25 dose modifications should be considered, after discussion with the medical monitor.

5.1.7. Storage and Handling

In this study, 2 formulations of zanidatamab are available:

- Generation 1 (Gen 1) zanidatamab solution. **Vials containing Gen 1 zanidatamab should be stored at –20°C (± 5°C)** and protected from light until ready for use.

- Generation 2 (Gen 2) zanidatamab lyophilized powder. **Vials containing Gen 2 lyophilized zanidatamab must be stored at 2 to 8°C** and protected from light until ready for use.

To the extent possible, subjects should be administered the same formulation of zanidatamab for the duration of their study treatment, i.e., subjects that start on Gen 1 zanidatamab should stay on Gen 1, and subjects that start on Gen 2 zanidatamab should stay on Gen 2.

Zanidatamab must be stored in a controlled location, where access is limited to only designated site staff. For both formulations of zanidatamab study drug, refer to the Pharmacy Manual for detailed drug storage, preparation, and administration information.

5.1.8. Packaging and Labeling
Refer to the Pharmacy Manual for packaging and labeling.

5.1.9. Preparation
Detailed drug preparation instructions are provided in the Pharmacy Manual.

5.1.10. Concomitant Therapy
All medications being taken at the time of study entry should be continued as necessary and at a stable dose level and frequency, if possible, unless prohibited for study entry.

5.1.10.1. Required Concomitant Therapy
Prior to dosing with ZW25, all subjects must receive prophylactic treatment for infusion reactions that includes a corticosteroid. The mandated regimen includes acetaminophen orally, diphenhydramine (or equivalent) orally or IV, and a corticosteroid (recommend either hydrocortisone 100 mg IV or dexamethasone 10 mg IV) 30 to 60 minutes prior to infusion of ZW25. If an alternative premedication regimen is thought to be required, sponsor approval should be sought. For subjects who experience an infusion reaction despite initial premedication, additional prophylactic treatment may be added prior to subsequent doses, including an H2 blocker such as ranitidine.

All subjects receiving ZW25 in combination with chemotherapy require mandatory anti-diarrheal prophylaxis during Cycle 1 of treatment with loperamide 4 mg twice daily (BID) starting on the first day of treatment and continuing for at least 7 days, unless subjects develop significant constipation (no bowel movement for 48 hours). If subjects develop diarrhea despite mandatory prophylaxis or after completion of the 7 days of mandatory prophylaxis, they should be instructed to take loperamide 4 mg at the first loose stool followed by 2 mg after each loose stool, and to contact the treating clinic for further guidance; temporary hold of capecitabine (if applicable) and use of additional anti-diarrheal medications should be considered. After Cycle 1, continued loperamide prophylaxis is at the discretion of the investigator. However, if subjects develop Grade 1 or higher diarrhea during Cycle 1 of therapy, prophylaxis for at least the first 7 days of treatment should be continued with subsequent cycles.

At any time during the study, the SMC may recommend or modify other premedications or supportive medications and the sponsor may implement these recommendations without amending the protocol.

5.1.10.2. Allowed Concomitant Therapy

Supportive therapies, including transfusions and bisphosphonates (e.g., Zometa®), are allowed on study. Supportive care treatments, including supportive growth factors and colony-stimulating factors, are also allowed. Corticosteroid treatment is permitted only as follows:

- Topical, ocular, intra-articular, intranasal, and/or inhalational corticosteroids
- Physiologic replacement doses of systemic corticosteroids (i.e., < 15 mg/day)
- As part of pre-medication for ZW25 or chemotherapy
- For prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed hypersensitivity reaction caused by a contact allergen)
- For acute medical conditions (higher doses permitted, but not to exceed 4 weeks with medical monitor approval)
- Ongoing treatment for pre-existing conditions as detailed in study inclusion/exclusion criteria (Section 4.1)

Routine prophylaxis with vaccines is generally permitted; however, live vaccines are prohibited.

All other therapies not specifically listed in the exclusion criteria or in prohibited therapy are allowed.

5.1.10.3. Prohibited Concomitant Therapy

Subjects may not receive cancer related surgery, radiotherapy, other investigational, or systemic anti-neoplastic therapy during the study. Use of alternative supplemental therapies is discouraged, and use of any such product must be recorded.

5.2. XELOX Multi-agent Combination Chemotherapeutic Regimen

The chemotherapy components and regimens for XELOX-1, XELOX-2, and XELOX-3 are the same.

If the investigator would prefer to use a different starting dose or recommended dose modification for any of the components of the chemotherapy regimen, the investigator should discuss the clinical reasons for this with the sponsor's medical monitor.

Note: At any time during the study, the SMC may recommend modifying the chemotherapy component(s) of any regimen. The sponsor may implement these SMC recommendations without amending the study protocol.

5.2.1. Description of XELOX

XELOX (also known as CAPOX) is a multi-agent chemotherapy regimen consisting of capecitabine and oxaliplatin. XELOX has been established as a well-tolerated and efficacious cytotoxic regimen for the treatment of various cancers, including advanced or metastatic GEA,

BTC, and CRC (Cunningham 2008; Haller 2011; Hochster 2008; Nehls 2008). In some cases, XELOX is also used as an adjuvant therapy in earlier stages of disease (CRC).

5.2.2. Dose and Administration of XELOX

Dosing for both parts of the study will be given in 21-day cycles.

XELOX will be administered as follows: capecitabine 1,000 mg/m^2 PO bid (total daily dose of 2000 mg/m^2) starting on the evening of Day 1 and continuing through the morning of Day 15 of each 21-day cycle plus oxaliplatin 130 mg/m^2 IV Q3W dosing on Day 1 of each 21-day cycle. Subjects who discontinue chemotherapy without disease progression and for reasons that are not related to ZW25 toxicity may continue on ZW25 alone.

The dose levels, schedule, and administration of each component of XELOX are presented in Table 5 below. The combination chemotherapy should be given to each subject after receiving ZW25.

Table 5: XELOX Dose Levels, Schedule, and Administration

Drug	Dose/Route	Schedule
Capecitabine	1,000 mg/m^2 PO bid	Starting the evening of Day 1 and continuing through the morning of Day 15, every 21-day cycle
Oxaliplatin	130 mg/m^2 IV	Day 1, every 21-day cycle

bid = twice a day; IV = intravenously; m = meter; mg = milligrams; PO = by mouth

5.2.3. Dose Modifications for XELOX

Below are recommendations for dose modification for XELOX toxicity. However, in case of conflict between these recommendations and either the most recent prescribing information for the chemotherapy components or institutional standard of care, investigators should use their best medical judgment. In general, if treatment is interrupted due to toxicity, retain the original stop and start dates; do not make up for missed doses when treatment is resumed.

Dose modifications for toxicities potentially associated with components of the XELOX combination chemotherapy are presented in Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, and Table 12.

Table 6: Dose Reduction Levels for Toxicities Associated with XELOX for Non-Neurologic Toxicity

Agent	Starting Dose	Reduced Dose Level -1	Reduced Dose Level -2	Reduced Dose Level -3
Oxaliplatin (IV)	130 mg/m^2	100 mg/m^2	85 mg/m^2	Discontinue
Capecitabine (PO)	1000 mg/m^2 bid	750 mg/m^2 bid	500 mg/m^2 bid	Discontinue[a]

bid = twice daily; IV = intravenous; m = meter; mg = milligrams; PO = per oral
[a] If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.

Table 7: Dose Reduction Levels for Toxicities Associated with Oxaliplatin for Neurologic Toxicity

Agent	Starting Dose	Reduced Dose Level -1	Reduced Dose Level -2	Reduced Dose Level -3
Oxaliplatin (IV)	130 mg/m^2	100 mg/m^2	65 mg/m^2 [a]	Discontinue

IV = intravenous; m = meter; mg = milligrams
[a] The second dose reduction for oxaliplatin for neurologic toxicity should be 65 mg/m^2. If a subject has both neurologic and non-neurologic toxicity, the final dose of oxaliplatin is the LOWER of the dose adjustments (i.e., if hematologic toxicity mandates dose –2 reduction (85 mg/m^2) and neurologic toxicity mandates dose –2 reduction (65 mg/m^2), then 65 mg/m^2 is given)

Table 8: Recommended Dose Modifications for Hematologic Toxicities Associated with XELOX

Absolute neutrophil count (ANC)

Prior to a Cycle (Day 1)	Toxicity		Dose Level for Subsequent Cycles[b]	
	Grade	ANC (x10^9/L)	Oxaliplatin	Capecitabine
• If ANC less than 1.0 x 10^9/L on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. • If ANC is greater than or equal to 1.0 x 10^9/L within 2 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). • If ANC remains less than 1.0 x 10^9/L after 2 weeks, discontinue treatment with combination chemotherapy regimen.	1	< LLN to ≥ 1.5	Maintain dose level	Maintain dose level
	2	1.0 to < 1.5	Maintain dose level	Maintain dose level
	3	0.5 to < 1.0	Decrease 1 dose level	Decrease 1 dose level[a]
	4	< 0.5	Decrease 2 dose levels	Decrease 2 dose levels[a]

ANC = absolute neutrophil count; CBC = complete blood count; IV = intravenous; L = liter; LLN = Lower Limit of Normal
[a] If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.
[b] Use of growth factor support is allowed and is at the discretion of the investigator. If growth factor support is used, dose reductions may not be necessary.

Platelets

Prior to a Cycle (Day 1)	Toxicity		Dose Level for Subsequent Cycles	
	Grade	Platelets (x10^9/L)	Oxaliplatin	Capecitabine
• If platelets less than 75 x 10^9/L on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. • If platelets are greater than or equal to 75 x 10^9/L within 2 weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). • If platelets remain less than 75 x 10^9/L after 2 weeks, discontinue treatment with combination chemotherapy regimen.	1	< LLN to ≥ 75	Maintain dose level	Maintain dose level
	2	50 to < 75	Maintain dose level	Maintain dose level
	3	10 to < 50	Decrease 1 dose level	Decrease 1 dose level[a]
	4	< 10	Decrease 2 dose levels	Decrease 2 dose levels[a]

CBC = complete blood count; L = liter; LLN = Lower Limit of Normal

[a] If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.

Table 9: Recommended Dose Modifications for Renal Impairment Associated with XELOX

Drug	Renal Impairment	
	CrCL (ml/min)	Dose
Capecitabine	51 – 80	100%
	30 – 50	No dose adjustment
	< 30	Discontinue[a]
Oxaliplatin	Moderate renal impairment	100%, but monitor and dose adjust according to toxicity
	<20	Dose reduce – clinical decision

CrCL = creatinine clearance by Cockcroft/Gault formula
[a] If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.

Table 10: Dose Modification of Capecitabine for Treatment-Related Hepatotoxicity

Bilirubin		ALT, AST	Capecitabine Dose Modification[a]
> 3 x ULN	*OR*	> 2.5 x ULN	Withhold treatment until bilirubin decreases to ≤ 3.0 x ULN or ALT, AST decrease to ≤ 2.5 x ULN

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal
[a] If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.

For non-hematological and non-neurological toxicities, if Grade 2, 3 or 4 toxicities occur, daily administration of capecitabine should be immediately interrupted until these symptoms resolve or decrease in intensity to Grade 1.

Table 11: Recommended Dose Modifications for Non-Hematologic/Non-Neurologic Toxicities (Diarrhea, Stomatitis, or Palmar/Plantar Erythema)

Diarrhea

Prior to a Cycle (Day 1)	Toxicity		Current Cycle	Suggested Dose Level for Subsequent Cycles		
	Grade		Capecitabine	Oxaliplatin	Capecitabine	ZW25
• If diarrhea grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks maximum 2 times. • If diarrhea < Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the highest grade experienced. • If diarrhea remains Grade 2 after 2 weeks, discontinue treatment.	1	Increase of < 4 stools/day over baseline	Continue capecitabine	Maintain dose level	Maintain dose level	For guidance on management of diarrhea potentially associated with ZW25, see Table 2. In general, ZW25 should only be reduced if grade 3 diarrhea recurs after at least one dose reduction of chemotherapy component(s).
	2	Increase of 4 to 6 stools/day over baseline	Immediately interrupt capecitabine until diarrhea resolves to ≤ grade 1, or until end of current 14 day cycle	Maintain dose level	Decrease 1 dose level[a]	
	3	Increase of ≥ 7 stools/day	Immediately interrupt capecitabine until Day 1 of next cycle	Decrease 1 dose level	Decrease 1 dose level[a]	
	4	Increase of 10 or more stools/day or grossly bloody diarrhea; may require par enternal support. Urgent intervent ion indicated		Decrease 1 dose level	Decrease 2 dose levels or permanently discontinue[a]	

[a] If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.

Stomatitis

Prior to a Cycle (Day 1)	Toxicity		Dose Level for Subsequent Cycles	
	Grade		Oxaliplatin	Capecitabine
• If stomatitis ≥ Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. • If stomatitis < Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced. • If stomatitis remains ≥Grade 2 after 2 weeks, discontinue treatment.	1	Asymptomatic or mild symptoms; intervention not indicated	Maintain dose level	Maintain dose level
	2	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Maintain dose level	Maintain dose level
	3	Severe pain; interfering with oral intake	Maintain dose level	Decrease 1 dose level[a]
	4	As above but mucosal necrosis and/or requires enteral support, dehydration. Urgent intervention indicated	Decrease 1 dose level	Decrease 2 dose levels[a]

[a] If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.

Palmar-Plantar Erythrodysesthesia (Hand-Foot Skin Reaction)

Prior to a Cycle (Day 1)	Toxicity		Dose Level for Subsequent Cycles	
	Grade		**Oxaliplatin**	**Capecitabine**
• If hand-foot skin reaction ≥ Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. • If hand-foot skin reaction is < Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the highest Grade experienced • If hand-foot skin reaction remains ≥ Grade 2 after 2 weeks, discontinue treatment	1	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Maintain dose level	Maintain dose level
	2	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Maintain dose level	Maintain dose level
	3	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL	Maintain dose level	Decrease 1 dose level[a]

ADL = activities of daily living
[a] If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.

Table 12: Dose Modifications for Neurologic Toxicity due to Oxaliplatin

Toxicity		Duration of Toxicity		Persistent (present at start of next cycle)
Grade		**1–7 days**	**> 7 days**	
1	Asymptomatic	Maintain dose level	Maintain dose level	Maintain dose level
2	Moderate symptoms; limiting instrumental ADL	Maintain dose level	Maintain dose level	Decrease 1 neurotoxicity dose level
3	Severe symptoms; limiting self care ADL	Decrease 1 neurotoxicity dose level	Decrease 1 neurotoxicity dose level	Discontinue
4	Life-threatening consequences; urgent intervention indicated	Discontinue	Discontinue	Discontinue
	Pharyngo-Laryngeal dysethesia	Increase infusion time from 2 to 6 hours	N/A	N/A

N/A = not applicable

5.2.4. Precautions for XELOX

5.2.4.1. Allergy to Platinum

Anaphylactic-like reactions to oxaliplatin and cisplatin have been reported. Facial edema, bronchonconstriction, tachycardia and hypotension may occur within minutes of platinum administration. Adrenaline, corticosteroids and antihistamines have been effectively employed to alleviate symptoms. No further oxaliplatin or cisplatin should be given.

5.2.4.2. Platinum Hypersensitivity

Platinum hypersensitivity can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required (see below).

For Grade 1 or 2 acute hypersensitivity reactions no dose modification of oxaliplatin or cisplatin is required and the subject can continue treatment with standard hypersensitivity premedications:

45 minutes prior to platinum dosing:

- Dexamethasone 20 mg IV in 50 mL normal saline (NS) over 15 minutes

30 minutes prior to platinum dosing:

- Diphenhydramine 50 mg IV and ranitidine 50 mg IV in 50 mL NS over 20 minutes (compatible up to 3 hours when mixed in bag)

Reducing infusion rates (e.g., from the usual 2 hours to 4 to 6 hours) should also be considered since some subjects may develop more severe reactions when rechallenged, despite premedications.

The practice of rechallenging after severe life-threatening reactions is usually discouraged, although desensitization protocols have been successful in some subjects.

5.2.4.3. Pharyngo-largyngeal Dysesthesia

Pharyngo-laryngeal dysesthesia is an unusual dysesthesia characterized by an uncomfortable persistent sensation in the area of the laryngopharynx without any objective evidence of respiratory distress (i.e., absence of hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air or foods/fluids. If this occurs during infusion, stop infusion immediately and observe subject. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the investigator's discretion. In subsequent cycles, the duration of infusion should be prolonged.

Differential diagnosis of platinum hypersensitivity and pharyngo-laryngeal dysesthesia based on clinical symptoms and recommended treatments is shown in Table 13.

Table 13: Platinum Hypersensitivity and Pharyngo-laryngeal Dysesthesia Clinical Symptoms

Clinical Symptoms	Platinum Hypersensitivity	Pharyngo-laryngeal Dysesthesia
Dyspnea	Present	Present
Bronchospasm	Present	Absent
Laryngospasm	Present	Absent
Anxiety	Present	Present
O2 Saturation	Decreased	Normal
Difficulty swallowing	Absent	Present (loss of sensation)
Pruritis	Present	Absent
Cold induced symptoms	No	Yes
Blood pressure	Normal or decreased	Normal or increased
Treatment	Oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors if appropriate	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at the investigator's discretion

5.2.4.4. Diarrhea and Dehydration

All subjects should receive anti-diarrheal prophylaxis during the first cycle of treatment (see Section 5.1.10.1).

For precautions regarding diarrhea associated with ZW25 in combination with chemotherapy, as well as guidance regarding management of diarrhea, see Section 5.1.6.

If subjects develop diarrhea, suggested dose reductions of ZW25 and XELOX can be found in Table 2 and Table 11. In general, ZW25 should only be reduced if grade 3 diarrhea recurs after at least one dose reduction of chemotherapy component(s).

5.2.4.5. Cardiotoxicity

Myocardial ischemia and angina occurs rarely in patients receiving 5-FU (a metabolite of capecitabine) or capecitabine. Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms, subjects should have urgent cardiac assessment. Generally re-challenge with either 5-FU or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about 5-FU/capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the subject's AE electronic case report form (CRF).

QT prolongation and torsades de pointes are reported with platinum agents. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in subjects with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities. In case of QT prolongation, treatment with platinum agents should be discontinued. QT effect of cisplatin with single dose ondansetron 8 mg prechemotherapy has not been formally studied. However, single dose ondansetron 8 mg PO would be considered a lower risk for QT prolongation than multiple or higher doses of ondansetron, as long as the subject does not have other contributing factors as listed above.

Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in subjects with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities.

5.2.4.6. Dihydroyprimidine Dehydrogenase (DYPD) Deficiency

Individuals who are carriers of non-functional dihydropyrimidine dehydrogenase (DYPD) variants, such as DYPD*2A, may not be able to metabolize capecitabine at normal rates, and are at risk of potentially life-threatening capecitabine toxicity, such as bone marrow suppression, stomatitis, diarrhea and neurotoxicity. The prevalence of DYPD deficiency in Caucasians is approximately 3% to 5%. No capecitabine dose has been proven safe for patients with complete absence of DYPD activity. If subjects complain of toxicity very soon after administration, it is important to ensure supportive measures are implemented as soon as possible.

Note: DYPD deficiency also affects subjects on 5-FU, which is a metabolite of capecitabine.

5.2.4.7. Pulmonary Fibrosis

Treatment with platinum agents should be interrupted if symptoms indicative of pulmonary fibrosis develop (nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea, or radiological pulmonary infiltrates). If pulmonary fibrosis is confirmed, the platinum agent should be discontinued.

5.2.4.8. Veno-Occlusive Disease

Veno-occlusive Disease (VOD) is a rare but serious complication that has been reported in patients receiving platinium-based therapy in combination with 5-FU (a metabolite of capecitabine). This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Subjects should be instructed to report any jaundice, ascites, or hematemesis immediately.

5.2.4.9. Hemolytic Uremic Syndrome

Platinum-based therapy should be interrupted if Hemolytic Uremic Syndrome (HUS) is suspected: hematocrit is less than 25%, platelets less than 100,000, and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, the platinum agent should be permanently discontinued.

5.2.4.10. Extravasation

Oxaliplatin causes irritation if extravasated; refer to local standard of care for mitigations.

5.2.5. Storage, Handling, Packaging, Labeling, and Preparation for XELOX

Refer to the prescribing information for each of the components of the combination chemotherapy.

5.2.6. Concomitant Therapy for XELOX

Capecitabine enhances the anticoagulant effect of warfarin. Subjects taking coumarin-derivative anticoagulants should be monitored regularly for alterations in their coagulation parameters and the anti-coagulant dose adjusted accordingly. Subjects taking phenytoin or fosphenytoin

concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations. Current drug interaction databases should be consulted for more information.

5.2.6.1. Required Concomitant Therapy

All subjects should receive anti-diarrheal prophylaxis during the first cycle of treatment (see Section 5.1.10.1).

Additional premedications and supportive medications should be administered per the prescribing information for the chemotherapeutic component, as long as they are not contraindicated by the protocol.

At any time during the study, the SMC may recommend or modify premedications or supportive medications and the sponsor may implement these recommendations without amending the protocol.

5.2.6.2. Prohibited Concomitant Therapy

Refer to the prescribing information for each of the components of the combination chemotherapy for any other prohibited concomitant medications. Subjects should avoid sorivudine or its chemically related analogues due to toxicity that can occur due to inhibition of DYPD caused by capecitabine. See also Section 5.1.10.3.

5.2.6.3. Drug Interactions

Capecitabine

- Warfarin: Subjects receiving concomitant capecitabine and oral coumadin-derivative anticoagulant therapy should have their anticoagulant response (international normalized ratio [INR] or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly.
- Phenytoin: Monitor phenytoin levels in subjects taking capecitabine concomitantly with phenytoin. The phenytoin dose may need to be reduced.
- CYP2C9 substrates: Care should be exercised when capecitabine is coadministered with CYP2C9 substrates.

Oxaliplatin

- Nephrotoxic compounds: Because platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by coadministration of potentially nephrotoxic compounds; although, this has not been specifically studied.

5.3. FP Multi-agent Combination Chemotherapeutic Regimen

The chemotherapy components and regimens for FP-1 and FP-2 are the same.

If the investigator would prefer to use a different starting dose or recommended dose modification for any of the components of the chemotherapy regimen, the investigator should discuss the clinical reasons for this with the sponsor’s medical monitor.

Note: At any time during the study, the SMC may recommend modifying the chemotherapy component(s) of any regimen. The sponsor may implement these SMC recommendations without amending the study protocol.

5.3.1. Description of FP

FP is a multi-agent chemotherapy regimen consisting of fluorouracil (5-FU) and cisplatin. FP has been established as an efficacious cytotoxic regimen for the treatment of gastric cancer and is also used as a neoadjuvant/adjuvant therapy. FP has been evaluated in combination with trastuzumab to treat HER2-positive advanced gastric or GEJ cancer in a Phase 3, open-label, randomized, controlled trial (Bang 2010) and is currently considered a standard of care first-line chemotherapy in combination with trastuzumab in HER2-expressing GEA.

5.3.2. Dose and Administration of FP

Dosing for both parts of the study will be given in 21-day cycles.

FP will be administered as follows: 5-FU 800 mg/m^2/day continuous IV infusion Days 1–5 of each 21-day cycle plus cisplatin 80 mg/m^2 IV Q3W on Day 1 of each 21-day cycle. Subjects who discontinue chemotherapy without disease progression and for reasons that are not related to ZW25 toxicity may continue on ZW25 alone.

The dose levels, schedule, and administration of each component of FP are presented in Table 14 below. The combination chemotherapy should be given to each subject after receiving ZW25.

Table 14: FP Dose Levels, Schedule, and Administration

Drug	Dose/Route	Schedule
5-FU	800 mg/m^2/day continuous IV infusion	Days 1–5
Cisplatin	80 mg/m^2 IV	Day 1

IV = intravenously; m = meter; mg = milligrams

5.3.3. Dose Modifications for FP

Below are recommended guidelines for dose modification. However, in case of conflict between these recommendations and either the most recent prescribing information for the chemotherapy components or institutional standard of care, investigators should use their best medical judgment. In general, if treatment is interrupted due to toxicity, retain the original stop and start dates; do not make up for missed doses when treatment is resumed.

Dose modifications for toxicities potentially associated with components of the FP combination chemotherapy are presented in Table 15, Table 16, Table 17, Table 18, Table 19, and Table 20.

Table 15: Dose Reduction Levels for Toxicities Associated with FP

Agent	Starting Dose	Reduced Dose Level -1	Reduced Dose Level -2	Reduced Dose Level -3
Cisplatin (IV)	80 mg/m^2	60 mg/m^2	40 mg/m^2	Discontinue
5-FU (IV)	800 mg/m^2/day	600 mg/m^2/day	400 mg/m^2/day	Discontinue

IV = intravenous; m = meter; mg = milligrams

Table 16: Recommended Dose Modifications for Hematologic Toxicities Associated with FP

Absolute neutrophil count (ANC)

Prior to a Cycle (Day 1)	Toxicity		Dose Level for Subsequent Cycles[a]	
	Grade	ANC ($x10^9$/L)	Cisplatin	5-FU
• If ANC less than 1.0 x 10^9/L on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. • If ANC is greater than or equal to 1.0 x 10^9/L within 2 weeks, proceed with treatment at the dose level noted across from the lowest ANC result of the delayed week(s). • If ANC remains less than 1.0 x 10^9/L after 2 weeks, discontinue treatment with combination chemotherapy regimen.	1	< LLN to ≥ 1.5	Maintain dose level	Maintain dose level
	2	1.0 to < 1.5	Maintain dose level	Maintain dose level
	3	0.5 to < 1.0	Decrease 1 dose level	Maintain dose level
	4	< 0.5	Decrease 1 dose level	Decrease 1 dose level

ANC = absolute neutrophil count; CBC = complete blood count; IV = intravenous; L = liter; LLN = Lower Limit of Normal
[a] Use of growth factor support is allowed and is at the discretion of the investigator. If growth factor support is used, dose reductions may not be necessary.

Platelets

Prior to a Cycle (Day 1)	Toxicity		Dose Level for Subsequent Cycles	
	Grade	Platelets ($x10^9$/L)	Cisplatin	5-FU
• If platelets less than 75 x 10^9/L on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. • If platelets are greater than or equal to 75 x 10^9/L within 2 weeks, proceed with treatment at the dose level noted across from the lowest platelets result of the delayed week(s). • If platelets remain less than 75 x 10^9/L after 2 weeks, discontinue treatment with combination chemotherapy regimen.	1	< LLN to ≥ 75	Maintain dose level	Maintain dose level
	2	50 to < 75	Maintain dose level	Maintain dose level
	3	10 to < 50	Decrease 1 dose level	Maintain dose level
	4	< 10	Decrease 2 dose levels	Maintain dose level

CBC = complete blood count; L = liter; LLN = Lower Limit of Normal

Table 17: Recommended Dose Modifications for Renal Impairment Associated with Cisplatin

CrCL (ml/min)	Cisplatin Dose
> 60	100%
51 - 60	75%
40 - 50	50%
< 40	Contraindicated

CrCL = creatinine clearance by Cockcroft/Gault formula; min = minute; mL = milliliter

5-FU does not require dose modification in subjects with renal impairment.

Table 18: Recommended Dose Modifications for 5-FU-Induced Hepatic Impairment

Bilirubin	AST	5-FU Dose
< 5x ULN	< 5 x ULN	100%
> 5x ULN	> 5 x ULN	Contraindicated

AST = aspartate aminotransferase; ULN = upper limit of normal.

Cisplatin does not require dose modification in subjects with hepatic impairment.

Table 19: Recommended Dose Modifications for 5-FU-Induced Palmar/Plantar Erythema (PPE), Mucositis, or Diarrhea

Grade	PPE	Mucositis	Diarrhea[a]	5-FU Dose
1	Minimal skin changes (erythema) without pain	Erythema of the mucosa but normal diet	< 4 stools/day	Maintain dose level
2	Skin changes (peeling, blisters, edema) or pain, not interfering with function	Patchy ulcerations, can eat and swallow modified diet	4 – 6 stools/day	Decrease 1 dose level
3	Ulcerative dermatitis or skin changes with pain interfering with function	Confluent ulcerations; bleeding with minor trauma. Unable to adequately eat or hydrate orally	≥ 7 stools/day	Decrease 2 dose levels
4	N/A	Tissue necrosis; significant spontaneous bleeding; life threatening consequences	Life-threatening consequences	Discontinue

N/A = not applicable; PPE = palmar/plantar erythema
[a] For further guidance on management of diarrhea potentially associated with ZW25, see Table 2.

Table 20: Recommended Dose Modifications for Cisplatin Neurologic Toxicities

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1 to 7 days	Greater than 7 days	
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level	Decrease 1 dose level
Grade 3	Decrease 1 dose level	Decrease 1 dose level	Discontinue therapy
Grade 4	Discontinue therapy	Discontinue therapy	Discontinue therapy

5.3.4. Precautions for FP

5.3.4.1. Allergy to Platinium

Refer to Section 5.2.4.1 for a description and recommended mitigations.

5.3.4.2. Platinum Hypersensitivity

Refer to Section 5.2.4.2 for a description and recommended mitigations.

5.3.4.3. Pharyngo-largyngeal Dysesthesia

Refer to Section 5.2.4.3 for a description and recommended mitigations.

5.3.4.4. Diarrhea and Dehydration

All subjects should receive anti-diarrheal prophylaxis during the first cycle of treatment (see Section 5.1.10.1).

For precautions regarding diarrhea associated with ZW25 in combination with chemotherapy, as well as guidance regarding management of diarrhea, see Section 5.1.6.

If subjects develop diarrhea, suggested dose reductions of ZW25 and FP can be found in Table 2 and Table 19. In general, ZW25 should only be reduced if grade 3 diarrhea recurs after at least one dose reduction of chemotherapy component(s).

5.3.4.5. Cardiotoxicity

Refer to Section 5.2.4.5 for descriptions and suggested management of myocardial ischemia, angina, QT prolongation, and torsades de pointes.

5.3.4.6. Dihydroyprimidine Dehydrogenase (DYPD) Deficiency

DYPD deficiency also affects subjects on 5-FU. Refer to Section 5.2.4.6 for descriptions and recommended mitigations of DYPD deficiency.

5.3.4.7. Pulmonary Fibrosis

Refer to Section 5.2.4.7 for recommended mitigations.

5.3.4.8. Veno-Occlusive Disease

Refer to Section 5.2.4.8 for recommended mitigations.

5.3.4.9. Hemolytic Uremic Syndrome

Refer to Section 5.2.4.9 for recommended mitigations.

5.3.5. Storage, Handling, Packaging, Labeling, and Preparation for FP

Refer to the prescribing information for each of the components of the combination chemotherapy.

5.3.6. Concomitant Therapy for FP

5.3.6.1. Required Concomitant Therapy

All subjects should receive anti-diarrheal prophylaxis during the first cycle of treatment (see Section 5.1.10.1).

Additional premedications and supportive medications should be administered per the prescribing information for the chemotherapeutic component, as long as they are not contraindicated by the protocol.

At any time during the study, the SMC may recommend or modify premedications or supportive medications and the sponsor may implement these recommendations without amending the protocol.

5.3.6.2. Prohibited Concomitant Therapy

Refer to the prescribing information for each of the components of the combination chemotherapy for any other prohibited concomitant medications. See also Section 5.1.10.3.

5.3.6.3. Drug Interactions

Fluorouracil

- Warfarin: Concurrent administration with warfarin can result in clinically significant increases in coagulation parameters: Closely monitor INR and prothrombin time.

Cisplatin

- Plasma levels of anticonvulsant agents may become subtherapeutic during cisplatin therapy.
- Cisplatin should be used with caution in patients receiving potentially nephrotoxic agents.

5.4. mFOLFOX6 ± Bevacizumab Multi-agent Combination Chemotherapy

The chemotherapy regimens for mFOLFOX6-1 and mFOLFOX6-2 are different in that mFOLFOX6-2 lacks the 5-FU IV bolus on Days 1 and 15 of each 28-day cycle.

mFOLFOX6-1 is closed to further enrollment.

GEA subjects will receive mFOLFOX 6-2.

CRC subjects will receive either mFOLFOX6-2 alone or mFOLFOX6-2 with bevacizumab or bevacizumab biosimilar.

If the investigator would prefer to use a different starting dose or recommended dose modification for any of the components of the chemotherapy regimen, the investigator should discuss the clinical reasons for this with the sponsor's medical monitor.

Note: At any time during the study, the SMC may recommend modifying the chemotherapy component(s) of any regimen. The sponsor may implement these SMC recommendations without amending the study protocol.

5.4.1. Description of mFOLFOX6 ± Bevacizumab

mFOLFOX6 is a multi-agent chemotherapy regimen consisting of oxaliplatin plus 5-FU and leucovorin. mFOLFOX6 has been established as an efficacious cytotoxic regimen with a manageable safety profile in various cancers, including GEA and CRC (Enzinger 2016; Hurwitz 2004). In CRC, the addition of bevacizumab (or bevacizumab biosimilar) to mFOLFOX6 and other chemotherapy regimens improves treatment efficacy. Although there are additional contraindications and precautions to consider when bevacizumab (or biosimilar) is added to mFOLFOX, assuming these are followed, the safety profile of the combination is manageable and is similar to mFOLFOX alone (Botrel 2016; Hochster 2008).

5.4.2. Dose and Administration of mFOLFOX6 ± Bevacizumab

Dosing for both parts of the study will be given in 28-day cycles.

mFOLFOX6-1 will be administered as follows: 5-FU 400 mg/m^2 IV bolus, leucovorin 400 mg/m^2 IV, and oxaliplatin 85 mg/m^2 IV on Days 1 and 15 of each 28-day cycle. Additionally, mFOLFOX6-1 includes 5-FU 1200 mg/m^2/day continuous IV infusion for a total of 2400 mg/m2 over 48 hours on Days 1 and 2 and Days 15 and 16 of each 28-day cycle.

mFOLFOX6-2 will be the same as mFOLFOX6-1 except for not including the IV boluses of 5-FU on Days 1 and 15.

mFOLFOX6-2+bevacizumab or bevacizumab biosimilar will be the same as mFOLFOX6-2 with the addition bevacizumab (or biosimilar) at 5 mg/kg IV on Days 1 and 15.

Subjects who discontinue chemotherapy without disease progression and for reasons that are not related to ZW25 toxicity may continue on ZW25 alone.

The dose levels, schedule, and administration of each component of mFOLFOX6 ± bevacizumab or bevacizumab biosmiliar are presented in Table 21 below. The combination chemotherapy should be given to each subject after receiving ZW25.

Table 21: mFOLFOX6 ± Bevacizumab Dose Levels, Schedule, and Administration

Drug	Dose/Route	Schedule
5-FU bolus (mFOLFOX6-1 only)	400 mg/m^2 IV bolus	Days 1 and 15
5-FU continuous IV infusion (both mFOLFOX6 regimens)	1200 mg/m^2/day continuous IV infusion for a total of 2400 mg/m^2 over 48 hours	Continuous IV infusion Days 1, 2 and 15, 16
Leucovorin	400 mg/m^2 IV	Days 1 and 15
Oxaliplatin (both mFOLFOX6 regimens)	85 mg/m^2 IV	Days 1 and 15
Bevacizumab (or biosimilar) (mFOLFOX6-2+bevacizumab only)	5mg/kg	Days 1 and 15

IV=intravenously, m = meter, mg = milligram, kg = kilogram

5.4.3. Dose Modifications for mFOLFOX6 ± Bevacizumab

Below are recommended guidelines for dose modification. However, in case of conflict between these recommendations and either the most recent prescribing information for the various components or the institutional standard of care, investigators should use their best medical judgment. In general, if treatment is interrupted due to toxicity, retain the original stop and start dates; do not make up for missed doses when treatment is resumed.

5.4.3.1. Dose Modifications for mFOLFOX6

Dose reduction levels for toxicities potentially associated with components of the mFOLFOX6 combination chemotherapy are presented in Table 22.

Table 22: Dose Reduction Levels for Toxicities Associated with mFOLFOX6

Agent	Starting Dose	Reduced Dose Level -1	Reduced Dose Level -2	Reduced Dose Level -3
Oxaliplatin (IV)	85 mg/m^2	65 mg/m^2	50 mg/m^2	Discontinue
Fluorouracil IV bolus[a]	400 mg/m^2	320 mg/m^2	200 mg/m^2	Discontinue
Fluorouracil IV infusion	2400 mg/m^2	2000 mg/m^2	1600 mg/m^2	Discontinue

IV=intravenously; m = meter; mg = milligram
[a]Applicable only to mFOLFOX6-1.

Refer to Table 20 for general guidelines for dose modifications for neurologic toxicity of cisplatin, which may also be applied to oxaliplatin-associated neurotoxicity.

Refer to

Table 8 for recommended dose modifications for hematologic toxicities (ANC and platelet decreases) that may be associated with 5-FU or oxaliplatin administration. Dose modifications for these hematologic toxicities may follow those recommended for XELOX-associated toxicities.

Dose modifications for other toxicities potentially associated with components of the mFOLFOX combination chemotherapy are presented in Table 23, Table 24, and Table 25.

Table 23: Recommended Dose Modifications for 5-FU-Induced Palmar/Plantar Erythema (PPE), or Mucositis

Grade	PPE	Mucositis	5-FU Dose
1	Minimal skin changes (erythema) without pain	Erythema of the mucosa but normal diet	Maintain dose level
2	Skin changes (peeling, blisters, edema) or pain, not interfering with function	Patchy ulcerations, can eat and swallow modified diet	Decrease 1 dose level
3	Ulcerative dermatitis or skin changes with pain interfering with function	Confluent ulcerations; bleeding with minor trauma. Unable to adequately eat or hydrate orally	Decrease 2 dose levels
4	N/A	Tissue necrosis; significant spontaneous bleeding; life threatening consequences	Discontinue

Table 24: Recommended Dose Modifications for Renal Impairment Associated with Oxaliplatin

Drug	Renal Impairment	
	CrCL (ml/min)	Dose
Oxaliplatin	Moderate renal impairment	100%, but monitor and dose adjust according to toxicity
	< 20	Dose reduce – clinical decision

CrCL = creatinine clearance by Cockcroft/Gault formula

5-FU does not require dose modification in subjects with renal impairment.

For recommended dose modifications for 5-FU-induced hepatic impairment, see Table 18.

Oxaliplatin does not require dose modification in subjects with hepatic impairment.

Table 25: Recommended Dose Modifications for FOLFOX-induced diarrhea

Prior to a Cycle (Day 1)	Toxicity		Current Cycle	Suggested Dose Level for Subsequent Cycles		
	Grade		5-FU	Oxaliplatin	5-FU	ZW25
• If diarrhea grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks maximum 2 times. • If diarrhea < Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the highest grade experienced. • If diarrhea remains Grade 2 after 2 weeks, discontinue treatment.	1	Increase of < 4 stools/day over baseline	Continue 5-FU infusion	Maintain dose level	Maintain dose level	For guidance on management of diarrhea potentially associated with ZW25, see Table 2. In general, ZW25 should only be reduced if grade 3 diarrhea recurs after at least one dose reduction of chemotherapy component(s).
	2	Increase of 4 to 6 stools/days over baseline	Continue 5-FU infusion	Maintain dose level	Decrease 1 dose level[a]	
	3	Increase of ≥ 7 stools/day	Immediately interrupt 5-FU infusion until Day 1 of next cycle	Decrease 1 dose level	Decrease 1 dose level[a]	
	4	Increase of 10 or more stools/day or grossly bloody diarrhea; may require par enternal support. Urgent intervent ion indicated		Decrease 1 dose level	Decrease 2 dose levels or permanently discontinue[a]	

[a] If treatment with 5-FU is discontinued, then oxaliplatin is also discontinued.

5.4.3.2. Dose Modifications for Bevacizumab

Bevacizumab (or bevacizumab biosmiliar) dose modification should be per the prescribing information and per institutional standard of care. See also Section 5.4.5. In general, bevacizumab (or biosimilar) dose modifications are discouraged. If bevacizumab (or biosimilar) associated AEs occur, bevacizumab (or biosimilar) should be temporarily held or premanently discontinued rather than dose reduced.

Consider periodically monitoring urine protein via protein dipstick. For significant proteinuria via protein dipstick, consider 24 hour urine collection. Consider holding or discontinuing bevacizumab (or biosimilar) in subjects with significant proteinuria.

Blood pressure should be monitored at every clinic visit. Patients with significant hypertension should be treated with appropriate antihypertensive medications. If significant hypertension persists despite maximal antihypertensives, or subjects develop hypertensive crisis, bevacizumab or bevacizumab biosimilar should be permanently discontinued.

Bevacizumab (or biosimilar) does not require dose modification in subjects with renal or hepatic impairment.

5.4.4. Precautions for mFOLFOX6

5.4.4.1. Allergy to Platinium

Refer to Section 5.2.4.1 for a description and recommended mitigations.

5.4.4.2. Platinum Hypersensitivity

Refer to Section 5.2.4.2 for a description and recommended mitigations.

5.4.4.3. Pharyngo-largyngeal Dysesthesia

Refer to Section 5.2.4.3 for a description and recommended mitigations.

5.4.4.4. Diarrhea and Dehydration

All subjects should receive anti-diarrheal prophylaxis during the first cycle of treatment (see Section 5.1.10.1).

For precautions regarding diarrhea associated with ZW25 in combination with chemotherapy, as well as guidance regarding management of diarrhea, see Section 5.1.6.

If subjects develop diarrhea, suggested dose reductions of ZW25 and mFOLFOX6 can be found in Table 2 and Table 25. In general, ZW25 should only be reduced if grade 3 diarrhea recurs after at least one dose reduction of chemotherapy component(s).

5.4.4.5. Cardiotoxicity

Refer to Section 5.2.4.5 for descriptions and suggested management of myocardial ischemia, angina, QT prolongation, and torsades de pointes.

5.4.4.6. Dihydroyprimidine Dehydrogenase (DYPD) Deficiency

Refer to Section 5.2.4.6 for descriptions and recommended mitigations of DYPD deficiency. DYPD deficiency also affects subjects on 5-FU, which is a metabolite of capecitabine.

5.4.4.7. Pulmonary Fibrosis

Refer to Section 5.2.4.7 for recommended mitigations.

5.4.4.8. Veno-Occlusive Disease

Refer to Section 5.2.4.8 for recommended mitigations.

5.4.4.9. Hemolytic Uremic Syndrome

Refer to Section 5.2.4.9 for recommended mitigations.

5.4.5. Precautions for mFOLFOX6 + Bevacizumab

In addition to the precautions listed for mFOLFOX6 listed in 5.4.4, bevacizumab (or biosimilar) adds the following precautions per the USPI (AVASTIN® 2020):

5.4.5.1. Gastrointestinal Perforation and Fistulae

Serious, and sometimes fatal, gastrointestinal perforation or fistulae occurred at a higher incidence in patients receiving bevacizumab or biosmiliar compared to patients receiving chemotherapy. Discontinue in patients who develop gastrointestinal perforation, tracheoesophageal fistula or any Grade 4 fistula. Discontinue in patients with gastrointestinal perforation or fistula formation involving any internal organ.

5.4.5.2. Surgery and Wound Healing Complications

Bevacizumab and bevacizumab biosimilars can impair wound healing. In patients who experience wound healing complications during bevacizumab (or biosimilar) treatment, withhold bevacizumab (or biosimilar) until adequate wound healing. Withhold for at least 28 days prior to elective surgery. Do not administer for at least 28 days following major surgery and until adequate wound healing.

5.4.5.3. Hemorrhage

Bevacizuamab and bevacizumab biosimilars can result in two distinct patterns of bleeding: minor hemorrhage, which is most commonly Grade 1 epistaxis, and serious hemorrhage, which in some cases has been fatal. Severe or fatal hemorrhage, including hemoptysis, gastrointestinal bleeding, hematemesis, CNS hemorrhage, epistaxis, and vaginal bleeding, occurred up to 5-fold more frequently in patients receiving bevacizumab (or biosimilar) compared to patients receiving chemotherapy alone. Do not administer bevacizumab (or biosmiliar) to patients with recent history of hemoptysis of 1/2 teaspoon or more of red blood. Discontinue in patients who develop Grades ≥3 hemorrhage.

5.4.5.4. Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATE) including cerebral infarction, transient ischemic attacks, myocardial infarction, and angina; and venous thromboembolic events (VTE), including pulmonary embolism, occurred at a higher incidence in patients receiving bevacizumab (or biosimilar) compared to chemotherapy. Permanently discontinue in patients who develop a severe ATE or a Grade 4 VTE, including pulmonary embolism.

5.4.5.5. Hypertension

Severe hypertension occurred at a higher incidence in patients receiving bevacizumab and bevacizumab biosimilars as compared to patients receiving chemotherapy alone. Monitor blood pressure regularly during treatment with bevacizumab (or biosimilar) and treat with appropriate anti-hypertensive therapy as needed. Continue to monitor blood pressure at regular intervals in patients with bevacizumab-induced or -exacerbated hypertension after discontinuing bevacizumab or bevacizumab biosimilar. Withhold bevacizumab (or biosimilar) in patients with severe hypertension that is not controlled with medical management; resume once controlled with medical management. Discontinue in patients who develop hypertensive crisis or hypertensive encephalopathy.

5.4.5.6. Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving bevacizumab and bevacizumab biosimilars. PRES can present with headache, seizure, lethargy, hypertension, confusion, blindness, and other visual and neurologic disturbances. Confirm the diagnosis of PRES with magnetic resonance imaging (MRI). Permanently discontinue bevacizumab (or biosimilar) in patients who develop PRES. Symptoms usually resolve or improve within days after discontinuing bevacizumab (or biosimilar), although some patients have experienced ongoing neurologic sequelae.

5.4.5.7. Renal Injury and Proteinuria

The incidence and severity of proteinuria was higher in patients receiving bevacizumab and bevacizumab biosimilars as compared to patients receiving chemotherapy. Nephrotic syndrome occurred in < 1% of patients receiving bevacizumab (or biosimilar) across clinical studies, in some instances with fatal outcome. Bevacizumab (or biosimilar) in combination with chemotherapy may increase the risk of renal injury, as assessed by serum creatinine, and this effect may be permanent. Consider monitoring proteinuria by dipstick urinalysis for the development or worsening of proteinuria with serial urinalyses during bevacizumab (or biosimilar) therapy. Discontinue bevacizumab (or biosimilar) in patients who develop nephrotic syndrome.

5.4.5.8. Infusion-Related Reactions

Infusion-related reactions can occur with bevacizumab and bevacizumab biosimilars. These are most likely during the initial infusion but can occur at later timepoints as well. For further guidance regarding IRR, see Section 5.1.5.

5.4.5.9. Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal studies, bevacizumab and bevacizumab biosimilars may cause fetal harm when administered to pregnant women. Advise females of reproductive potential to use effective contraception during treatment with bevacizumab (or biosimilars) and for 6 months after the last dose.

5.4.5.10. Ovarian Failure

Bevacizumab and bevacizumab biosimilars in combination with chemotherapy may increase the risk of ovarian failure and in some cases, this ovarian failure can be permanent. Inform females of reproductive potential of the risk of ovarian failure prior to initiating bevacizumab or biosimilars.

5.4.5.11. Congestive Heart Failure (CHF)

Bevacizumab and bevacizumab biosimilars may increase the risk of CHF when combined with chemotherapy and ZW25. Periodic monitoring of cardiac function is required. If significant left ventricular dysfunction is seen, bevacizumab (or biosimilar) should be permanently discontinued. For guidance on the management of left ventricular dysfunction, see Section 5.1.4 and Table 3.

5.4.6. Storage, Handling, Packaging, Labeling, and Preparation for mFOLFOX6 +/- Bevacizumab

Refer to the prescribing information for each of the components of the combination chemotherapy.

5.4.7. Concomitant Therapy for mFOLFOX6 +/- Bevacizumab

5.4.7.1. Required Concomitant Therapy

All subjects should receive anti-diarrheal prophylaxis during the first cycle of treatment (see Section 5.1.10.1).

Additional premedications and supportive medications should be administered per the prescribing information for the chemotherapeutic component, as long as they are not contraindicated by the protocol.

At any time during the study, the SMC may recommend or modify premedications or supportive medications and the sponsor may implement these recommendations without amending the protocol.

5.4.7.2. Prohibited Concomitant Therapy

Refer to the prescribing information for each of the components of the combination chemotherapy for any other prohibited concomitant medications. See also Section 5.1.10.3.

5.4.7.3. Drug Interactions

Fluorouracil: Refer to Section 5.3.6.3.

Oxaliplatin: Refer to Section 5.2.6.3.

The bevacizumab USPI lists no specific drug interactions.

5.5. CisGem Multi-agent Combination Chemotherapy

If the investigator would prefer to use a different starting dose or recommended dose modification for any of the components of the chemotherapy regimen, the investigator should discuss the clinical reasons for this with the sponsor's medical monitor.

Note: At any time during the study, the SMC may recommend modifying the chemotherapy component(s) of any regimen. The sponsor may implement these SMC recommendations without amending the study protocol.

5.5.1. Description of CisGem:

CisGem is a multi-agent chemotherapy regimen consisting of cisplatin and gemcitabine. CisGem has been established as an efficacious cytotoxic regimen with a manageable safety profile in various cancers including non-small cell lung cancer, bladder cancer, and BTC (Valle 2010).

5.5.2. Dose and Administration of CisGem

Dosing for both parts of the study will be given in 21-day cycles.

CisGem will be administered as follows: Cisplatin 25 mg/m^2 IV on Days 1 and 8 of each 21-day cycle plus gemcitabine 1,000 mg/m^2 IV on Days 1 and 8 of each 21-day cycle. Subjects who discontinue chemotherapy without disease progression and for reasons that are not related to ZW25 toxicity may continue on ZW25 alone.

The dose levels, schedule, and administration of each component of CisGem are presented in Table 26 below. The combination chemotherapy should be given to each subject after receiving ZW25.

Table 26: CisGem Dose Levels, Schedule, and Administration

Drug	Dose/Route	Schedule
Cisplatin	25 mg/m^2 IV	Days 1 and 8
Gemcitabine	1000 mg/m^2 IV	Days 1 and 8

IV=intravenously; m = meter; mg = milligrams

5.5.3. Dose Modifications for CisGem

Below are recommendations for dose modification for CisGem toxicity. However, in case of conflict between these recommendations and either the most recent prescribing information for the chemotherapy components or institutional standard of care, investigators should use their best medical judgment. In general, if treatment is interrupted due to toxicity, retain the original stop and start dates; do not make up for missed doses when treatment is resumed.

Dose modifications for toxicities potentially associated with components of the CisGem combination chemotherapy are presented in Table 27, Table 28, and Table 29.

Table 27: Recommended Dose Modifications for Hematologic Toxicities Associated with CisGem

ANC (x10^9/L)		Platelets (x10^9/L)	Day 1		Day 8	
			Gemcitabine	Cisplatin	Gemcitabine	Cisplatin
> 1000	and	> 100,000	100%	100%	100%	100%
500-1000	or	75-100	75%	100%	75%	100%
500	or	< 75	Delay	Delay	Omit	Omit

ANC = absolute neutrophil count; L = liter

For recommended dose modifications for renal impairment associated with cisplatin, see Table 16.

Gemcitabine does not require dose reduction in mild to moderate renal impairment. Consider dose reduction if the GFR < 30 mL/min.

Table 28: Recommended Gemcitabine Dose Modifications in Subjects with Hepatic Impairment

Bilirubin	Gemcitabine Dose
< 1.6x ULN	100%
> 1.6x ULN	80%

AST = aspartate aminotransferase; L = liter

Cisplatin does not require dose reduction in subjects with hepatic impairment.

Table 29: Recommended Dose Modifications for Non-Hematologic Toxicities Associated with CisGem

Worst Non-Hematologic Toxicity with previous cycle	**Dose on Day 1 of Cycle**	
	Gemcitabine	**Cisplatin**
Grade 3	75%	75%
Grade 4	50%, or consider discontinuing	50%, or consider discontinuing
Toxicity on Day 8 of cycle	**Dose on Day 8 of Cycle:**	
	Gemcitabine	**Cisplatin**
Grade 3 or Grade 4	Omit	Omit

For dose modifications for Cisplatin Neurologic Toxicities, see Table 20.

5.5.4. Precautions for CisGem

5.5.4.1. Allergy to Platinium
Refer to Section 5.2.4.1 for a description and recommended mitigations.

5.5.4.2. Platinum Hypersensitivity
Refer to Section 5.2.4.2 for a description and recommended mitigations.

5.5.4.3. Pharyngo-largyngeal Dysesthesia
Refer to Section 5.2.4.3 for a description and recommended mitigations.

5.5.4.4. Diarrhea and Dehydration
All subjects should receive anti-diarrheal prophylaxis during the first cycle of treatment (see Section 5.1.10.1).

For precautions regarding diarrhea associated with ZW25 in combination with chemotherapy, as well as guidance regarding management of diarrhea, see Section 5.1.6.

If subjects develop diarrhea, suggested dose reductions of ZW25 and CisGem can be found in Table 2 and Table 29. In general, ZW25 should only be reduced if grade 3 diarrhea recurs after at least one dose reduction of chemotherapy component(s).

5.5.4.5. Gemcitabine Hypersensitivity
Gemcitabine can cause hypersensitivity reactions similar to those seen with platinum agents. Refer to Section 5.2.4.2 for a description and recommended mitigations.

5.5.4.6. Pulmonary Toxicity and Respiratory Failure
Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), has been reported with gemcitabine. In some

cases, these pulmonary events can lead to fatal respiratory failure despite the discontinuation of therapy. The onset of pulmonary symptoms may occur up to 2 weeks after the last dose of gemcitabine.

Permanently discontinue gemcitabine in patients who develop unexplained dyspnea, with or without bronchospasm, or evidence of severe pulmonary toxicity.

5.5.4.7. Hemolytic Uremic Syndrome

Discontinue gemcitabine for hemolytic uremic syndrome or severe renal impairment. Monitor renal function prior to initiation and during treatment. Refer to Section 5.2.4.9 for a description and recommended mitigations.

5.5.4.8. Hepatic Toxicity

Drug-induced liver injury, including liver failure and death, has been reported in patients receiving gemcitabine alone or with other potentially hepatotoxic drugs. Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis can lead to exacerbation of the underlying hepatic insufficiency. Assess hepatic function prior to initiation of gemcitabine and periodically during treatment. Permanently discontinue gemcitabine in patients who develop severe hepatic toxicity.

5.5.4.9. Embryo-Fetal Toxicity

Based on animal data and its mechanism of action, gemcitabine can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with gemcitabine and for 6 months after the final dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with gemcitabine and for 3 months following the final dose.

5.5.4.10. Radiation Recall

Gemcitabine should not be administered concurrently with radiation or within 7 days of completion of radiation. Radiation recall has been reported in patients who received gemcitabine after prior radiation.

5.5.4.11. Capillary Leak Syndrome

Capillary leak syndrome (CLS) with severe consequences has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Permanently discontinue gemcitabine if CLS develops during therapy.

5.5.4.12. Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) has been reported in patients receiving gemcitabine as a single agent or in combination with other chemotherapeutic agents. Refer to Section 5.4.5.6 for a description and recommended mitigations.

5.5.5. Storage, Handling, Packaging, Labeling, and Preparation for CisGem

Refer to the prescribing information for each of the components of the combination chemotherapy.

5.5.6. Concomitant Therapy for CisGem

5.5.6.1. Required Concomitant Therapy for CisGem

All subjects should receive anti-diarrheal prophylaxis during the first cycle of treatment (see Section 5.1.10.1).

Additional premedications and supportive medications should be administered per the prescribing information for the chemotherapeutic component, as long as they are not contraindicated by the protocol.

At any time during the study, the SMC may recommend or modify premedications or supportive medications and the sponsor may implement these recommendations without amending the protocol.

5.5.6.2. Prohibited Concomitant Therapy

Refer to the prescribing information for each of the components of the combination chemotherapy for any other prohibited concomitant medications. See also Section 5.1.10.3.

5.5.6.3. Drug Interactions

For cisplatin drug interactions see Section 5.3.6.3.

The gemcitabine USPI lists no specific drug interactions.

5.6. Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents and the CRF.

6. TIMING OF STUDY PROCEDURES

Subjects will provide written informed consent before any study-related procedures are performed; however, after a subject consents to pre-screening, tumor samples may be sent to the local (only for subjects with GEA in Part 1; see Section 4.1.1) or central laboratory for analysis/review of HER2 status before the subject signs informed consent for all other study procedures. The planned study assessments are presented in Appendix A (XELOX-1 and XELOX-2), Appendix B (XELOX-3), Appendix C (FP-1 and FP-2), Appendix D (mFOLFOX6-1 and mFOLFOX6-2 ± bevacizumab or biosimilar), and Appendix E (CisGem). Specific time points for PK sampling are presented Appendix F (extensive sampling for ZW25 plus any XELOX, FP, or CisGem regimen), Appendix G (extensive sampling for ZW25+mFOLFOX6), Appendix H (sparse sampling for ZW25 plus any XELOX, FP, or CisGem regimen), and Appendix I (sparse sampling for ZW25+mFOLFOX6).

6.1. HER2 Pre-screening Visit (After Diagnosis and Prior to Screening Visit)

Subject's tumors (new tumor biopsy or archived tissue) may be pre-screened for HER2 status any time after diagnosis of advanced or metastatic disease and before study enrollment. Informed consent for collection and analysis of the tumor tissue will be required. Subjects who consent to this pre-screening procedure will be required to be registered in the interactive response technology (IRT) system. See the Laboratory Manual for details regarding sample collection and assessment.

The main consent for the remaining screening assessments listed below must be signed prior to the start of any screening procedures.

For subjects with BTC, the definition of advanced disease includes previously resected advanced (Stage 3) disease, with the intent to allow pre-screening of participants with BTC prior to diagnosis of metastatic disease.

6.2. Screening Visit (Day –28 to Predose Day 1) for All Subjects

Screening procedures will be completed within 28 days before first administration of study treatment. In case a subject cannot receive their first treatment within the required time windows for the screening assessments, rescreening should be performed. Procedures done as part of standard of care within the 28-day window and meeting study requirements may be used for study purposes.

- Informed consent
- Register in IRT system to obtain a Subject ID
- Full medical history
- Eligibility (per the inclusion and exclusion criteria)
- Demographic data
- New tumor biopsy (archival tumor tissue is allowed if new is unobtainable)
- Disease assessment per RECIST 1.1 (CT/MRI scans)
- Physical examination, including height and body weight
- ECOG performance status
- Vital signs
- Hematology, coagulation, and serum chemistry panels
- Urinalysis
- Pregnancy tests (only for women of childbearing potential)
- 12-lead ECG

- Echocardiogram/MUGA
- Hepatitis B surface antigen, hepatitis C antibody, and HIV tests (if indicated) (Note: Subjects with well-controlled HIV [e.g., CD4 > 350/mm^3 and undetectable viral load] are eligible.)
- Carcinoembryonic antigen (CEA) sample, if available locally
- Carbohydrate antigen 19-9 (CA 19-9) sample, if available locally (BTC only)

6.3. Treatment Cycle for ZW25+XELOX-1 and ZW25+XELOX-2

The schedule of assessments for the XELOX-1 and XELOX-2 regimens are shown in Appendix A. Subjects will remain on study treatment until criteria for discontinuation (Section 6.14) are met.

6.3.1. Day 1 (± 2 Days for Cycles Beyond Cycle 1)

Prior to dosing

- Eligibility (Cycle 1 only; subjects must still meet inclusion/exclusion criteria prior to receiving treatment)
- Register in IRT system
- Physical examination, including weight
- ECOG performance status
- Vital signs
- Hematology, coagulation (Cycle 1 only), and serum chemistry panels
- Urinalysis
- Pregnancy test (only for women of childbearing potential)
- 12-lead ECG (Cycles 1 and 4 only)
- ADA samples (Cycles 1 and 2, then every even-numbered cycle thereafter)
- Circulating tumor DNA (ctDNA) samples (Cycles 1 and 3 only)
- PK assessment samples (Cycles 1, 2, 3, and 4, then every even-numbered cycle thereafter)

Administer study treatment

- ZW25 administration (Section 5.1)
- XELOX administration (Section 5.2)

Postdose Activities

- Vital signs (within 30 minutes of the end of the infusion)
- 12-lead ECG (at 1 hour [±15 minutes] and 4 hours [±15 minutes] after the end of ZW25 infusion [Cycles 1 and 4 only])
- PK assessment samples (Cycles 1, 2, 3, and 4, then every even-numbered cycle thereafter)

Note: Physical examination, ECOG performance status, and samples for hematology, coagulation, serum chemistry, urinalysis, and pregnancy (if applicable) tests may be done within 3 days prior to administration of study drug and do not need to be repeated if done within the prior 3 days.

Note: Cycle # is based on counting from the first treatment cycle (when subject was taking chemotherapy). Cycle numbering does not restart if/when the subject stops chemotherapy.

6.3.2. Days 1 – 15

- Capecitabine administration starting on the evening of Day 1 and continuing through the morning of Day 15

6.3.3. Day 2

- PK assessment samples (Cycle 1, for extensive sampling schedule only)

6.3.4. Day 5

- PK assessment samples (Cycle 1, for extensive sampling schedule only)

6.4. Treatment Cycle for ZW25+XELOX-3

The schedule of assessments for the XELOX-3 regimen is shown in Appendix B. Subjects will remain on study treatment until criteria for discontinuation (Section 6.14) are met.

6.4.1. Day 1 (± 2 Days for Cycles Beyond Cycle 1)

Prior to dosing

- Eligibility (Cycle 1 only; subjects must still meet inclusion/exclusion criteria prior to receiving treatment)
- Register in IRT system
- Physical examination, including weight
- ECOG performance status
- Vital signs
- Hematology, coagulation (Cycle 1 only), and serum chemistry panels
- Urinalysis
- Pregnancy test (only for women of childbearing potential)

- 12-lead ECG (Cycles 1 and 4 only)
- ADA samples (Cycles 1 and 2, then every even-numbered cycle thereafter)
- Circulating tumor DNA (ctDNA) samples (Cycles 1 and 3 only)
- PK assessment samples (Cycles 1 and 2, 3, 4, and then every even-numbered cycle thereafter)

Administer study treatment

- ZW25 administration (Section 5.1)
- XELOX administration (Section 5.2)

Postdose activities

- Vital signs (within 30 minutes of the end of the infusion)
- 12-lead ECG (at 1 hour [±15 minutes] and 4 hours [±15 minutes] after the end of ZW25 infusion [Cycles 1 and 4 only])
- PK assessment samples (Cycles 1 and 2, 3, and 4, then every even-numbered cycle thereafter)

Note: Physical examination, ECOG performance status, and samples for hematology, coagulation, serum chemistry, urinalysis, and pregnancy (if applicable) tests may be done within 3 days prior to administration of study drug and do not need to be repeated if done within the prior 3 days.

Note: Cycle # is based on counting from the first treatment cycle (when subject was taking chemotherapy). Cycle numbering does not restart if/when the subject stops chemotherapy.

6.4.2. Days 1 – 15

- Capecitabine administration starting on the evening of Day 1 and continuing through the morning of Day 15

6.4.3. Day 2

- PK assessment samples (Cycle 1, for extensive sampling schedule only)

6.4.4. Day 5

- PK assessment samples (Cycle 1, for extensive sampling schedule only)

6.4.5. Day 8 (± 2 Days)

- ZW25 administration
- PK assessment samples (predose and after dosing, Cycles 1, 2, and 3)

6.5. Treatment Cycle for ZW25+FP-1 and ZW25+FP-2

The schedule of assessments for the FP regimens is shown in Appendix C. Subjects will remain on study treatment until criteria for discontinuation (Section 6.14) are met.

6.5.1. Day 1 (± 2 Days for Cycles Beyond Cycle 1)

Prior to dosing

- Eligibility (Cycle 1 only; subjects must still meet inclusion/exclusion criteria prior to receiving treatment)
- Register in IRT system
- Physical examination, including weight
- ECOG performance status
- Vital signs
- Hematology, coagulation (Cycle 1 only), and serum chemistry panels
- Urinalysis
- Pregnancy test (only for women of childbearing potential)
- 12-lead ECG (Cycles 1 and 4 only)
- ADA samples (Cycles 1 and 2, then every even-numbered cycle thereafter)
- Circulating tumor DNA (ctDNA) samples (Cycles 1 and 3 only)
- PK assessment samples (Cycles 1, 2, 3, and 4, then every even-numbered cycle thereafter)

Administer study treatment

- ZW25 administration (Section 5.1)
- FP administration (Section 5.3)

Postdose activities

- Vital signs (within 30 minutes of the end of the infusion)
- 12-lead ECG (at 1 hour [±15 minutes] and 4 hours [±15 minutes] after the end of ZW25 infusion [Cycles 1 and 4 only])
- PK assessment samples (Cycles 1, 2, 3, and 4, then every even-numbered cycle thereafter)

Note: Physical examination, ECOG performance status, and samples for hematology, coagulation, serum chemistry, urinalysis, and pregnancy (if applicable) tests may be done within

3 days prior to administration of study drug and do not need to be repeated if done within the prior 3 days.

Note: Cycle # is based on counting from the first treatment cycle (when subject was taking chemotherapy). Cycle numbering does not restart if/when the subject stops chemotherapy.

6.5.2. Days 1 – 5

- 5-FU administration

6.5.3. Day 2

- PK assessment samples (Cycle 1, for extensive sampling schedule only)

6.5.4. Day 5

- PK assessment samples (Cycle 1, for extensive sampling schedule only)

6.6. Treatment Cycle for ZW25+mFOLFOX6-1 and ZW25+mFOLFOX6-2 ± bevacizumab

The schedule of assessments for the mFOLFOX6 regimens are shown in Appendix D. Subjects will remain on study treatment until criteria for discontinuation (Section 6.14) are met.

6.6.1. Day 1 (± 2 Days for Cycles Beyond Cycle 1)

Prior to dosing

- Eligibility (Cycle 1 only; subjects must still meet inclusion/exclusion criteria prior to receiving treatment)
- Register in IRT system
- Physical examination, including weight
- ECOG performance status
- Vital signs
- Hematology, coagulation (Cycle 1 only), and serum chemistry panels
- Urinalysis
- Pregnancy test (only for women of childbearing potential)
- 12-lead ECG (Cycles 1 and 4 only)
- ADA samples (Cycles 1 and 2, then every even-numbered cycle thereafter)
- Circulating tumor DNA (ctDNA) samples (Cycle 1 only)
- PK assessment samples (Cycles 1, 2, 3, and 4, then every even-numbered cycle thereafter)

Administer study treatment

- ZW25 administration (Section 5.1)
- mFOLFOX6 ± bevacizumab or bevacizumab biosimilar administration (Section 5.4), including start of continuous IV infusion 5-FU administration

Postdose activities

- Vital signs (within 30 minutes of the end of the infusion)
- 12-lead ECG (at 1 hour [±15 minutes] and 4 hours [±15 minutes] after the end of ZW25 infusion [Cycles 1 and 4 only])
- PK assessment samples (Cycles 1, 2, 3, and 4, then every even-numbered cycle thereafter)

Note: Physical examination, ECOG performance status, and samples for hematology, coagulation, serum chemistry, urinalysis, and pregnancy (if applicable) tests may be done within 3 days prior to administration of study drug and do not need to be repeated if done within the prior 3 days.

Note: Cycle # is based on counting from the first treatment cycle (when subject was taking chemotherapy). Cycle numbering does not restart if/when the subject stops chemotherapy.

6.6.2. Day 2

- 5-FU administration
- PK assessment samples (Cycle 1, for extensive sampling schedule only)

6.6.3. Day 5

- PK assessment samples (Cycle 1, for extensive sampling schedule only)

6.6.4. Day 15 (± 2 Days)

Prior to dosing

- Physical examination, including weight
- Vital signs
- Hematology and serum chemistry panels
- ADA samples (Cycles 1 and 2 only)
- ctDNA samples (Cycle 2 only)
- PK assessment samples (Cycles 1 and 2 only)

Administer study treatment

- ZW25 administration (Section 5.1)

- mFOLFOX6 administration (Section 5.4), including start of continuous IV infusion 5-FU administration

Postdose activities

- Vital signs (within 30 minutes of the end of the infusion)
- PK assessment samples (Cycles 1, 2, and 3)

Note: Cycle # is based on counting from the first treatment cycle (when subject was taking chemotherapy). Cycle numbering does not restart if/when the subject stops chemotherapy.

6.6.5. Day 16

- 5-FU administration

6.7. Treatment Cycle for ZW25+CisGem

The schedule of assessments for the CisGem regimen is shown in Appendix E. Subjects will remain on study treatment until criteria for discontinuation (Section 6.14) are met.

6.7.1. Day 1 (± 2 Days for Cycles Beyond Cycle 1)

Prior to dosing

- Eligibility (Cycle 1 only; subjects must still meet inclusion/exclusion criteria prior to receiving treatment)
- Register in IRT system
- Physical examination, including weight
- ECOG performance status
- Vital signs
- Hematology, coagulation (Cycle 1 only), and serum chemistry panels
- Urinalysis
- Pregnancy test (only for women of childbearing potential)
- 12-lead ECG (Cycles 1 and 4 only)
- ADA samples (Cycles 1 and 2, then every even-numbered cycle thereafter)
- Circulating tumor DNA (ctDNA) samples (Cycles 1 and 3 only)
- PK assessment samples (Cycles 1, 2, 3, and 4, then every even-numbered cycle thereafter)

Administer study treatment

- ZW25 administration (Section 5.1)

- CisGem administration (Section 5.5)

Postdose activities

- Vital signs (within 30 minutes of the end of the infusion)
- 12-lead ECG (at 1 hour [±15 minutes] and 4 hours [±15 minutes] after the end of ZW25 infusion [Cycles 1 and 4 only])
- PK assessment samples (Cycles 1, 2, 3, and 4, then every even-numbered cycle thereafter)

Note: Physical examination, ECOG performance status, and samples for hematology, coagulation, serum chemistry, urinalysis, and pregnancy (if applicable) tests may be done within 3 days prior to administration of study drug and do not need to be repeated if done within the prior 3 days.

Note: Cycle # is based on counting from the first treatment cycle (when subject was taking chemotherapy). Cycle numbering does not restart if/when the subject stops chemotherapy.

6.7.2. Day 2

- PK assessment samples (Cycle 1 for extensive sampling schedule only)

6.7.3. Day 5

- PK assessment samples (Cycle 1 for extensive sampling schedule only)

6.7.4. Day 8 (± 2 Days)

- CisGem administration (Section 5.5)
- PK assessment sample (Cycles 1, 2, and 3)

6.8. Every 6 Weeks (± 7 Days) for All Subjects

- Disease assessment per RECIST 1.1 (CT/MRI scans every 6 weeks [± 7 days] timed from Cycle 1 Day 1)
- CEA sample and/or CA 19-9 sample (BTC), if available locally (each time CT/MRI scans are done)

6.9. Every 12 Weeks (± 7 Days) for All Subjects

- Echocardiogram/MUGA (First post-baseline scans should be done at 6 weeks [± 7 days] from Cycle 1 Day 1. All subsequent scans should be done in 12-week intervals [± 7 days] thereafter; scans are not required at EOT if ≤ 3 months since the previous scan.)

6.10. End of Treatment (EOT) Visit for All Subjects

The EOT visit will be performed for subjects who are withdrawn from treatment for any reason and will take place as soon as possible after a subject permanently stops study treatment (within 7 days after the last dose [ZW25 or any chemotherapy component]).

- Optional tumor biopsy at disease progression if the subject provides additional consent
- Register in IRT system
- Disease assessment per RECIST 1.1 (CT/MRI scans, not required if ≤ 4 weeks since previous scan)
- Physical examination, including weight
- ECOG performance status
- Vital signs
- Hematology and serum chemistry panels
- Urinalysis
- Pregnancy test (if applicable)
- 12-lead ECG
- Echocardiogram/MUGA (not required if ≤ 3 months since last scan)
- ADA samples
- ctDNA samples (only at time of disease progression, if applicable)
- CEA sample and/or CA 19-9 sample (BTC), if available locally (if CT/MRI scans are done)
- PK assessment samples (only if the subject has completed < 6 months of treatment)

6.11. Safety Follow-up for All Subjects

Approximately 30 days (window of + 7 days) after the last dose of study drug (ZW25 or any chemotherapy component), all subjects will have a safety follow-up visit, which will include the below assessments.

- Disease assessment per RECIST 1.1 (CT/MRI scans, not required if done at EOT visit and/or ≤ 4 weeks since previous scan)
- Physical examination, including weight
- ECOG performance status
- Vital signs
- Hematology and serum chemistry panels
- Urinalysis
- Pregnancy test (if applicable)
- 12-lead ECG
- ADA samples (not required if ≤ 2 weeks since last sample)

- ctDNA samples (only at time of disease progression, if applicable, and not previously collected at EOT)
- CEA sample and/or CA 19-9 sample (BTC), if available locally (if CT/MRI scans are done)

Additionally, treatment-emergent AESIs (defined in Section 7.2.4) should continue to be followed until resolution or return to baseline or study closure.

6.12. Efficacy Follow-up for All Subjects

If CT/MRI scans were not done at the EOT visit nor within the 4 weeks prior to the 30-day safety follow-up visit, disease assessment per RECIST 1.1 should be performed at the time of the safety follow-up visit (CT/MRI scans). If a subject experiences disease progression prior to the safety follow-up visit, radiographic scans should be obtained at the time of progression.

6.13. Survival Follow-up for All Subjects

After discontinuing study treatment and/or disease progression, whichever comes later, all subjects who receive any amount of study treatment will be followed for survival approximately every 3 months (± 14 days) until death, withdrawal from the study, or study closure, whichever occurs first. Information about subsequent anticancer therapies initiated during follow-up will be collected, if available.

6.14. Duration of Treatment for All Subjects

For both parts of the study, subjects may continue on ZW25 until evidence of clinical disease progression, radiographically-confirmed disease progression as defined by RECIST 1.1, unacceptable toxicity, investigator decision, consent withdrawal, start of a subsequent anticancer therapy, or study termination by the sponsor. Also, if a subject has not taken ZW25 for more than 4 weeks, he/she will be withdrawn from study treatment unless approval is obtained from the medical monitor to continue on study treatment.

Physician's choice of combination chemotherapy may be administered for the following durations:

- During the first 6 cycles: Discontinue chemotherapy only for evidence of clinical disease progression, radiographically-confirmed disease progression as defined by RECIST version 1.1, unacceptable toxicity, consent withdrawal, start of a subsequent anticancer therapy, or study termination by the sponsor.
- After Cycle 6, continuation of chemotherapy is at the discretion of the investigator and the subject.

For both parts of the study, for subjects receiving XELOX or mFOLFOX6 regimens, if oxaliplatin is discontinued due to toxicity unrelated to ZW25, subjects may continue to receive capecitabine (in XELOX) or 5-FU (in mFOLFOX6) with ZW25. However, if capecitabine or 5-FU is discontinued due to toxicity unrelated to ZW25, oxaliplatin should also be discontinued.

For both parts of the study, for subjects receiving the mFOLFOX6+bevacizumab or bevacizumab biosimilar regimen, if oxaliplatin is discontinued due to toxicity unrelated to ZW25, subjects may continue to receive 5-FU and bevacizumab (or biosimilar) with ZW25. However, if 5-FU is discontinued due to toxicity unrelated to ZW25, oxaliplatin should also be discontinued. Furthermore, if both oxaliplatin and 5-FU are discontinued, bevacizumab (or biosimilar) should also be discontinued.

If in the opinion of the investigator, all components of the combination chemotherapy should be discontinued due to toxicity unrelated to ZW25, a subject may continue to receive treatment with ZW25 monotherapy. Subjects may not continue on combination chemotherapy alone on study if ZW25 is discontinued; however, subjects who discontinue treatment with ZW25 in either part of the study for any reason should enter long-term follow-up for survival.

7. EFFICACY, PHARMACOKINETIC, AND SAFETY ASSESSMENTS

The planned study assessments for each combination treatment are presented in Appendix A (XELOX-1 and XELOX-2), Appendix B (XELOX-3), Appendix C (FP-1 and FP-2), Appendix D (mFOLFOX6-1 and mFOLFOX6-2), and Appendix E (CisGem). Specific PK sampling timepoints are presented in Appendix F extensive sampling for ZW25 plus any XELOX, FP, or CisGem regimen), Appendix G (extensive sampling for ZW25+mFOLFOX6), Appendix H (sparse sampling for ZW25 plus any XELOX, FP, or CisGem regimen), and Appendix I (sparse sampling for ZW25+mFOLFOX6). For all regimens, 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.

7.1. Efficacy Assessments

7.1.1. CT and MRI Scans for Tumor Response

Tumor response will be evaluated based on CT and/or MRI scans (using the same methodology for each scan of the same subject) of the chest, abdomen, and pelvis plus additional areas of known or suspected tumor involvement (e.g., brain). The radiological assessment will be performed at the visits according to the description provided in the applicable assessment schedule.

Objective responses and tumor progression will be evaluated by the investigator. Initial responses should be confirmed with a scan obtained not less than 4 weeks following initial documentation of objective response.

Scans from subjects will be collected and may undergo centralized review at the discretion of the sponsor. The investigator assessment will be used for all treatment-related decisions.

7.1.2. Biopsy for Biomarkers

In both study parts, all subjects must be able to provide new tissue biopsies or archived tumor biopsies for central review. For both Part 1 and 2, archival tumor biopsies that were obtained ≤ 6

months prior to screening may be used; otherwise, new biopsies are required unless archival biopsies > 6 months are approved by the medical monitor.

In Part 1, subjects with archived tissue showing HER2-expressing GEA based upon local assessment that used FDA approved HER2 testing for GEA may be eligible to enroll, but archival tissues must be submitted for retrospective central review after enrollment. The two FDA-approved tests for diagnosing the HER2 status of gastric cancers are the Hercept test (IHC) and the Dako HER2 FISH pharmDx (FISH) test, and status should be assessed using the College of American Pathologists/American Society for Clinical Pathology/American Society of Clinical Oncology guideline for HER2 testing and clinical decision making in GEA (Bartley 2017). If a study site does not have the capacity to use the FDA-approved tests, then a biopsy sample must be submitted for prospective central assessment before enrollment in Part 1. For Part 2, central review confirmation of HER2 status is required prior to enrollment of subjects with GEA.

Enrollment of subjects with BTC and CRC will be based on central assessment of HER2 status for both study parts.

If possible and additional consent is provided, an optional tumor biopsy may be obtained at the time of disease progression from an accessible site to assess changes in HER2 expression as well as the presence of other [redacted]. If a study subject is independently tested for other biomarkers while on-study (e.g., FoundationOne® CDx or other genomic sequencing), the results may be collected. [redacted]

No genomic testing of germ-line DNA will performed in this study.

7.1.3. Blood Samples for Biomarkers

Additional blood samples will be taken at selected time points specified in the applicable assessment schedules for assessment of biomarkers, including but not limited to ctDNA. If a study subject is independently tested for other biomarkers while on-study, the results may be collected.

Samples should be collected for local assessment of CEA and/or CA 19-9 (BTC), (if available locally) each time CT/MRI scans are done.

7.1.4. Pharmacokinetic Assessments

Venous blood samples for measurement of serum concentrations of ZW25 will be drawn at selected time points specified in the applicable assessment schedules. The actual date and time (24-hr clock time) of each sampling will be recorded in the subject's source document at the site. The sampling window for each time point is presented in Appendix F (extensive sampling for ZW25 plus any XELOX, FP, or CisGem regimen), Appendix G (extensive sampling for ZW25+mFOLFOX6), Appendix H (sparse sampling for ZW25 plus any XELOX, FP, or CisGem regimen), and Appendix I (sparse sampling for ZW25+mFOLFOX6). Deviations from planned sampling windows will be assessed before database lock for the impact on PK and may be excluded from time point summaries of PK concentrations. Actual time will be used for derivation of PK parameters.

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.

Subjects on any regimen who have completed 3 or more cycles of treatment may be assigned to an optional steady-state extensive PK sampling schedule (see Appendix J). This steady-state extensive sampling schedule is in addition to, rather than replacing, the previously assigned sampling schedule. This steady-state extensive sampling schedule may not be applied more than once to any subject. Additional consent will be required to be obtained for this optional sampling schedule.

Complete instructions for sample collection, processing, handling, and shipment will be provided in the Laboratory Manual.

If a subject experiences an AE that results in an unscheduled visit or meets SAE criteria, a blood sample for the measurement of serum concentrations of ZW25 should be collected if less than 24 hours have elapsed since the last dose of ZW25, if possible. The sample will be recorded as unscheduled time point and may be also used in PK parameters derivation using actual time. An additional sample may also be drawn in the event of an infusion reaction.

7.1.5. Immunogenicity (Anti-drug Antibody) Assessments

Blood samples to test for antibodies to ZW25 will be obtained at selected time points specified in the applicable assessment schedules. Blood samples for ADAs will be taken before the start of the ZW25 infusion. All ADA blood sample collection time points coincide with a pre-dose PK sample time point. If a subject terminates early from the clinical trial, all efforts will be made to collect blood samples to test for antibodies to ZW25 unless consent has been withdrawn. Additional samples may be drawn in the event of an infusion reaction.

The immunogenicity testing will be performed in 3 steps as follows: screening assay (Tier 1), confirmation assay (Tier 2), and titration (Tier 3). Only samples positive in the screening assay will be tested in confirmation and further titrated to determine the titer of ADA.

For any samples that are confirmed positive for anti-ZW25 antibody, there may be additional testing done to characterize domain specificity (T2a) and possibly the anti-ZW25 antibody potential for neutralizing activity on ZW25.

Additional sample handling, processing, storage, labeling, and shipping instructions will be provided to the site in the Laboratory Manual.

7.2. Safety Assessments

Safety assessments will consist of AEs, hematology, coagulation, serum chemistry, urinalysis, vital signs, physical examination (including body weight), ECG, ECOG performance status, and echocardiogram/MUGA.

7.2.1. Adverse Events

7.2.1.1. Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of preexisting conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the CRF under specific safety assessments. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome. In general, an abnormal laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”) if possible. It is the responsibility of the investigator to document all AEs that occur during the study. AEs will be elicited by asking the subject a nonleading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?” AEs should be reported on the appropriate page of the CRF.

Safety Reporting Period

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.

Assessment of Severity

Safety evaluations will be made on the basis of the NCI-CTCAE v5.0 (27 November 2017). Grades of the NCI-CTCAE refer to the severity of the AE:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL): Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE to ZW25 alone, chemotherapy alone, or to the combination of ZW25 and chemotherapy. Causality should be assessed using the categories below:

- Related: There is a plausible temporal relationship between the onset of the AE and administration of the study drug, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge. An AE will be considered related, unless it fulfills the criteria specified below. Related AEs will include any AE that is consider possibly related, probably related, or definitely related to study drugs.
- Not related: Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the study drug.

Action Taken

The investigator will describe the action taken in the appropriate section of the CRF.

Follow-up of Adverse Events

Subjects should be followed for at least 30 days after receiving the last dose of study treatment (ZW25 or any chemotherapy component) or study discontinuation, and any AEs that occur during this time should be reported according to the procedures outlined above.

Documentation and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. Record all AEs occurring from the start of dosing of any study drug on Cycle 1 Day 1 through 30 days after last study treatment or prior to beginning the next course of anticancer therapy, whichever occurs sooner. Record only protocol-related AEs from the time of signing of the informed consent to before the first dose of any study drug. AEs must be documented on the relevant CRF pages. The following data should be documented for each AE:

- Description of the symptom event

- Classification of “serious” or “not serious”
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event

7.2.2. Serious Adverse Events

7.2.2.1. Serious Adverse Event Definition

An SAE is any AE that, at any dose,

- Results in death
- Is life-threatening (an AE is life-threatening if the subject was at immediate risk of death from the event as it occurred, i.e., it does not include a reaction that might have caused death if it had occurred in a more serious form)
- The AE resulted in hospitalization of ≥ 24 hours or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject’s ability to carry out normal life functions)
- Results in a congenital anomaly/birth defect
- Is an important medical event which based on medical judgment may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the above outcomes (e.g. anaphylaxis).

Medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above (i.e., any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the test drug/investigational product).

Progression of the Underlying Cancer

Clinical manifestations of disease progression that meet the criteria for a SAE must be reported. Do not use the term 'disease progression' alone when reporting SAEs, because it is too nonspecific. Symptoms of disease progression that meet the criteria for an SAE must be reported. When possible, report the specific disease (clinical) manifestation of the progression (e.g., 'malignant pleural effusion', 'spinal bone metastases', 'lymphadenopathy', 'brain metastases').

Reporting of Serious Adverse Events

Any SAE (regardless of relationship to study drugs) must be reported by the investigator if it occurs between the start of dosing of any study drug on Cycle 1 Day 1 and 30 days after last dose of study drug (ZW25 or chemotherapy) or prior to beginning the next course of anticancer therapy, which ever occurs sooner. However, all study protocol-related AEs are to be recorded from the time of informed consent. An SAE report form must be reported **within 24 hours** of the time the site became aware of the SAE to the attention of the sponsor's Drug Safety Department using the contact information included on the SAE report form.

The investigator should not wait to receive additional information to fully document the event before notification of an SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

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.

The CRO will promptly notify all relevant investigators and the sponsor in conjunction with the CRO will promptly notify the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study, or alter the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) favorable opinion of the study. In addition, the CRO, on behalf of the sponsor, will expedite the reporting to all concerned investigators and to the central IRBs/IECs, where required, and the sponsor in conjunction with the CRO will expedite the reporting to the regulatory authorities of all adverse reactions that are both serious and unexpected.

Details of the procedures to be followed if a pregnancy occurs are provided in Section 4.2.

Follow-up of Serious Adverse Events

All investigators should follow up subjects with any SAE until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of SAE resolution must be documented in the CRF and on the SAE report form.

7.2.3. Unexpected Adverse Reactions

An unexpected adverse reaction is any untoward and unintended response that is related to the administration of a study drug(s) at any dose that is not consistent with the applicable product information (e.g., Investigator's Brochure for an unauthorized investigational medicinal product or summary of product characteristics for an authorized product).

All suspected unexpected serious adverse reactions (SUSARs) will be the subject of expedited reporting. The sponsor and/or the CRO shall ensure that all relevant information about a SUSAR that is fatal or life-threatening is reported to the relevant competent authorities and IRB/IEC within 7 days after knowledge by the sponsor of such a case. All other SUSARs will be reported to the relevant competent authorities and IRB/IEC within 15 days after knowledge by the sponsor of such a case. All investigators should follow up on SUSARs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic.

7.2.4. Adverse Events of Special Interest

AESIs are infusion-related reactions, absolute decrease in LVEF of ≥ 16 percentage points from pre-treatment baseline or LVEF decrease below institutional lower limit of normal and ≥ 10 percentage points from pre-treatment baseline, and grade ≥ 2 heart failure. If an institution does not define a normal range for LVEF, AESI is defined as an absolute decrease in LVEF of ≥ 10 percentage points from pretreatment baseline and absolute value < 50%.

AESIs should be recorded as AEs, and reported as SAEs when appropriate. When an event does not meet the criteria for an SAE, a form for AESIs should be completed and submitted to the sponsor or sponsor safety representative. AESIs should continue to be followed until resolution or return to baseline or study closure.

7.2.5. Clinical Laboratory Evaluation

Clinical laboratory analyses may be performed at local laboratories. Any abnormalities in any of the laboratory parameters will be judged in relation to the reference ranges from the laboratory and to the clinical relevance assessed by the investigator.

7.2.5.1. Hematology

The following parameters will be determined: hemoglobin, hematocrit, white blood cell count (total and differential), RBC count, platelet count, mean corpuscular volume, mean cell hemoglobin (MCH), and MCH concentration. Coagulation parameters such as INR and aPTT will be required.

7.2.5.2. Clinical Chemistry

The following parameters will be measured: creatinine, urea (or blood urea nitrogen [BUN]), AST, ALT, gamma glutamyltransferase, alkaline phosphatase, lactate dehydrogenase, creatine kinase, total bilirubin, albumin, total protein, sodium, potassium, chloride, glucose, uric acid, calcium, magnesium, and phosphorus.

7.2.5.3. Urinalysis

Urine will be screened for pH, glucose, ketones, blood, protein, and microscopy (if indicated).

7.2.5.4. Other Laboratory Variables

Screening for hepatitis B surface antigen, hepatitis C antibody, and HIV will be performed at screening if indicated in the opinion of the treating investigator. For female subjects of childbearing potential, screening for pregnancy will be performed at screening and at predetermined time points as shown in in Appendix A (XELOX-1 and XELOX-2), Appendix B

(XELOX-3), Appendix C (FP-1 and FP-2), Appendix D (mFOLFOX6-1 and mFOLFOX6-2), and Appendix E (CisGem). These tests will be done using the blood samples taken for clinical chemistry. A urine pregnancy test is also acceptable.

7.2.6. Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature) will be recorded at selected time points specified in the applicable assessment schedules and done in a standardized manner (i.e., after the subject has rested in the sitting position for 5 minutes). Postdose assessments should be done within approximately 30 minutes of the end of the infusion.

7.2.7. Physical Examination

A physical examination, including height (at screening only) and body weight (at each visit during which a physical examination is performed), will be performed at selected time points specified in the applicable assessment schedules. Any changes from the time of screening will be recorded.

7.2.8. Electrocardiogram

For screening, local equipment may be used for ECGs. After a participant is enrolled in the study, 12-lead ECG will be recorded at selected time points specified in the applicable assessment schedules. The ECG will be recorded after at least a 10-minute rest. The date and an overall interpretation of the ECG will be recorded in the CRF. The interpretation of the ECG will be assessed as normal or abnormal, and if abnormal as clinically significant or not. If the ECG is considered abnormal and clinically significant, the abnormality must be recorded in the CRF. At least the following parameters should be assessed: heart rate, PR interval, QRS complex, and QTcF.

The 12-lead ECG may be obtained using machines available locally or using machines and instructions provided by the sponsor and/or its designee. ECGs collected for this study will not be centrally read.

7.2.9. Echocardiogram/MUGA

Echocardiograms or MUGAs are recorded at selected time points specified in the applicable assessment schedules. Echocardiograms or MUGAs will be recorded locally and will be assessed for an estimate of the ejection fraction. The same method must be used throughout the study. Management of left ventricular dysfunction is described in Section 5.1.3.

7.3. Appropriateness of Measurements

The efficacy and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant to the disease condition.

7.4. Drug Concentration Measurements

The concentrations of ZW25 will be measured in serum from all subjects treated with ZW25 using a validated assay method. Samples will be collected from all subjects at selected time

points specified in the applicable assessment schedules. All serum PK samples will be stored at -70°C prior to shipping to the central laboratory for analysis.

PK parameters will be derived for ZW25, when possible, utilizing standard non-compartmental procedures.

Additional sampling handling, processing, storage, labeling, and shipping instructions will be provided to the site in the Laboratory Manual.

8. STATISTICAL CONSIDERATIONS

8.1. 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 RDs of ZW25 when administered with physician's choice chemotherapy (XELOX, FP, mFOLFOX6 ± bevacizumab [or biosimilar], 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 biosimilar], or CisGem).

8.2. Sample Size Determination

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8.3. Populations for Analysis

For the purposes of analysis, the subject analysis sets are defined in Table 34.

Table 34: Subject Analysis Sets

Analysis Set	Description
Enrolled	All participants who sign the main study informed consent and were eligible for the study (or an exception was given) at the end of Screening.
Safety	All participants enrolled in the study who receive any amount of ZW25 and/or combination chemotherapy.
Measurable Disease	All subjects in the safety analysis set who had at least one measurable target lesion (per RECIST 1.1) at baseline.
Response Evaluable	All subjects in the measurable disease analysis set who had at least one evaluable, post-baseline disease assessment (per RECIST 1.1) or discontinued study treatment due to death or clinical progression.
Pharmacokinetics	All subjects in the safety analysis set who have sufficient post-dose samples collected to allow estimation of the PK. Subjects who have protocol deviations that could affect the PK evaluation will be noted and may be excluded from the PK analysis set depending on the type of the deviation.

8.4. Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the subject analysis sets to be included in the analyses, the procedures for accounting for missing, unused, and spurious data, and the deviations from the statistical analysis methods described in the protocol. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints.

8.4.1. Baseline Characteristics and Disease Characteristics

Baseline subject characteristics and disease characteristics will be summarized using counts and percentages for categorical variables and summary statistics (e.g., mean, quartiles, standard deviation, and range) for continuous variables.

8.4.2. Efficacy

Efficacy analyses to evaluate antitumor activity of ZW25 will be conducted on the measurable disease and response evaluable analysis sets unless otherwise specified. Efficacy analysis to assess survival and progression free survival will be based on the safety analysis set. All efficacy analyses will be summarized overall for each cancer type and may also be summarized for each chemotherapy regimen/ZW25 dose combination within a cancer type.

8.4.2.1. Objective Response Rate

Objective response is defined as achieving a best overall response of CR or PR as determined per RECIST 1.1. The ORR or proportion of subjects with an objective response and the corresponding exact binomial 95% CI will be calculated.

8.4.2.2. Disease Control Rate

Disease control is defined as a best response of CR, PR, or SD per RECIST 1.1. The proportion of subjects who achieve a disease control response and the corresponding exact binomial 95% CI will be calculated.

8.4.2.3. Duration of Response

DOR is defined as the time from the first objective response (CR or PR) to documented PD per RECIST 1.1 or death from any cause. Only subjects who achieve an objective response will be included in the analysis.

Kaplan-Meier plots and estimates of the quartiles and their corresponding 95% CIs will be computed.

8.4.2.4. Clinical Benefit Rate

Clinical benefit is defined as achieving SD for ≥ 24 weeks or a confirmed, best overall response of CR or PR per RECIST 1.1. The proportion of subjects with clinical benefit and the corresponding exact binomial 95% CI will be calculated.

8.4.2.5. Progression-Free Survival

PFS time is defined as the time from the first dose of study treatment to the date of documented disease progression (per RECIST 1.1), clinical progression, or death from any cause. Clinical progression is defined as worsening or re-emergence of pre-existing symptoms relating to underlying cancers, or emergence of new symptoms that cannot be attributed to study drug toxicities or alternative causes. 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, or SD. Details of the censoring scheme for this analysis will be described in the SAP.

Kaplan-Meier plots and estimates of the quartiles and their corresponding 95% CIs will be computed.

8.4.2.6. Overall Survival

OS is defined as time from the date of first dose of study treatment until the date of death from any cause. Subjects who did not achieve the event (death) at the time of the analysis or are lost to

follow-up will be censored at the date they were last known to be alive (i.e., right censored). Imputation for partial or missing dates of death or last contact and details of the censoring scheme will be described in the SAP.

Kaplan-Meier plots and estimates of the quartiles and their corresponding 95% CIs will be computed.

8.4.3. Safety

All analyses of safety will be conducted on the safety analysis set unless otherwise specified and will be summarized separately for each cancer type, for each ZW25 dose combination, and for each chemotherapy regimen/ZW25 dose combination.

8.4.3.1. Dose-Limiting Toxicities

The frequency of DLTs (as defined in Section 3.1.1.1) and the corresponding exact binomial 95% CI will be calculated for Part 1 of the study only.

8.4.3.2. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment. All AEs will be coded by the sponsor to standard "preferred terms" and system organ classifications (SOC) using Medical Dictionary for Regulatory Activities (MedDRA). Severity will be graded by study investigators using NCI-CTCAE v5.0.

The frequency of AEs will be summarized by preferred term and SOC using counts and percentages. Multiple occurrences of the same AE within a subject will be summarized 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 study treatment (ZW25 or any chemotherapy component) will be excluded from summaries but included in data listings.

In addition, treatment-related AEs and AEs which lead to premature discontinuation of study treatment will summarized.

8.4.3.3. Serious Adverse Events

The frequency of SAEs will be summarized by preferred term and SOC using counts and percentages. Treatment-related SAEs will also be summarized.

8.4.3.4. Deaths

The frequency of deaths will be summarized using counts and percentages. By-subject listings of deaths will also be produced.

8.4.3.5. 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 will be graded using NCI-CTCAE v5.0 and summarized by laboratory test and toxicity grade using counts and percentages.

8.4.3.6. 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 < 50% and ≥ 50% and the percentage of subjects with cardiac AESIs will be summarized.

8.4.3.7. Extent of Exposure

The frequency of dose reductions of ZW25 and chemotherapy will be summarized using counts and percentages. In addition, duration of exposure and total cumulative dose of ZW25 and chemotherapy as well as the total number of treatment cycles received will be summarized descriptively.

8.4.3.8. Vital Signs

Vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature) will be summarized using descriptive statistics (i.e., mean, median, standard deviation, and range).

8.4.3.9. Health Outcomes

ECOG performance status and shifts from baseline will summarized using counts and percentages.

8.4.4. Exploratory

[redacted]

8.4.5. Pharmacokinetics

PK analyses will be performed based on PK analysis set as defined in Section 8.3.

PK concentrations and PK parameters will be summarized using descriptive statistics (i.e., n, arithmetic mean, geometric mean, median, standard deviation, range, coefficient of variance) by ZW25 dose and chemotherapy regimen combination and by subtype of cancer and presented graphically as individual and mean plots.

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

- $C_{max,1}$: maximum observed serum concentration for dose 1
- $t_{max,1}$: time to maximum observed serum concentration for dose 1
- AUC_{0-t}: area under the serum concentration-time curve from zero to the last measurable concentration for dose 1
- λ_z: terminal elimination rate constant
- $t_{½}$: apparent elimination half-life
- $AUC_{0-\infty}$: area under the serum concentration-time curve from zero to infinity for dose 1

- CL: serum clearance
- V_z: volume of distribution in the terminal elimination phase

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

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:

- AUC_{tau}: area under the serum concentration-time curve from zero to the last end of dosing interval for Dose 1
- C_{ave}: average concentration over dosing interval, calculated as $AUC_{tau/tau}$ 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.

- R_{Cmin}: accumulation index, calculated as C_{min} (last dose)/C_{min} (first dose)
- $C_{min,ss}$: trough concentration at steady state

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

Dose proportionality and effect of type of cancer and/or concomitant chemotherapy will be assessed by appropriate statistical methods based on number of available data. Single dose PK parameters (C_{max}, $AUC_{0-\infty}$, CL, etc) as well as multiple dose parameters such as $C_{max,1}$; $C_{min,1}$; and C_{ss} will be used in these analyses.

The following PK parameters will be determined for optional steady-state extensive sampling after Cycle 3: $AUC_{tau,ss}$, $C_{ave,ss}$, $C_{min,ss}$, $C_{max,ss}$, λ_z, $t_{1/2}$, and V_z.

Further details of PK analysis will be described in the SAP.

8.4.6. Immunogenicity

All immunogenicity listings and analyses will be based on the safety analysis set as described in Section 8.3.

Subjects who develop an antibody response will be listed. The listing will be done for Tier 1 – screening assay for each subject and time point in positive/negative format. For the samples positive in screening assay the confirmation positive/negative results (Tier 2) and titer (Tier 3) will be added. If available, domain specificity data and anti-ZW25 neutralizing antibodies will be listed and summarized as well.

Tables summarizing the frequency of the occurrence of ADAs by ZW25 dose and by time point with overall summary per ZW25 dose and chemotherapy regimen combination will be produced. Titers for confirmed positive ADA will be summarized. The time of onset of immunogenicity, duration, and number of resolved ADA cases will be summarized. Summary statistics for domain specificity and neutralizing potential will be included, if available.

Effect of immunogenicity on PK and specifically on clearance of ZW25 will be explored.

Further details of the immunogenicity analyses will be described in the SAP.

8.4.7. Interim Analyses

An SMC will be responsible for monitoring subject safety (see Section 3.2). Cumulative safety reviews by sponsor Global Patient Safety and by the sponsor medical monitor will be conducted per the SMC Guidelines and real-time review of related SAEs will be conducted. No formal interim analyses will be performed for the efficacy endpoints in Part 2 of the study.

Interim data from the study may be presented at scientific meetings, such as ASCO, or in manuscripts.

8.4.8. Handling of Missing, Unused, or Spurious Data

Methods for handling of missing, unused or spurious data will be detailed in the SAP.

8.5. Protocol Deviations

Investigators must apply due diligence to avoid protocol deviations, and the sponsor (and designees) will not pre-authorize deviations. If the investigator believes a change to the protocol would improve the conduct of the study, this should be considered for implementation in a protocol amendment. All protocol deviations will be recorded. Subjects will not be excluded from safety analyses due to a protocol deviation; consideration will be given to excluding subjects with protocol deviations from a secondary efficacy population and will be described in the SAP.

9. QUALITY ASSURANCE AND QUALITY CONTROL

9.1. Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audits during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities or the IRB/IEC at their discretion.

The investigator must permit the IRB/IEC, the sponsor’s auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs. Subject confidentiality will be protected at all times.

9.2. Monitoring

Data for each subject will be recorded on a CRF. Data collection must be completed for each subject who signs an ICF and undergoes any screening assessment.

In accordance with GCP and International Council for Harmonisation (ICH) guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF are accurate and reliable. The frequency of monitoring visits will be determined by the rate of subject recruitment.

A clinical monitoring plan will detail the tasks to be completed at each monitoring visit. This will at least include the following:

- Site monitoring procedures including review of the ICF, source document review, source data verification, and review of CRF data
- AE and SAE reporting
- Investigational product receipt, ordering, preparation and administration, storage, documentation, accountability, dosing compliance, and return/destruction

The monitoring visits also provide the sponsor with the opportunity to ensure the investigator's obligations and all applicable ICH or health authority regulation requirements are being fulfilled.

The investigator must permit the monitor direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRFs. Subject confidentiality will be protected at all times.

9.3. Data Management and Coding

Study centers will enter data directly into an electronic data capture system by completing the CRF via a secure internet connection. Data entered into the eCRF must be verifiable against source documents at the study center. Data to be recorded directly on the eCRF will be identified. Any changes to the data entered into the electronic data capture system will be recorded in the audit trail and will be FDA 21 Code of Federal Regulations (CFR) Part 11 compliant and/or compliant with other region-specific electronic records regulatory requirements.

Medical coding will use Medical Dictionary for Regulatory Activities (MedDRA) for concomitant diseases and AEs and WHO Drug Dictionary for medications.

Missing or inconsistent data in the electronic database will be queried to the investigator for clarification. Subsequent modifications to the database will be documented.

10. DRUG ACCOUNTABILITY

Each site will verify their inventory of study drug supplies throughout the study, and that study drug is received intact and in the correct amounts. The monitor may check the study supplies at each study center at any time during the study.

The study monitor will ensure that the site has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log. A full drug accountability log will be maintained at the study center at all times. All discrepancies must be accounted for and documented.

11. FINANCING AND INSURANCE

Financing and insurance of this study will be outlined in a separate agreement between the CRO and the sponsor.

12. ETHICS

12.1. Institutional Review Board/IEC

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IRB/IEC. Written approval or favorable opinion of the study and all relevant study information must be obtained before the study center can be initiated. Any necessary extensions or renewals of IRB/IEC approval/favorable opinion must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IRB/IEC together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IRB/IEC any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IRB/IEC as required. On completion of the study, the IRB/IEC will be notified that the study has ended.

12.2. Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

12.3. Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines, and the applicable national and local laws and regulatory requirements.

12.3.1. Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study. Pre-screening of HER2 status, after the subject consents to allow the local or central laboratory analysis/review of HER2 status, is allowed before written informed consent for all other study procedures is given.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points he or she does not understand and,

if necessary, ask for more information. At the end of the interview, the subject will be given ample time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or their authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be submitted to the IRB(s)/IEC(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and re-consent will be obtained.

12.3.2. Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IRB(s)/IEC(s) approving this research, and the US FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, in accordance with the Health Insurance Portability and Accountability Act (HIPAA 1996), as well as with applicable national and/or local laws and regulations on personal data protection.

13. STUDY DOCUMENTATION AND RECORDS RETENTION

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval, for at least 2 years since the discontinuation of clinical development of the investigational product, or for the time period required by the applicable regulatory authorities. It is the responsibility of the sponsor to inform the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study-related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

14. PUBLICATION POLICIES

Publication policies and processes are detailed in the Clinical Trial Agreement.

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APPENDIX A. SCHEDULE OF ASSESSMENTS (XELOX-1 [PARTS 1 AND 2] AND XELOX-2 [PART 2])

Assessment	HER2 Pre-screening	Screening Visit (≤ 28 days)	Cycle 1 (21 days)				Cycle 2 (21 days)		Additional 21-day Cycles		Q6W	Q12W	EOT[p]	Safety and Efficacy Follow-up (30 days post last dose)	Survival Follow-up
			D1	D2	D5	D15	D1 (±2)	D15	D1 (±2)	D15	(±7)	(±7)	(+7)	(+7)	
ZW25[a]			X				X		X						Approximately every 3 months (± 14 days) until death, withdrawal from the study, or study closure, whichever occurs first. Subsequent therapies initiated during follow up will be collected, if available.
Oxaliplatin[b]			X				X		X						
Capecitabine[b]			X (D1–D15)				X (D1–D15)		X (D1–D15)						
Informed consent	X	X													
Register in IRT system	X	X	X				X		X		X	X	X		
Medical history		X													
Eligibility[h]		X	X												
Demographics		X													
New tumor biopsy or archived tissue	X[g]	X[g]											X[n]		
Disease assessment (CT/MRI)[c, h]		X									X[c]		X	X[q]	
Physical examination[d, h]		X	X				X		X				X	X	
ECOG PS[d, h]		X	X				X		X				X	X	
Vital signs[i, j]		X	X				X		X				X	X	
Hematology[d, h]		X	X				X		X				X	X	
Coagulation[d, h]		X	X												
Serum chemistry[d, h]		X	X				X		X				X	X	
Urinalysis[d, h]		X	X				X		X				X	X	
Pregnancy test[d, h]		X	X				X		X				X	X	
12-lead ECG[k]		X	X						X				X	X	
Echo/MUGA[h, o]		X	First post-baseline scan at 6 weeks from Cycle 1 Day 1, then every 12 weeks thereafter									X[o]			
Hepatitis B and C and HIV[e]		X													
ADA[h]			X				X		X[m]				X	X[s]	
ctDNA[h]			X						X[u]				X[l]	X[l]	
Tumor markers[t]		X									X		X	X	

PK samples[f]			See Appendix F and Appendix H		
AEs[r]		AEs and concomitant medications will be recorded from time of consent (protocol-related AEs) or first dose of any study drug on Cycle 1 Day 1 (all AEs) through the end of the safety reporting period (30 days after the last study treatment [ZW25 or any chemotherapy component]or prior to beginning the next course of anticancer therapy, whichever occurs sooner)			
Concomitant medications					

ADA = anti-drug antibody; CA = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; ctDNA: circulating tumor DNA; D = day; ECG = electrocardiogram; Echo = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; HIV = human immunodeficiency virus; mos = months; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PK = pharmacokinetics; Q6W = every 6 weeks; Q12W = every 12 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event

[a] See Section 5.1 for ZW25 dosing and administration. ZW25 dosing is weight-based for XELOX-1 and flat for XELOX-2.

[b] See Section 5.2 for XELOX dosing and administration. Capecitabine administration starts on the evening of Day 1 and continues through the morning of Day 15

[c] After screening, all subsequent radiographic scans for disease assessments may be done within a ±7 day time window and based on 6-week intervals timed from Cycle 1 Day 1. Radiographic scans for disease assessments do not have to be performed at EOT if ≤ 4 weeks since the previous scans.

[d] May be done within 3 days before study drug administration; tests do not need to be repeated if done within the prior 3 days. Pregnancy test is only for women of childbearing potential.

[e] Only if indicated.

[f] See Appendix F for extensive sampling timepoints or Appendix H for sparse sampling timepoint. Note: Day 2 and Day 5 visits are not required for subjects on sparse sampling.

[g] See Section 7.1.2 for details. Archival tumor tissue is allowed if new is unobtainable.

[h] On applicable dosing days, the assessment should be performed predose. Body weight will be used to calculate weight-based doses. Height will be measured only at screening.

[i] On applicable dosing days, the assessment should be performed predose and postdose.

[j] On applicable dosing days, the assessment should be performed within 30 minutes of the end of the infusion.

[k] On Cycle 1 Day 1 and Cycle 4 Day 1, a 12-lead ECG will be recorded predose and at 1 hour (±15 minutes) and 4 hours (±15 minutes) after the end of ZW25 infusion. ECGs will also be done at screening, EOT visit, and 30-day follow-up visit.

[l] ctDNA samples should be collected at the EOT visit for subjects with disease progression, or at the Safety and Efficacy Follow-up visit if not previously collected at EOT.

[m] Cycle 4 and every even-numbered cycle thereafter.

[n] Optional biopsy at disease progression if subject provides additional consent.

[o] After screening, an echocardiogram/MUGA should be done at 6 weeks (±7 days) after Cycle 1 Day 1, then all subsequent scans should be done every 12 weeks thereafter within a ±7 day time window. An echocardiogram/MUGA is not required at EOT if ≤ 3 months since the previous scan.

[p] Should take place as soon as possible after a subject permanently stops treatment.

[q] If radiographic scans were not done at the EOT visit nor within the 4 weeks prior to the safety follow-up visit, disease assessments should be performed at the time of the safety follow-up visit.

[r] AESIs should continue to be followed until resolution or return to baseline or study closure.

[s] Not required if ≤ 2 weeks since last sample.

[t] Samples should be collected for local assessment of CEA and/or CA19-9 (if available) each time radiographic scans are done.

[u] Cycle 3 only. Note: All references to Cycle # consider Cycle 1 Day 1 to be the first day that the subject receives any study drug. If/when the subject stops chemotherapy but continues ZW25 alone, the Cycle # continues (i.e., does not restart with another Cycle 1).

APPENDIX B. SCHEDULE OF ASSESSMENTS (XELOX-3; PART 2)

Assessment	HER2 Pre-screening	Screening Visit (≤ 28 days)	Cycle 1 (21 days)					Cycle 2 (21 days)			Additional 21-day Cycles			Q6W	Q12W	EOT[p]	Safety and Efficacy Follow-up (30 days post last dose)	Survival Follow-up
			D1	D2	D5	D8	D15	D1 (±2)	D8 (±2)	D15	D1 (±2)	D8 (±2)	D15	(±7)	(±7)	(+7)	(+7)	
ZW25[a]			X			X		X	X		X	X						Approximately every 3 months (± 14 days) until death, withdrawal from the study, or study closure, whichever occurs first. Subsequent therapies initiated during follow up will be collected, if available.
Oxaliplatin[b]			X					X			X							
Capecitabine[b]			X (D1–D15)					X (D1–D15)			X (D1–D15)							
Informed consent	X	X																
Register in IRT system	X	X	X					X			X			X	X	X		
Medical history		X																
Eligibility[h]		X	X															
Demographics		X																
New tumor biopsy or archived tissue	X[g]	X[g]														X[n]		
Disease assessment (CT/MRI)[c, h]		X												X[c]		X	X[q]	
Physical examination[d, h]		X	X					X			X					X	X	
ECOG PS[d, h]		X	X					X			X					X	X	
Vital signs[i, j]		X	X					X			X					X	X	
Hematology[d, h]		X	X					X			X					X	X	
Coagulation[d, h]		X	X															
Serum chemistry[d, h]		X	X					X			X					X	X	
Urinalysis[d, h]		X	X					X			X					X	X	
Pregnancy test[d, h]		X	X					X			X					X	X	
12-lead ECG[k]		X	X								X					X	X	
Echo/MUGA[h, o]		X	First post-baseline scan at 6 weeks from Cycle 1 Day 1, then every 12 weeks thereafter												X[o]			
Hepatitis B and C and HIV[e]		X																
ADA[h]			X					X			X[m]					X	X[s]	
ctDNA[h]			X								X[u]					X[l]	X[l]	
Tumor markers[t]		X												X		X	X	

PK samples[f]			See Appendix F and Appendix H		
AEs[r]		AEs and concomitant medications will be recorded from time of consent (protocol-related AEs) or first dose of any study drug on Cycle 1 Day 1 (all AEs) through the end of the safety reporting period (30 days after the last study treatment [ZW25 or any chemotherapy component]or prior to beginning the next course of anticancer therapy, whichever occurs sooner)			
Concomitant medications					

ADA = anti-drug antibody; CA = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; ctDNA: circulating tumor DNA; D = day; ECG = electrocardiogram; Echo = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; HIV = human immunodeficiency virus; mos = months; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PK = pharmacokinetics; Q6W = every 6 weeks; Q12W = every 12 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event

[a] See Section 5.1 for ZW25 dosing and administration. ZW25 dosing is flat for XELOX-3.

[b] See Section 5.2 for XELOX dosing and administration. Capecitabine administration starts on the evening of Day 1 and continues through the morning of Day 15

[c] After screening, all subsequent radiographic scans for disease assessments may be done within a ±7 day time window and based on 6-week intervals timed from Cycle 1 Day 1. Radiographic scans for disease assessments do not have to be performed at EOT if ≤ 4 weeks since the previous scans.

[d] May be done within 3 days before study drug administration; tests do not need to be repeated if done within the prior 3 days. Pregnancy test is only for women of childbearing potential.

[e] Only if indicated.

[f] See Appendix F for extensive sampling timepoints or Appendix H for sparse sampling timepoint. Note: Day 2 and Day 5 visits are not required for subjects on sparse sampling.

[g] See Section 7.1.2 for details. Archival tumor tissue is allowed if new is unobtainable.

[h] On applicable dosing days, the assessment should be performed predose. Body weight will be used to calculate weight-based doses. Height will be measured only at screening.

[i] On applicable dosing days, the assessment should be performed predose and postdose.

[j] On applicable dosing days, the assessment should be performed within 30 minutes of the end of the infusion.

[k] On Cycle 1 Day 1 and Cycle 4 Day 1, a 12-lead ECG will be recorded predose and at 1 hour (±15 minutes) and 4 hours (±15 minutes) after the end of ZW25 infusion. ECGs will also be done at screening, EOT visit, and 30-day follow-up visit.

[l] ctDNA samples should be collected at the EOT visit for subjects with disease progression, or at the Safety and Efficacy Follow-up visit if not previously collected at EOT.

[m] Cycle 4 and every even-numbered cycle thereafter.

[n] Optional biopsy at disease progression if subject provides additional consent.

[o] After screening, an echocardiogram/MUGA should be done at 6 weeks (±7 days) after Cycle 1 Day 1, then all subsequent scans should be done every 12 weeks thereafter within a ±7 day time window. An echocardiogram/MUGA is not required at EOT if ≤ 3 months since the previous scan.

[p] Should take place as soon as possible after a subject permanently stops treatment.

[q] If radiographic scans were not done at the EOT visit nor within the 4 weeks prior to the safety follow-up visit, disease assessments should be performed at the time of the safety follow-up visit.

[r] AESIs should continue to be followed until resolution or return to baseline or study closure.

[s] Not required if ≤ 2 weeks since last sample.

[t] Samples should be collected for local assessment of CEA and/or CA19-9 (if available) each time radiographic scans are done.

[u] Cycle 3 only. Note: All references to Cycle # consider Cycle 1 Day 1 to be the first day that the subject receives any study drug. If/when the subject stops chemotherapy but continues ZW25 alone, the Cycle # continues (i.e., does not restart with another Cycle 1).

APPENDIX C. SCHEDULE OF ASSESSMENTS (FP-1 [PART 1] AND FP-2 [PARTS 1 AND 2])

			Cycle 1 (21 days)			Cycle 2 (21 days)		Additional 21-day Cycles		Q6W	Q12W	EOT[p]	Safety and Efficacy Follow-up (30 days post last dose)	Survival Follow-up
Assessment	**HER2 Pre-screening**	**Screening Visit (≤ 28 days)**	**D1**	**D2**	**D5**	**D1 (±2)**	**D5 (±2)**	**D1 (±2)**	**D5 (±2)**	**(±7)**	**(±7)**	**(+7)**	**(+7)**	Approximately every 3 months (± 14 days) until death, withdrawal from the study, or study closure, whichever occurs first. Subsequent therapies initiated during follow up will be collected, if available.
ZW25[a]			X			X		X						
5-FU[b]			X (D1–D5)			X (D1–D5)		X (D1–D5)						
Cisplatin[b]			X			X		X						
Informed consent	X	X												
Register in IRT system	X	X	X			X		X		X	X	X		
Medical history		X												
Eligibility[h]		X	X											
Demographics		X												
New tumor biopsy or archived tissue	X[g]	X[g]										X[n]		
Disease assessment (CT/MRI)[c, h]		X								X[c]		X	X[q]	
Physical examination[d, h]		X	X			X		X				X	X	
ECOG PS[d, h]		X	X			X		X				X	X	
Vital signs[i, j]		X	X			X		X				X	X	
Hematology[d, h]		X	X			X		X				X	X	
Coagulation[d, h]		X	X											
Serum chemistry[d, h]		X	X			X		X				X	X	
Urinalysis[d, h]		X	X			X		X				X	X	
Pregnancy test[d, h]		X	X			X		X				X	X	
12-lead ECG[k]		X	X					X				X	X	
Echo/MUGA[h, o]		X	First post-baseline scan at 6 weeks from Cycle 1 Day 1, then every 12 weeks thereafter								X[o]			
Hepatitis B and C and HIV[e]		X												

ADA[h]			X			X		X[m]				X	X[s]	
ctDNA[h]			X					X[u]				X[l]	X[l]	
Tumor markers[t]		X								X		X	X	
PK samples[f]			See Appendix F and Appendix H											
AEs[r]		AEs and concomitant medications will be recorded from time of consent (protocol-related AEs) or first dose of any study drug on Cycle 1 Day 1 (all AEs) through the end of the safety reporting period (30 days after the last study treatment [ZW25 or any chemotherapy component]or prior to beginning the next course of anticancer therapy, whichever occurs sooner)										
Concomitant medications														

ADA = anti-drug antibody; CA = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; ctDNA: circulating tumor DNA; D = day; ECG = electrocardiogram; Echo = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; HIV = human immunodeficiency virus; mos = months; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PK = pharmacokinetics; Q6W = every 6 weeks; Q12W = every 12 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event

[a] See Section 5.1 for ZW25 dosing and administration. ZW25 dosing is weight-based for FP-1 and flat for FP-2.

[b] See Section 5.3 for FP dosing and administration.

[c] After screening, all subsequent radiographic scans for disease assessments may be done within a ±7 day time window and based on 6-week intervals timed from Cycle 1 Day 1. Radiographic scans for disease assessments do not have to be performed at EOT if ≤ 4 weeks since the previous scans.

[d] May be done within 3 days before study drug administration; tests do not need to be repeated if done within the prior 3 days. Pregnancy test is only for women of childbearing potential.

[e] Only if indicated.

[f] See Appendix F for extensive sampling timepoints or Appendix H for sparse sampling timepoint. Note: Day 2 and Day 5 visits are not required for subjects on sparse sampling.

[g] See Section 7.1.2 for details. Archival tumor tissue is allowed if new is unobtainable.

[h] On applicable dosing days, the assessment should be performed predose. Body weight will be used to calculate weight-based doses. Height will be measured only at screening.

[i] On applicable dosing days, the assessment should be performed predose and postdose.

[j] On applicable dosing days, the assessment should be performed within 30 minutes of the end of the infusion.

[k] On Cycle 1 Day 1 and Cycle 4 Day 1, a 12-lead ECG will be recorded predose and at 1 hour (±15 minutes) and 4 hours (±15 minutes) after the end of ZW25 infusion. ECGs will also be done at screening, EOT visit, and 30-day follow-up visit.

[l] ctDNA samples should be collected at the EOT visit for subjects with disease progression, or at the Safety and Efficacy Follow-up visit if not previously collected at EOT.

[m] Cycle 4 and every even-numbered cycle thereafter.

[n] Optional biopsy at disease progression if subject provides additional consent.

[o] After screening, an echocardiogram/MUGA should be done at 6 weeks (±7 days) after Cycle 1 Day 1, then all subsequent scans should be done every 12 weeks thereafter within a ±7 day time window. An echocardiogram/MUGA is not required at EOT if ≤ 3 months since the previous scan.

[p] Should take place as soon as possible after a subject permanently stops treatment.

[q] If radiographic scans were not done at the EOT visit nor within the 4 weeks prior to the safety follow-up visit, disease assessments should be performed at the time of the safety follow-up visit.

[r] AESIs should continue to be followed until resolution or return to baseline or study closure.

[s] Not required if ≤ 2 weeks since last sample.

[t] Samples should be collected for local assessment of CEA and/or CA19-9 (if available) each time radiographic scans are done.

[u] Cycle 3 only. Note: All references to Cycle # consider Cycle 1 Day 1 to be the first day that the subject receives any study drug. If/when the subject stops chemotherapy but continues ZW25 alone, the Cycle # continues (i.e., does not restart with another Cycle 1).

APPENDIX D. SCHEDULE OF ASSESSMENTS (MFOLFOX6-1 AND MFOLFOX6-2 ± BEVACIZUMAB; PARTS 1 AND 2)

Assessment	HER2 Pre-screening	Screening Visit (≤ 28 days)	Cycle 1 (28 days)					Cycle 2 (28 days)				Additional 28-day Cycles				Q6W	Q12W	EOT[p]	Safety and Efficacy Follow-up (30 days post last dose)	Survival Follow-up
			D1	D2	D5	D15 (±2)	D16	D1 (±2)	D2	D15 (±2)	D16	D1 (±2)	D2	D15 (±2)	D16	(±7)	(±7)	(+7)	(+7)	
ZW25[a]			X			X		X		X		X		X						Approximately every 3 months (± 14 days) until death, withdrawal from the study, or study closure, whichever occurs first. Subsequent therapies initiated during follow up will be collected, if available.
Leucovorin[b]			X			X		X		X		X		X						
Oxaliplatin[b]			X			X		X		X		X		X						
5-FU[b]			X	X		X	X	X	X	X	X	X	X	X	X					
Bevacizumab or biosimilar (if included)			X			X		X		X		X		X						
Informed consent	X	X																		
Register in IRT system	X	X	X					X				X				X	X	X		
Medical history		X																		
Eligibility[h]		X	X																	
Demographics		X																		
New tumor biopsy or archived tissue	X[g]	X[g]																X[n]		
Disease assessment (CT/MRI)[c, h]		X														X[c]		X	X[q]	
Physical examination[d, h]		X	X			X		X		X		X		X				X	X	
ECOG PS[d, h]		X	X					X				X						X	X	
Vital signs[i, j]		X	X			X		X		X		X		X				X	X	
Hematology[d, h]		X	X			X		X		X		X		X				X	X	
Coagulation[d, h]		X	X																	
Serum chemistry[d, h]		X	X			X		X		X		X		X				X	X	
Urinalysis[d, h]		X	X					X				X						X	X	
Pregnancy test[d, h]		X	X					X				X						X	X	
12-lead ECG[k]		X	X									X						X	X	
Echo/MUGA[h, o]		X	First post-baseline scan at 6 weeks from Cycle 1 Day 1, then every 12 weeks thereafter														X[o]			

Hepatitis B and C and HIV[e]		X																	
ADA[h]			X			X		X		X		X[m]						X	X[s]
ctDNA[h]			X							X								X[l]	X[l]
Tumor markers[t]		X														X		X	X
PK samples[f]			See Appendix G and Appendix I																
AEs[r]		AEs and concomitant medications will be recorded from time of consent (protocol-related AEs) or first dose of any study drug on Cycle 1 Day 1 (all AEs) through the end of the safety reporting period (30 days after the last study treatment [ZW25 or any chemotherapy component] or prior to beginning the next course of anticancer therapy, whichever occurs sooner)																	
Concomitant medications																			

ADA = anti-drug antibody; CA = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; ctDNA: circulating tumor DNA; D = day; ECG = electrocardiogram; Echo = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; HIV = human immunodeficiency virus; mos = months; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PK = pharmacokinetics; Q6W = every 6 weeks; Q12W = every 12 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event

[a] See Section 5.1 for ZW25 dosing and administration. ZW25 dosing is weight-based for mFOLFOX6-1-1 and flat for mFOLFOX6-2.

[b] See Section 5.4 for mFOLFOX ± bevacizumab (or biosmiliar) dosing and administration.

[c] After screening, all subsequent radiographic scans for disease assessments may be done within a ±7 day time window and based on 6-week intervals timed from Cycle 1 Day 1. Radiographic scans for disease assessments do not have to be performed at EOT if ≤ 4 weeks since the previous scans.

[d] May be done within 3 days before study drug administration; tests do not need to be repeated if done within the prior 3 days. Pregnancy test is only for women of childbearing potential.

[e] Only if indicated.

[f] See Appendix G for extensive sampling timepoints or Appendix I for sparse sampling timepoint. Note: Day 2 and Day 5 visits are not required for subjects on sparse sampling.

[g] See Section 7.1.2 for details. Archival tumor tissue is allowed if new is unobtainable.

[h] On applicable dosing days, the assessment should be performed predose. Body weight will be used to calculate weight-based doses. Height will be measured only at screening.

[i] On applicable dosing days, the assessment should be performed predose and postdose.

[j] On applicable dosing days, the assessment should be performed within 30 minutes of the end of the infusion.

[k] On Cycle 1 Day 1 and Cycle 4 Day 1, a 12-lead ECG will be recorded predose and at 1 hour (±15 minutes) and 4 hours (±15 minutes) after the end of ZW25 infusion. ECGs will also be done at screening, EOT visit, and 30-day follow-up visit.

[l] ctDNA samples should be collected at the EOT visit for subjects with disease progression, or at the Safety and Efficacy Follow-up visit if not previously collected at EOT.

[m] Cycle 4 and every even-numbered cycle thereafter.

[n] Optional biopsy at disease progression if subject provides additional consent.

[o] After screening, an echocardiogram/MUGA should be done at 6 weeks (±7 days) after Cycle 1 Day 1, then all subsequent scans should be done every 12 weeks thereafter within a ±7 day time window. An echocardiogram/MUGA is not required at EOT if ≤ 3 months since the previous scan.

[p] Should take place as soon as possible after a subject permanently stops treatment.

[q] If radiographic scans were not done at the EOT visit nor within the 4 weeks prior to the safety follow-up visit, disease assessments should be performed at the time of the safety follow-up visit.

[r] AESIs should continue to be followed until resolution or return to baseline or study closure.

[s] Not required if ≤ 2 weeks since last sample.

[t] Samples should be collected for local assessment of CEA and/or CA19-9 (if available) each time radiographic scans are done.

APPENDIX E. SCHEDULE OF ASSESSMENTS (CISGEM; PARTS 1 AND 2)

Assessment	HER2 Pre-screening	Screening Visit (≤ 28 days)	Cycle 1 (21 days)				Cycle 2 (21 days)		Additional 21-day Cycles		Q6W	Q12W	EOT[p]	Safety and Efficacy Follow-up (30 days post last dose)	Survival Follow-up
			D1	D2	D5	D8	D1 (±2)	D8 (±2)	D1 (±2)	D8 (±2)	(±7)	(±7)	(+7)	(+7)	
ZW25[a]			X				X		X						Approximately every 3 months (± 14 days) until death, withdrawal from the study, or study closure, whichever occurs first. Subsequent therapies initiated during follow up will be collected, if available.
Cisplatin[b]			X			X	X	X	X	X					
Gemcitabine[b]			X			X	X	X	X	X					
Informed consent	X	X													
Register in IRT system	X	X	X				X		X		X	X	X		
Medical history		X													
Eligibility[h]		X	X												
Demographics		X													
New tumor biopsy or archived tissue	X[g]	X[g]											X[n]		
Disease assessment (CT/MRI)[c, h]		X									X[c]		X	X[q]	
Physical examination[d, h]		X	X				X		X				X	X	
ECOG PS[d, h]		X	X				X		X				X	X	
Vital signs[i, j]		X	X				X		X				X	X	
Hematology[d, h]		X	X				X		X				X	X	
Coagulation[d, h]		X	X												
Serum chemistry[d, h]		X	X				X		X				X	X	
Urinalysis[d, h]		X	X				X		X				X	X	
Pregnancy test[d, h]		X	X				X		X				X	X	
12-lead ECG[k]		X	X						X				X	X	
Echo/MUGA[h, o]		X	First post-baseline scan at 6 weeks from Cycle 1 Day 1, then Q12W thereafter									X[o]			
Hepatitis B and C and HIV[e]		X													
ADA[h]			X				X		X[m]				X	X[s]	
ctDNA[h]			X						X[u]				X[l]	X[l]	
Tumor markers[t]		X									X		X	X	
PK samples[f]			See Appendix F and Appendix H												
AEs[r]		AEs and concomitant medications will be recorded from time of consent (protocol-related AEs) or first dose of any study drug													

Concomitant medications		on Cycle 1 Day 1 (all AEs) through the end of the safety reporting period (30 days after the last study treatment [ZW25 or any chemotherapy component]or prior to beginning the next course of anticancer therapy, whichever occurs sooner)	

ADA = anti-drug antibody; CA = carbohydrate antigen 19-9; CEA = carcinoembryonic antigen; CT = computed tomography; ctDNA: circulating tumor DNA; D = day; ECG = electrocardiogram; Echo = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; HIV = human immunodeficiency virus; mos = months; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition scan; PK = pharmacokinetics; Q6W = every 6 weeks; Q12W = every 12 weeks; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SAE = serious adverse event

[a] See Section 5.1 for ZW25 dosing and administration. ZW25 dosing is flat for CisGem.

[b] See Section 5.5 for CisGem dosing and administration.

[c] After screening, all subsequent radiographic scans for disease assessments may be done within a ±7 day time window and based on 6-week intervals timed from Cycle 1 Day 1. Radiographic scans for disease assessments do not have to be performed at EOT if ≤ 4 weeks since the previous scans.

[d] May be done within 3 days before study drug administration; tests do not need to be repeated if done within the prior 3 days. Pregnancy test is only for women of childbearing potential.

[e] Only if indicated.

[f] See Appendix F for extensive sampling timepoints or Appendix H for sparse sampling timepoint. Note: Day 2 and Day 5 visits are not required for subjects on sparse sampling.

[g] See Section 7.1.2 for details. Archival tumor tissue is allowed if new is unobtainable.

[h] On applicable dosing days, the assessment should be performed predose. Body weight will be used to calculate weight-based doses. Height will be measured only at screening.

[i] On applicable dosing days, the assessment should be performed predose and postdose.

[j] On applicable dosing days, the assessment should be performed within 30 minutes of the end of the infusion.

[k] On Cycle 1 Day 1 and Cycle 4 Day 1, a 12-lead ECG will be recorded predose and at 1 hour (±15 minutes) and 4 hours (±15 minutes) after the end of ZW25 infusion. ECGs will also be done at screening, EOT visit, and 30-day follow-up visit.

[l] ctDNA samples should be collected at the EOT visit for subjects with disease progression, or at the Safety and Efficacy Follow-up visit if not previously collected at EOT.

[m] Cycle 4 and every even-numbered cycle thereafter.

[n] Optional biopsy at disease progression if subject provides additional consent.

[o] After screening, an echocardiogram/MUGA should be done at 6 weeks (±7 days) after Cycle 1 Day 1, then all subsequent scans should be done every 12 weeks thereafter within a ±7 day time window. An echocardiogram/MUGA is not required at EOT if ≤ 3 months since the previous scan.

[p] Should take place as soon as possible after a subject permanently stops treatment.

[q] If radiographic scans were not done at the EOT visit nor within the 4 weeks prior to the safety follow-up visit, disease assessments should be performed at the time of the safety follow-up visit.

[r] AESIs should continue to be followed until resolution or return to baseline or study closure.

[s] Not required if ≤ 2 weeks since last sample.

[t] Samples should be collected for local assessment of CEA and/or CA19-9 (if available) each time radiographic scans are done.

[u] Cycle 3 only. Note: All references to Cycle # consider Cycle 1 Day 1 to be the first day that the subject receives any study drug. If/when the subject stops chemotherapy but continues ZW25 alone, the Cycle # continues (i.e., does not restart with another Cycle 1).

APPENDIX F. PHARMACOKINETIC EXTENSIVE SAMPLING TIME POINTS (ALL XELOX REGIMENS, BOTH FP REGIMENS, AND CISGEM, PARTS 1 AND 2)

Extensive PK: XELOX-1 and XELOX-2 Regimens, Parts 1 and 2

	Cycle 1 (21 days)							Cycle 2, 3 and 4 and Every Even-numbered Cycle Thereafter (21 days)		
	D1					D2	D5	D1		
Time	**Pre-dose[a]**	**End of ZW25 infusion**	**2 h post-dose[b]**	**4 h post-dose[b]**	**8 h post-dose[b]**	**24 h post-dose[b]**	**96 h post-dose[b]**	**Pre-dose[a]**	**End of ZW25 infusion**	**EOT**
Allowed time window		+15 min	± 15 min	± 15 min	± 3 hr[d]	± 1 hr	± 1 hr	– 4 hr	+30 min	
PK serum sample	X	X	X	X	X	X	X	X	X	X[c]

D=day; EOT=End of Treatment; h=hour; min=minutes; PK=pharmacokinetic

[a] Relative to start of ZW25 administration.

[b] Relative to the end of ZW25 administration.

[c] Only required if the subject has completed less than 6 months of treatment.

[d] Last sample on Day 1 before the patient leaves the clinic.

Note: At least 6 subjects from each combination and at each dose schedule will be assigned to an applicable extensive PK schedule. Further subjects will be then be assigned to the sparse PK schedule. Dates and times of the start and end of ZW25 infusions and dates and times of the PK samples must be recorded.

Extensive PK: XELOX-3 Only, Parts 1 and 2

	Cycle 1 (21 days)									Cycle 2 and Cycle 3 (21 days)				Cycle 4 and Every Even-numbered Cycle Thereafter (21 days Each)		EOT
	D1					D2	D5	D8		D1[a]		D8		D1		
Time	**Pre-dose[a]**	**End of ZW25 infusion**	**2 h post-dose[b]**	**4 h post-dose[b]**	**8 h post-dose[b]**	**24 h post-dose[b]**	**96 h post-dose[b]**	**Pre-dose[a]**	**End of ZW25 infusion**	**Pre-dose[a]**	**End of ZW25 infusion**	**Pre-dose[a]**	**End of ZW25 infusion**	**Pre-dose[a]**	**End of ZW25 infusion**	
Allowed time window		+15 min	± 15 min	± 15 min	± 3 hr[d]	± 1 hr	± 1 hr	– 4 hr	+30 min	– 4 hr	+30 min	– 4 hr	+30 min	– 4 hr	+30 min	
PK serum sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]

D=day; EOT=End of Treatment; h=hour; min=minutes; PK=pharmacokinetic

[a] Relative to start of ZW25 administration.

[b] Relative to the end of ZW25 administration.

[c] Only required if the subject has completed less than 6 months of treatment.

[d] Last sample on Day 1 before the patient leaves the clinic.

Note: At least 6 subjects from each combination and at each dose schedule will be assigned to an applicable extensive PK schedule. Further subjects will be then be assigned to the sparse PK schedule. Dates and times of the start and end of ZW25 infusions and dates and times of the PK samples must be recorded.

Extensive PK: Both FP Regimens, Parts 1 and 2

	Cycle 1 (21 days)							Cycle 2, 3 and 4 and Every Even-numbered Cycle Thereafter (21 days)		
	D1					D2	D5	D1		
Time	**Pre-dose[a]**	**End of ZW25 infusion**	**2 h post-dose[b]**	**4 h post-dose[b]**	**8 h post-dose[b]**	**24 h post-dose[b]**	**96 h post-dose[b]**	**Pre-dose[a]**	**End of ZW25 infusion**	**EOT**
Allowed time window		+15 min	± 15 min	± 15 min	± 3 hr[d]	± 1 hr	± 1 hr	– 4 hr	+30 min	
PK serum sample	X	X	X	X	X	X	X	X	X	X[c]

D=day; EOT=End of Treatment; h=hour; min=minutes; PK=pharmacokinetic

[a] Relative to start of ZW25 administration.

[b] Relative to the end of ZW25 administration.

[c] Only required if the subject has completed less than 6 months of treatment.

[d] Last sample on Day 1 before the patient leaves the clinic.

Note: At least 6 subjects from each combination and at each dose schedule will be assigned to an applicable extensive PK schedule. Further subjects will be then be assigned to the sparse PK schedule. Dates and times of the start and end of ZW25 infusions and dates and times of the PK samples must be recorded.

Extensive PK: CisGem Regimen, Parts 1 and 2

	Cycle 1 (21 days)								Cycle 2 and Cycle 3 (21 days)			Cycle 4 and Every Even-numbered Cycle Thereafter (21 days Each)		EOT
	D1					D2	D5	D8	D1[a]		D8	D1		
Time	**Pre-dose[a]**	**End of ZW25 infusion**	**2 h post-dose[b]**	**4 h post-dose[b]**	**8 h post-dose[b]**	**24 h post-dose[b]**	**96 h post-dose[b]**	**192 h post-dose**	**Pre-dose[a]**	**End of ZW25 infusion**	**192 h post-dose**	**Pre-dose[a]**	**End of ZW25 infusion**	
Allowed time window		+ 15 min	± 15 min	± 15 min	± 3 hr[d]	± 1 hr	± 1 hr	N/A[e]	– 4 hr	+ 30 min	N/A[e]	– 4 hr	+ 30 min	
PK serum sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]

D=day; EOT=End of Treatment; h=hour; min=minutes; PK=pharmacokinetic

[a] Relative to start of ZW25 administration.

[b] Relative to the end of ZW25 administration.

[c] Only required if the subject has completed less than 6 months of treatment.

[d] Last sample on Day 1 before the patient leaves the clinic.

[e] Any time during Day 8 visit

Note: At least 6 subjects from each combination and at each dose schedule will be assigned to an applicable extensive PK schedule. Further subjects will be then be assigned to the sparse PK schedule. Dates and times of the start and end of ZW25 infusions and dates and times of the PK samples must be recorded.

APPENDIX G. PHARMACOKINETIC EXTENSIVE SAMPLING TIME POINTS (BOTH MFOLFOX6 REGIMENS; PARTS 1 AND 2)

	Cycle 1 (28 days)									**Cycle 2 and 3 (28 days)**		**Cycle 4 and Every Even-numbered Cycle Thereafter (28 days Each)**		
	D1					**D2**	**D5**	**D15**		**D1 and D15**		**D1**		
Time	**Pre-dose[a]**	**End of ZW25 infusion**	**2 h post-dose[b]**	**4 h post-dose[b]**	**8 h post-dose[b]**	**24 h post-dose[b]**	**96 h post-dose[b]**	**Pre-dose[a]**	**End of ZW25 infusion**	**Pre-dose[a]**	**End of ZW25 infusion**	**Pre-dose[a]**	**End of ZW25 infusion**	**EOT**
Allowed time window		+15 min	± 15 min	± 15 min	± 3 hr[d]	± 1 hr	± 1 hr	– 4 hr	+30 min	– 4 hr	+30 min	– 4 hr	+ 30 min	
PK serum sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]

D=day; EOT=End of Treatment; h=hour; min=minutes; PK=pharmacokinetic

[a] Relative to start of ZW25 administration.

[b] Relative to the end of ZW25 administration.

[c] Only required if the subject has completed less than 6 months of treatment.

[d] Last sample on Day 1 before the patient leaves the clinic.

Note: At least 6 subjects from each combination and at each dose schedule will be assigned to an applicable extensive PK schedule. Further subjects will be then be assigned to the sparse PK schedule. Dates and times of the start and end of ZW25 infusions and dates and times of the PK samples must be recorded.

APPENDIX H. PHARMACOKINETIC SPARSE SAMPLING TIME POINTS (XELOX-1 AND XELOX-2 REGIMENS, BOTH FP REGIMENS, AND CISGEM)

Sparse PK: XELOX-1 and XELOX-2 regimens and both FP regimens, Parts 1 and 2

	Cycle 1 (21 days)		Cycles 2, 3, and 4 and Every Even-numbered Cycle Thereafter (21 days Each)		
	D1		D1		
Time	Pre-dose[a]	End of ZW25 infusion	Pre-dose[a]	End of ZW25 infusion	EOT
Allowed time window		+ 30 min	– 4 hr	+ 30 min	
PK serum sample	X	X	X	X	X[b]

D=day; EOT=End of Treatment; h=hour; min=minutes; PK=pharmacokinetic

[a] Relative to start of ZW25 administration.

[b] Only required if the subject has completed less than 6 months of treatment.

Note: Dates and times of the start and end of ZW25 infusions and dates and times of the PK samples must be recorded.

Sparse PK: XELOX-3 Only, Parts 1 and 2

	Cycle 1 (21 days)				Cycles 2 and 3 (21 days Each)				Cycle 4 and Every Even-numbered Cycle Thereafter (21 days Each)		
	D1		D8		D1		D8		D1		
Time	Pre-dose[a]	End of ZW25 infusion	Pre-dose[a]	End of ZW25 infusion	Pre-dose[a]	End of ZW25 infusion	Pre-dose[a]	End of ZW25 infusion	Pre-dose[a]	End of ZW25 infusion	EOT
Allowed time window		+30 min		+30 min	– 4 hr	+30 min	– 4 hr	+30 min	– 4 hr	+30 min	
PK serum sample	X	X	X	X	X	X	X	X	X	X	X[b]

D=day; EOT=End of Treatment; h=hour; min=minutes; PK=pharmacokinetic

[a] Relative to start of ZW25 administration.

[b] Only required if the subject has completed less than 6 months of treatment.

Note: Dates and times of the start and end of ZW25 infusions and dates and times of the PK samples must be recorded.

Sparse PK: CisGem Regimen Only, Parts 1 and 2

	Cycle 1 (21 days)			**Cycles 2 and 3 (21 days Each)**			**Cycle 4 and Every Even-numbered Cycle Thereafter (21 days Each)**		
	D1		**D8**	**D1**		**D8**	**D1**		
Time	**Pre-dose[a]**	**End of ZW25 infusion**	**192 h post-dose**	**Pre-dose[a]**	**End of ZW25 infusion**	**192 h post-dose**	**Pre-dose[a]**	**End of ZW25 infusion**	**EOT**
Allowed time window		+ 30 min	N/A[c]	– 4 hr	+ 30 min	**N/A[c]**		+ 30 min	
PK serum sample	X	X	X	X	X	X	X	X	X[b]

D=day; EOT=End of Treatment; h=hour; min=minutes; PK=pharmacokinetic

[a] Relative to start of ZW25 administration.

[b] Only required if the subject has completed less than 6 months of treatment.

[c] Any time during Day 8 visit.

Note: Dates and times of the start and end of ZW25 infusions and dates and times of the PK samples must be recorded.

APPENDIX I. PHARMACOKINETIC SPARSE SAMPLING TIME POINTS (BOTH MFOLFOX6 REGIMENS; PARTS 1 AND 2)

	Cycle 1 (28 days)				**Cycle 2 and Cycle 3 (28 days)**		**Cycle 4 and Every Even-numbered Cycle Thereafter (28 days Each)**		
	D1		**D15**		**D1 and D15**		**D1**		
Time	**Pre-dose[a]**	**End of ZW25 infusion**	**Pre-dose[a]**	**End of ZW25 infusion**	**Pre-dose[a]**	**End of ZW25 infusion**	**Pre-dose[a]**	**End of ZW25 infusion**	**EOT**
Allowed time window		+ 30 min	– 4 hr	+ 30 min	– 4 hr	+ 30 min	– 4 hr	+ 30 min	
PK serum sample	X	X	X	X	X	X	X	X	X[b]

D=day; EOT=End of Treatment; h=hour; min=minutes; PK=pharmacokinetic

[a] Relative to start of ZW25 administration.

[b] Only required if the subject has completed less than 6 months of treatment.

Note: Dates and times of the start and end of ZW25 infusions and dates and times of the PK samples must be recorded.

APPENDIX J. OPTIONAL STEADY-STATE EXTENSIVE PHARMACOKINETIC SAMPLING SCHEDULE

Time	Cycle 4 or any Subsequent Cycle							
	D1					D3	D5	D15
	Pre-dose	0 h post-dose[a]	2 h post-dose[a]	4 h post-dose[a]	8 h post-dose[a]	48 h post-dose[a]	96 h post-dose[a]	336 h post-dose[a]
Allowed time window		+5 min	± 15 min	± 30 min	± 3 hr	± 1 day	± 1 day	± 3 days
PK serum sample	X	X	X	X	X	X	X	X

D=day; h=hour; min=minutes; PK=pharmacokinetic

[a] Relative to the end of ZW25 administration.

Note: Dates and times of the start and end of ZW25 infusions and dates and times of the PK samples must be recorded.

APPENDIX K. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

MEASUREMENT OF EFFECT

Antitumor Effect – Solid Tumors

For the purposes of this study, subjects should be re-evaluated for response every 6 weeks (±7 days, timed from Cycle 1 Day 1). In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST version 1.1 criteria.

Definitions

Evaluable for toxicity: All subjects will be evaluable for toxicity from the time of their first treatment with ZW25.

Evaluable for objective response: Only those subjects who have measurable disease present at baseline, have received at least 1 cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below. (Note: Subjects who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least 1 cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and at follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

"Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Magnetic resonance imaging is also acceptable in certain situations (e.g., for body scans).

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or principal investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[a]
CR	CR	No	CR	≥ 4 wks. Confirmation[b]
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation[b]
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥ 4 wks. from baseline[b]
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD[c]	Yes or No	PD	
Any	Any	Yes	PD	

CR = complete response; PD = progressive disease; SD = stable disease; wks = weeks.

[a] See RECIST version 1.1 manuscript for further details on what is evidence of a new lesion.

[b] Only for non-randomized trials with response as primary endpoint.

[c] In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response; PD = progressive disease; SD = stable disease.

[a] Non-CR/non-PD" is preferred over "stable disease" for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

APPENDIX L. PERFORMANCE STATUS SCALES CONVERSION

Karnofsky		Lansky		ECOG	
Percent	**Description**	**Percent**	**Description**	**Score**	**Description**
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.	0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.		
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.	1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
70	Cares for self, unable to carry on normal activity or to do active work.	70	Both greater restriction of, and less time spent in, play activity.		
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.	2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet active play and activities.		
40	Disabled, requires special care and assistance.	40	Mostly in bed, participates in quiet activities.	3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed, needs assistance even for quiet play.		

20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping, play entirely limited to very passive activities.	4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly.	10	No play, does not get out of bed.		
0	Dead.	0	Dead.	5	Dead.

ECOG = Eastern Cooperative Oncology Group

APPENDIX M. INVESTIGATOR SIGNATURE PAGE

Protocol Title: Phase 2 Study of ZW25 Plus First-line Combination Chemotherapy in HER2- Expressing Gastrointenstinal (GI) Cancers, Including Gastroesophageal Adenocarcinoma (GEA), Biliary Tract Cancer (BTC), and Colorectal Cancer (CRC)

Protocol Number: ZWI-ZW25-201

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IRB/IEC, I will not modify this protocol without obtaining prior approval of Jazz Pharmaceuticals and of the IRB/IEC. I will submit the protocol amendments and/or any ICF modifications to Jazz Pharmaceuticals and IRB/IEC, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all CRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Jazz Pharmaceuticals, to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

Investigator Signature

Date

Printed Name

Title

Institution, Address, and Phone

APPENDIX N. DOCUMENT HISTORY

Amendment 6	16-OCT-2023
Amendment 5	1-DEC-2020
Amendment 4	31-Jul-2020
Amendment 3	6-May-2019
Amendment 2	28-Jan-2019
Amendment 1	14-Jan-2019
Original	24-Oct-2018

Summary of Changes in Amendment 6

Editorial changes and changes that do not impact patient care of safety are not included in this list.

Section(s)	Change	Rationale
Global	• Updated name and organizational affilliation of medical monitor • Changed name and address of Sponsor (Rest of World) from Zymeworks, Inc to Jazz Pharmaceuticals Ireland Limited • Added zanidatamab and JZP598 as synonyms for ZW25	Administrative changes: Incorporating most current updates to Sponsor and/or Medical Monitor information,which has been further updated since the changes in Administrative Letters 6 (08 Nov 2021), 7 (24 Mar 2022), 8 (16 Feb 2023), and 9 (14 Mar 2023) and since Jazz Pharmaceuticals acquired zanidatamab from Zymeworks, Inc.
Global	Clarify that subjects in cohorts 3.3 and 11 receiving ZW25 + mFOLFOX6-2 + bevacizumab may, at the discretion of the investigator, use an FDA-approved bevacizumab biosimilar	Incorporating update from Administrative Letter 4 (26 Feb 2021). The initial protocol was not worded to allow for inclusion of bevacizumab biosimilars, and the Sponsor would like that choice to be available to investigators if they deem that is what is best for participants.
Section 3.1, Table 1 (and corresponding synopsis table)	Tables amended to clarify that oxaliplatin should be administered on both Day 1 and Day 15 of each cycle during mFOLFOX6-2 ± bevacizumab (or biosimilar) treatment.	Incorporating update from Administrative Letter 5 (12 May 2021). Inconcistancies surrounding the oxaliplatin administration schedule required correction to cladify that oxaliplatin should be administered on both Day 1 and Day 15 of each cycle for participants in the mFOLFOX9-2 ± bevacizumab groups.

Section(s)	Change	Rationale
Section 4.1.1 (and corresponding synopsis text)	The following bolded text was added to expand eligibility to allow local RAS and BRAF testing: "Subjects' tumors will be required to be extended RAS (KRAS and NRAS) and BRAF wild-type based upon **local or** central assessment**. If local assessment is used for eligibility, central confirmation is required (Exception: If the "FoundationOne CDx" test is used to perform this testing locally, the BRAF, KRAS, and NRAS results can be used to confirm eligibility for the study and no central testing will be required. Submit formal report of results for sponsor review)."**	Incorporating update from Administrative Letter 6 (08 Nov 2021), clarifying and expanding tests which can be used to determine study eligibility.
Section 5.1.4, Table 3, and Section 7.2.4	Direct investigators whose institutions do not define a normal range for LVEF. The following sentence was added: "If an institution does not define a normal range for LVEF, AESI is defined as an absolute decrease in LVEF of ≥ 10 percentage points from pretreatment baseline and absolute value < 50%"	Incorporating update from Administrative Letter 5 (12 May 2021). (Note: in Administrative Letter 5, Section 7.2.4 was incorrectly referenced as Section 7.4.2, a Section which does not exist. In this Amendment, the change has been incorporated into the intented Section, 7.2.4). Original wording assumed each institution defined a normal range, so language was added giving direction to institutions that do not define a normal LVEF range.

Section(s)	Change	Rationale
Section 5.1.7	Update: changed language to reflect both generations of zanidatamab. The section now reads: In this study, 2 formulations of zanidatamab are available: • Generation 1 (Gen 1) zanidatamab solution. **Vials containing Gen 1 zanidatamab should be stored at –20°C (± 5°C**) and protected from light until ready for use. • Generation 2 (Gen 2) zanidatamab lyophilized powder. **Vials containing Gen 2 lyophilized zanidatamab must be stored at 2 to 8°C** and protected from light until ready for use. To the extent possible, subjects should be administered the same formulation of zanidatamab for the duration of their study treatment, i.e., subjects that start on Gen 1 zanidatamab should stay on Gen 1, and subjects that start on Gen 2 zanidatamab should stay on Gen 2. Zanidatamab must be stored in a controlled location, where access is limited to only designated site staff. For both formulations of zanidatamab study drug, refer to the Pharmacy Manual for detailed drug storage, preparation, and administration information.	This section was originally written when there was only one generation of zanidatamab. Now that another generation is available with different storage requirements, the Sponsor wishes to update this section with storage guidance for both generations of zanidatamab. The Sponsor is also providing investigators with guidance on avoidance of mixed generations whenever possible to aid in simplification of safety reporting.
Section 6.1	Clarification. Added a clarifying sentence on the definition of the term “advanced:” “For subjects with BTC, the definition of advanced disease includes previously resected advanced (Stage 3) disease, with the intent to allow pre-screening of participants with BTC prior to diagnosis of metastatic disease.”	Incorporating update from Administrative Letter 4 (26 Feb 2021). The Sponsor desires a logical and straightforward screening process, and felt expanding and further clarifying the term “advanced” would assist with this goal.
Section 7.1.4 and Section 8.4.5	Correct a discrepancy regarding the timing for extensive PK testing: sections which incorrectly stated participants may opt in after completing 4 or more cycles now correctly state that participants are elibigle to opt in after completing 3 or more cycles of treatment.	Incorporating update from Administrative Letter 5 (12 May 2021). An inconsistency surrounding timing of when participants could opt in to extensive PK sampling required correction.

Section(s)	Change	Rationale
Section 7.2.8	Clarification. Added the following bolded text to clarify that local equipment may be used for ECG collected during screening: "**For screening, local equipment may be used for ECGs. A**fter **a participant is enrolled in the study,** 12-lead ECG will be recorded at selected time points specified in the applicable assessment schedules."	Incorporating update from Administrative Letter 4 (26 Feb 2021). The Sponsor felt that as worded, the statement may be not be sufficiently clear so expanded the text, adding that local equipment may be used for ECG screening.
Section 7.2.8	Clarify that sites may use their own machines to obtain 12-lead ECGs during the study, and that those ECGs will not be centrally read. Changes were made as follows, with additions in bold and deletions in strikethrough: The 12-lead ECG ~~will~~ **may** be obtained **using machines available locally or** using machines and instructions provided by the sponsor and/or its designee. ECGs ~~may~~ **collected for this study will not** be centrally read.	Incorporating update from Administrative Letter 7 (24 Mar 2022), clarifying that local machines may be used to obtain 12-lead ECGs and locally run tests will not be centrally read.
Section 8.4.2.3	Struck the following text that was inconsistent with the DOR definition in other studies and in the draft SAP for this study: DOR is defined as the time from the first objective response (CR or PR) to documented PD per RECIST 1.1 or death ~~within 30 days of last dose of any study treatment (ZW25 or any chemotherapy component)~~ from any cause. Only subjects who achieve an objective response will be included in the analysis.	Changed the wording to align with the DOR definition used in the ZWI-ZW25-201 draft SAP and to maintain consistency across studies.
Appendix A	Correction. Appendix A incorrectly indicated that CT/MRI scans should be collected every 12 weeks, when in actuality they should be performed every 6 weeks. In the "Disease assessment (CT/MRI)" row, moved the X from the 12QW column to the 6QW column	Incorporating update from Administrative Letter 4 (26 Feb 2021). The Schedule of Assessments for XELOX-1 and XELOX-2 contained important omissions, which required correction.
Appendix D	Update. The Schedule of Assessments on Day 15 for participants receiving mFOLFOX6-2 ± bevacizumab was updated to match what appears in Section 6.6.4. Boxes are now checked in Appendix D to correctly reflect that physical examination, vital signs, hematology, and serum chemistry assessments are to be performed on Day 15 of each cycle.	Incorporating update from Administrative Letter 5 (12 May 2021). The text in Section 6.4.4 stated the correct assessments expected on each dosing day, but the Schedule of Events did not adequately reflect expectations and only indicated assessments were needed on Day 1. The Schedule of Events was corrected to clearly indicate that physical examination, vital signs, hematology, and serum chemistry assessments are to be performed on both Day 1 and Day 15 of each cycle.

Section(s)	Change	Rationale
Appendix A Appendix B Appendix C Appendix D Appendix E	Correct Schedule of Assessments to match Section 6.2 and show that echocardiogram/MUGA must be performed for all participants at the screening visit. An “X” was added to the screening column in the Echo/MUGA row in each of the appendices listed.	Incorporating update from Administrative Letter 7 (24 Mar 2022). Correcting an omission in Schedule of Assessments that indicated echocardiogram/MUGA assessments are not required at screening when in actuality, they are.

Summary of Changes in Amendment 5

Section(s)	Change	Rationale
Title page	Updated medical monitor name and contact information	Sponsor personnel change
Protocol approval page	Updated signatory	Sponsor business practice change
Title page and page headers	Updated date and amendment number	To update the information for Amendment 5
Section 1.3 Section 2 Section 3.1 Section 3.3 Section 4.1 Section 5.5 Appendix E	Incorporated BTC cohort and treatment with CisGem	To enable enrollment of subjects with HER2-expressing BTC for treatment with standard of care CisGem chemotherapy in combination with ZW25
Section 1.4 Section 2 Section 3.1 Section 3.3 Section 4.1 Section 5.4 Appendix D	Incorporated CRC cohorts and treatments with mFOLFOX6 ± bevacizumab	To enable enrollment of subjects with HER2-expressing CRC for treatment with standard of care mFOLFOX6 ± bevacizumab chemotherapy in combination with ZW25
Section 5.1.3 Section 5.1.6 Section 5.2 Section 5.3 Section 5.4 Section 5.5	Mandated universal prophylaxis with antidiarrheals for the first cycle of treatment, and clarified guidance for diarrhea management	To mitigate the potential for severe diarrhea in subjects receiving ZW25 plus combination chemotherapy

Section(s)	Change	Rationale
Section 5.1.3 Table 2	Revised guidance for management of potential ZW25-associated toxicities, including dose modifications for nausea/vomiting, diarrhea, rash, and other toxicities; management of LVEF dysfunction; and management of infusion-related reactions	To clarify guidance for managing potential ZW25-related AEs, including recommended ZW25 dose modifications for severe AEs of vomiting, diarrhea, rash, and other toxicities
Section 5.1.3 Section 5.1.4	Revised guidance for management of LVEF dysfunction and infusion-related reactions	To align with program-level assessment of cardiac risk and infusion reactions
Section 5.2 Section 5.3 Section 5.4 Section 5.5	Added/revised guidance for management of toxicities potentially associated with components of combination chemotherapy	To provide (for CisGem) or clarify (for other chemotherapy regimens) guidance for managing potential chemotherapy-related AEs, including recommended dose modifications of individual chemotherapy components.
Section 7.1.4 Section 8.4.5 Appendix J	Added optional steady-state extensive PK substudy	To enable collection of additional extensive PK data in subjects who have received at least 4 cycles of ZW25 plus combination chemotherapy
Section 6.1 Appendix A - Appendix E	Added optional pre-screening visit for HER2 status	To enable assessment of HER2 status prior to initiating additional protocol-related screening activities
Section 7.2.2.1	Clarified reporting of AEs related to disease progression	To encourage sufficient detail when reporting of SAEs related to progression of the underlying malignancy

Summary of Changes in Amendment 4

Section(s)	Change	Rationale
Title page	Updated medical monitor name and contact information	Sponsor personnel change
Protocol approval page	Updated signatory	Sponsor business practice change
Title page and page headers	Updated date and amendment number	To update the information for Amendment 4
Throughout protocol	Made minor formatting and editorial changes. This includes changing patient to subject, changes to section and table numbering and Appendix lettering, and changes to cross-references to renumbered tables/sections/appendices.	To improve clarity and achieve consistency
Throughout protocol	Removed XP from the list of physician's choice chemotherapy regimens. Changed references to "4" chemotherapy regimens to just references to chemotherapy regimens.	To remove a chemotherapy option no longer being studied
Throughout protocol	Changed original ZW25 plus XELOX, FP, and mFOLFOX6 regimens to XELOX-1, FP-1, and mFOLFOX6-1 to accommodate adding modified regimens for combining ZW25 with XELOX, FP, and mFOLFOX6. New combinations are referred to as XELOX-2, XELOX-3, FP-2, and mFOLFOX6-2.	To incorporate changes in the planned dosing regimens of ZW25 and/or the chemotherapies in the combination regimens. The changes to the ZW25 regimen were a result of PK analyses of data from Study ZWI-ZW25-101. The changes to the mFOLFOX6 chemotherapy regimen are meant to reduce the diarrhea that made the original mFOLFOX6 regimen (mFOLFOX6-1) not tolerable.
Synopsis, Sections 2.1, 2.2, and 8.4.2.4	Add clinical benefit rate (CBR) to the list of study endpoints	Sponsor decision to have another efficacy endpoint
Synopsis, Section 3.1	Added general descriptions of how the three XELOX regimens differ, how the two FP regimens differ, and how the two mFOLFOX6 regimens differ	To incorporate changes in the planned dosing regimens of ZW25 and/or the chemotherapies in the combination regimens. Reasons for changes are in the 6th row of this Summary of Changes in Amendment 4.

Section(s)	Change	Rationale
Synopsis, Sections 3.1 and 7.1.4	Specified that subjects on combinations with ZW25 flat doses should be on the extensive PK sampling schedule unless otherwise approved by the sponsor's medical monitor	To enable the sponsor to get additional PK data on flat dosing of ZW25 and to allow select subjects to opt out of extensive PK sampling
Study Design figure in Synopsis and Figure 1	Updated Figure	To incorporate changes in the planned dosing regimens of ZW25 and/or the chemotherapies in the combination regimens. Reasons for changes are in the 6th row of this Summary of Changes in Amendment 4.
Figure 2	Updated DLT process figure	
Synopsis, Sections 5.1.2, Table 30	Updated ZW25 regimen for all combination regimens	
Synopsis, Section 5.2, Table 30	Updated XELOX regimens	
Synopsis, Section 5.3, Table 30	Updated FP regimens	
Synopsis, Sections 5.4 and 5.4.2, Table 30	Updated mFOLFOX regimens	
Synopsis Section 3.1.1 and 8.2	Updated sample size	
Synopsis, Sections 3.1, 3.1.1.1, and 3.2, Table 30	Clarified which combination regimens are expected to produce RDs for Part 2	To incorporate changes in the planned dosing regimens of ZW25 and/or the chemotherapies in the combination regimens. Reasons for changes are in the 6th row of this Summary of Changes in Amendment 4.

Section(s)	Change	Rationale
Synopsis and Sections 3.1.1, 3.1.1.1, and 3.2, Table 30	Clarified the process for step-down doses	To specify that step-down doses recommended by the SMC will be not less than [redacted] and require sponsor approval
Synopsis, Sections 3.1.2 and 3.3	Deleted reference to each combination regimen cohort in Part 2 enrolling approximately one-fourth of the Part 2 subjects	To be consistent with chemotherapy regimen being physician's choice
Synopsis and Section 4.1	Updated inclusion and exclusion criteria	To add clarifications based on study sites' questions over the course of the study
Synopsis and Section 6.14	Updated the conditions for discontinuing chemotherapy and eliminated the maximum of 6 cycles for chemotherapy	To allow subjects to continue on chemotherapy beyond 6 cycles per investigator and subject agreement and to accommodate sponsor's desire to have the subjects stay on chemotherapy through at least 6 cycles
Synopsis, Sections 3.1, 7.2.1, 7.2.2, and 7.2.4, and Appendices A through E	Edited text regarding the AE reporting period and definition of AESIs	To clarify the following: only study protocol-related AEs will be reported between the signing of informed consent and the first dose of any study drug, all AEs will be reported from the first dose of any study drug through the AE reporting period, and follow-up of AESIs (including revised definition of what constitutes an AESI) will continue until resolution, return to baseline, or study closure
Synopsis and Sections 3.1, 3.1.1, and 3.1.1.1	Edited the DLT evaluation period text	To accommodate sponsor decision change the DLT evaluation period from 28 days to the first cycle
Synopsis and Section 8	Removed all mention of Simon 2-stage design and attendant interim analysis in Part 2 and hypothesis testing in this study	To accommodate sponsor decision
Section 1.3	Added results of a population PK analysis of Study ZWI-ZW25-101 data	To provide the scientific basis for the changes in the ZW25 regimens

Section(s)	Change	Rationale
Sections 1.5 and 4.2	Edited pregnancy reporting text	To clarify the pregnancy reporting requirements
Section 3.1.1	Noted that XELOX-3 was prioritized above XELOX-2 in Part 2	To clarify which regimen has priority
Sections 3.2, 5.1.10.1, 5.2, 5.3, 5.4, 5.2.6.1, 5.3.6.1, and 5.4.7.1	Added text regarding modifications to the regimens of chemotherapy components and premedication requirements per SMC recommendation and sponsor approval Clarified text regarding when and how often the SMC will meet	To allow future changes to chemotherapy regimens and premedication regimens to be made by SMC recommendation and sponsor approval without amending the protocol
Section 3.3	Added text explaining how the changes to the ZW25 regimens reflect the results of the population PK analysis of Study ZWI-ZW25-101 data. Added text regarding the change to the mFOLFOX6 chemotherapy regimen.	To provide rationale for the changes to the ZW25 and mFOLFOX6 regimens.
Section 4.3.1	Removed the sentence that allowed subjects with radiographic disease progression to stay on study treatment if the investigator felt the subject was still receiving clinical benefit	To reflect sponsor decision
Section 5.1.2	Edited text regarding ZW25 dose changes in response to subject weight changes	To accommodate both weight-based (already in the protocol) and flat (newly added in this amendment) dosing of ZW25
Section 5.1.3	Edited text to clarify that ZW25 dose reductions for individual subjects are not based on the dose levels in the dose escalation cohorts. Edited text to specify the lower limit of dose reductions and that dose reductions must be discussed with and approved by the sponsor's medical monitor.	To provide clarity, to accommodate flat dosing, and to provide more sponsor control
Sections 5.2, 5.3, and 5.4	Added instructions for investigators to discuss different starting dose or recommended dose modification for any of the components of the chemotherapy regimen with the sponsor's medical monitor	To accommodate investigator's who may have specific reasons for wanting to modify the chemotherapy regimen of a protocol-specified regimen
Sections 5.2.2, 5.3.2, and 5.4.2	Specified that subjects who discontinue chemotherapy without disease progression and for reasons that are not related to ZW25 toxicity may continue on ZW25 alone	To provide clarification

Section(s)	Change	Rationale
Sections 5.2.3, 5.3.3, and 5.4.3	Added text regarding use of protocol recommended, prescribing information provided, and institutional standards for dose modifications of the chemotherapy components and expressly permitted use of the investigator's medical judgment to decide which dose modifications to apply in case of adverse events	To provide clarity/options and allow the use of investigator judgment
Section 5.2.4	Added subsections for Allergy to Platinum and Platinum Hypersensitivity	To remedy not having had these sections or cross references to these sections (originally in the XP precautions section) in the previous versions of the protocol (note: XELOX includes platinum)
Section 5.2.4	Replaced cross references with actual text for subsections on pharyngo-laryngeal dyesthesia, cardiotoxicity, DYPD, pulmonary fibrosis, venous occlusive disease, and hemolytic uremic syndrome	To keep the information which was previously in the XP precautions section and cross referenced in the XELOX precautions section
Section 5.2.4.3	Added text regarding management of diarrhea	To align with separate instructions to sites
Section 5.2.6.3	Replaced a cross reference with actual text for capecitabine drug interactions	To keep the information which was previously in the XP drug interactions section and cross referenced in the XELOX drug interactions section
Section 6	Removed text regarding AE reporting	To remove needless repetition of information elsewhere in the protocol
Section 6	Throughout this section: Added cross references to chemotherapy discontinuation criteria, added visit windows, deleted limits of 6 cycles for all the chemotherapy regimens, added visit by visit procedures for XELOX-2, XELOX-3, and FP-2, noted that the visit by visit procedures were the same for some regimens (XELOX-1 and XELOX-2, both FP regimens, and both mFOLFOX6 regimens), added notes that cycle counting is from Cycle 1 Day 1 and does not restart if/when a subject discontinues chemotherapy,	To incorporate changes in the planned dosing regimens of ZW25 and/or the chemotherapies in the combination regimens. Reasons for changes are in the 6th row of this Summary of Changes in Amendment 4.
Section 7.1.1 and Appendix J	Edited text regarding confirmatory scans for objective response	To clarify that confirmatory scans should occur not less than 4 weeks after the first scan showing objective response

Section(s)	Change	Rationale
Section 7.2.1	Removed the choices for action taken (with respect to study drug in response to an AE)	To accommodate possible changes in the CRF
Table 31	Added probabilities of observing DLTs in cohorts of 14 subjects	To accommodate the SMC expanding dose escalation cohorts to 14 subjects
Table 32	Added 95% CIs of observed ORR vs true ORR	To accommodate removal of Simon 2-stage design and the revised sample size [redacted]
Table 33	Added probabilities of observing AEs in a sample size of [redacted]	To accommodate the revised sample size of Part 2
Table 34	Modified the analysis sets planned for this study	To accommodate changes in planned statistical analyses
Section 8.4.2.4	Added section on clinical benefit rate	To accommodate addition of clinical benefit rate as an endpoint
Section 8.4.7	Deleted the Simon 2-stage interim analysis in Part 2. Added statement saying there is no formal interim analysis.	To accommodate removal of the Simon 2-stage design
Appendix A, Appendix B, Appendix C, and Appendix D	These are the schedule of assessment appendices. Added applicable regimens to each appendix (added XELOX-2 to the same appendix as XELOX-1, added FP-2 to the same appendix as FP-1, and added mFOLFOX6-2 to the same appendix as mFOLFOX6-1). Added an additional appendix for XELOX-3.	To incorporate changes in the planned dosing regimens of ZW25 and/or the chemotherapies in the combination regimens. Reasons for changes are in the 6th row of this Summary of Changes in Amendment 4.
Appendices A through D	Added visit windows as needed	To provide clarity
Appendices E through H	Edited the appendices titles to clarify which appendices applied to which combination regimens	To provide clarity
Appendix I	Added text regarding window for tumor assessments	To provide clarity and consistency with the rest of the protocol

Section(s)	Change	Rationale
Throughout protocol	Required female subjects of childbearing potential to practice contraception, report pregnancy, not breastfeed, and not donate eggs for 14 months after the last dose of ZW25 or chemotherapy if assigned to a cisplatin-containing regimen	To align with the cisplatin package insert/prescribing information

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Title page and page headers	Updated date and amendment number.	To update the information for Amendment 3.
Throughout protocol	Made minor formatting and editorial changes. This includes changes to section and table numbering and Appendix lettering and changes to cross-references to renumbered tables/sections/appendices.	To improve clarity and achieve consistency.
Throughout protocol	Added XELOX to the list of physician's choice chemotherapy regimens. Changed references to "3" chemotherapy regimens to "4" chemotherapy regimens.	To incorporate a new (4th) chemotherapy option.
Throughout protocol	Changed duration of treatment cycles from being described in weeks and/or days to being described in days. Changed the duration of the treatment cycle for ZW25+XP from 6 weeks to 21 days. Changed the duration of the treatment cycle for ZW25+FP from 4 weeks to 21 days. Changed the dosing frequency of ZW25 in the combinations with XP and FP from Q2W to Q3W.	To incorporate changes in the planned dosing frequency of ZW25 from Q2W to Q3W (for all regimens except ZW25+mFOLFOX6) in order to align ZW25 dosing frequency with that of trastuzumab in the TOGA study.
Synopsis and Sections 3.1, 3.1.1, and 7.1.2	Added text stipulating that local assessments must use FDA-approved tests for determining HER2 status for GEA.	To clarify that FDA-approved tests must be used.
Synopsis and Sections 3.1, 4.3.1, and 6.12	Clarified that if subjects discontinued ZW25, then they could not remain on chemotherapy alone as study drug and would enter long-term survival follow-up.	To clarify that the study will not provide chemotherapy without ZW25 as study drug and to clarify that subjects who discontinue study treatment will be followed for survival.
Synopsis and Sections 3.1, 7.2.6, and 8.4.3.8	Added oxygen saturation as one of the vital signs.	To gather additional data.
Synopsis, Sections 3.1 and 6.6, and RECIST appendix	Changed the frequency of post-baseline CT/MRI scans (disease assessments) from every 8 weeks to every 6 weeks.	To align with 3 of the 4 chemotherapy combinations' cycle length and to standardize across all chemotherapy combinations.

Section(s)	Change	Rationale
Synopsis and Figure 1	Updated study schematic to reflect addition of XELOX and changes in treatment cycle duration and CT/MRI every 6 weeks instead of every 8 weeks. Added a figure footnote indicating the order of drug administration (a clarification). The order of study drug administration was also noted in Section 5.1 (in text, not in a figure footnote).	To incorporate changes in the planned dosing frequency of ZW25 from Q2W to Q3W (for all regimens except ZW25+mFOLFOX6).
Synopsis and Sections 3.1.1, 5.1.2, and 5.1.3	Changed the dosing regimen of ZW25 from Q2W to Q3W for all regimens except ZW25+mFOLFOX6. Stipulated that the starting ZW25 Q3W dose would be decided by the SMC based on data from Study ZWI-ZW25-101. Provided for up to 2 step-down dose levels for ZW25 Q3W in combination with XP, XELOX, and FP. Stipulated that the lowest ZW25 Q3W dose would be at least 20 mg/kg. Set the DLT evaluation period as the first 28 days (was first 6 weeks in Amendment 2) even for regimens with 21-day treatment cycles.	To incorporate changes in the planned dosing frequency of ZW25 from Q2W to Q3W (for all regimens except ZW25+mFOLFOX6). To provide flexibility for the starting ZW25 Q3W dose. To standardize the number of step-down doses and DLT evaluation period across all chemotherapy combinations.
Synopsis and Sections 3.1.1 and 8.2	[redacted]	To accommodate addition of a 4th chemotherapy combination and the possibility of two ZW25 step-down doses per chemotherapy combination.
Synopsis and Sections 3.1.2, 3.3, and 3.3.1	Indicated that each chemotherapy regimen in Part 2 will enroll approximately one-fourth (not one-third) of the Part 2 subjects.	To accommodate addition of a 4th chemotherapy combination.
Synopsis and Section 4.1.1	Inclusion criterion 1a was edited to specify local or central assessment of HER2 status using an FDA approved HER2 test for GEA.	To clarify that local or central assessment can be used for Part 1 but either assessment must be done using specific FDA approved tests.
Synopsis and Section 4.1.1	Inclusion criterion 13 was edited to clarify the informed consent process.	To clarify that tumor samples may be sent to a central laboratory for analysis/review based on a consent for prescreening before the subject signs the informed consent for the rest of the study.

Section(s)	Change	Rationale
Synopsis and Section 4.1.2	Exclusion criterion 2 was modified to include other cancer therapy not otherwise specified in exclusion criteria. Exclusion criterion 15 regarding hypersensitivity to components of physician's choice chemotherapy was edited to reflect 4 such combinations rather than 3. Exclusion criteria for prior malignancy (exclusion criterion 16) and hepatitis and HIV (exclusion criterion 17) were edited to align with current FDA guidance.	To provide clarification on prior cancer therapy. To accommodate the addition of a 4th chemotherapy combination. To align with current regulatory guidance.
Synopsis and Section 5.1.2	In the description of ZW25 dosing in Part 1, text and formatting were modified to clearly delineate the ZW25+chemotherapy regimens that had 21-day cycles from the ZW25+chemotherapy regimen with 28-day cycles. Text was also modified to clearly state that the ZW25 Q3W recommended initial dose would be 30 mg/kg or lower.	To make the ZW25 regimen more reader friendly and to provide both flexibility and a ceiling for the ZW25 Q3W recommended initial dose.
Synopsis and Sections 5.1.4 and 5.1.8.1	Specified that premedication with acetaminophen, diphenhydramine, and a corticosteroid is mandatory before ZW25 infusions.	To clarify that these premedications (prophylaxis for infusion reactions) are mandatory (not just recommended).
Synopsis and Section 6.12	Test Product, Dose, and Mode of Administration and Treatment Duration were updated. Added ZW25 Q3W dosing to start at a to-be-determined dose level. Edited text to reflect changes in treatment cycle length for ZW25+XP and ZW25+FP. Added XELOX. Updated the maximum number of chemotherapy cycles allowed for all regimens to 6 and specified that, after a maximum of 6 cycles, subjects would continue on ZW25 alone.	To accommodate the addition of a 4th chemotherapy combination, incorporate changes in the planned dosing frequency of ZW25 from Q2W to Q3W (for all regimens except ZW25+mFOLFOX6), reflect changes in the cycle length of ZW25+XP and ZW25+FP which necessitated changes in some of the chemotherapy doses, and standardize the maximum number of allowed chemotherapy cycles (changed to approximate the TOGA study's maximum number of cycles).
Synopsis and Sections 3.1 and 7.1.4	Deleted the allowance for a site to opt out of an extensive PK schedule with sponsor approval.	To align with current sponsor position.

Section(s)	Change	Rationale
Synopsis and Sections 8.1 and 8.2	Changed null hypothesis from ORR $\leq$ 50% to $\leq$ 45%. Changed alternative hypothesis from ORR $\geq$ 70% to $\geq$ 65%. Changed Minmax to Optimum. Changed the numbers of subjects in stage 1 and stage 2 of Part 2. Changes the numbers and percentages of subjects with objective response needed in stage 1 to proceed to stage 2. Changes the numbers and percentages of subjects with objective response needed in Part 2 to reject the null hypothesis. Changed the type I error rate from 0.048 to 0.05. Changed the probability of early termination of the study in stage 1 if the true ORR matches the null hypothesis from 0.50 to 0.654.	To change the null and alternative hypotheses for the Simon 2-stage design. To correct the name of the Simon 2-stage design To align with the changes to the null and alternative hypotheses.
Synopsis and Section 8.2	Updated number of evaluable subjects for Part 1. Updated number of evaluable subjects for Part 2. Updated number of study centers.	To accommodate the addition of a 4th chemotherapy combination. To accommodate changes in the null and alternative hypotheses in Part 2. To accommodate change in the number of study centers.
Synopsis and Table 26	Modified the sample size determination (Parts 1 and 2) table by adding XELOX, changing the ZW25 dosing from Q2W to Q3W for the ZW25+XP and ZW25+FP combinations, specifying that the starting ZW25 Q3W dose is to-be-determined, and consistently having 2 step-down doses for ZW25 for all combinations (with a floor of 20 mg/kg Q3W for step-down doses for ZW25 Q3W). Added mg/kg Q2W or mg/kg Q3W to the description of ZW25 dose.	To accommodate the addition of a 4th chemotherapy combination, incorporate changes in the planned dosing frequency of ZW25 from Q2W to Q3W (for all regimens except ZW25+mFOLFOX6), provide flexibility for the starting ZW25 Q3W dose, and standardize the number of step-down doses across all chemotherapy combinations. To clarify ZW25 dose units and frequency.
Section 1.5	Updated the most common adverse events paragraph (second paragraph in this section).	To provide more up-to-date information.
Sections 3.1 and 3.2	Edited text regarding the timing of the SMC meetings.	To clarify the timing of the SMC meetings during Parts 1 and 2 of the study.

Section(s)	Change	Rationale
Section 3.1	Added text that the subject can remain on study treatment even if there is radiological evidence of disease progression if the investigator feels the subject is still deriving clinical benefit and the sponsor's Medical Monitor agrees.	To clarify and align with text in Section .
Sections 3.1.1 and 5.1.2	Added sentence specifying that subjects will not be given ZW25 at doses >20 mg/kg Q3W until this dose (or higher) has been found to be acceptable based on Study ZWI-ZW25-101 data.	To clarify that doses used in this current study will not be higher than doses found to be acceptable in the Phase 1 study.
Section 3.1.1.1	Updated DLT evaluation period from 6 weeks to 28 days. Specified that up to 2 step-down dose levels for ZW25 are allowed per chemotherapy combination in Part 1. Specified that if the reason a subject did not receive at least 75% of planned doses was a DLT, then the subject was DLT evaluable.	To apply change to DLT evaluation period caused by change to cycle lengths. To provide clarification and standardization on the number of step-down doses allowed for each chemotherapy combination. To provide clarity on the definition of DLT evaluable subject.
Section 3.3	Added text explaining ZW25 doses and schedules were selected based upon clinical and non-clinical safety, PK and modeling data and to complement chemotherapy dosing schedules.	To provide additional explanation for the ZW25 dosing regimens.
Figure 2	Updated figure to avoid specifying specific dose levels of ZW25.	To provide flexibility for ZW25 Q3W dosing because the starting dose is to be determined.
Sections 4.2, 6.8, 6.9, and 7.2.11 Follow-up of AEs subsection	Added text specifying that last dose of study drug or study treatment refers to last dose of ZW25 or any chemotherapy component	To clarify the starting or reference point for when to have the EOT visit and the 30-day follow-up visit and for how long to refrain from/report pregnancies and follow-up AEs.

Section(s)	Change	Rationale
Section 4.3.1	Changed Subject decision to Withdrawal of consent. Added text stating that subjects who do not take ZW25 for >4 weeks will be withdrawn from study treatment unless medical monitor agrees to allowed continued study treatment. Added text saying that, with the approval of the medical monitor, a subject with radiological disease progression can continue on study treatment if the investigator believes the subject is still deriving clinical benefit.	To align with CDISC terminology. To be consistent with other sections of the protocol. To be consistent with other sections of the protocol.
Section 4.3.2	Changed Subject decision to Withdrawal of consent.	To align with CDISC terminology.
Section 5.1	Added a note regarding the order of drug administration. Added text for ZW25 Q3W dosing starting at a to-be-determined dose and with the possibility of up to 2 step-down doses for ZW25 in combination with XP, XELOX, and FP. Clarified that no subject will be given any ZW25 Q3W dose greater than 20 mg/kg until that dose or higher has been shown to be a possible recommended monotherapy dose in Study ZWI-ZW25-101.	To provide clarification and consistency with other sections of the protocol. To accommodate the addition of a 4th chemotherapy combination, incorporate changes in the planned dosing frequency of ZW25 from Q2W to Q3W (for all regimens except ZW25+mFOLFOX6), provide flexibility for the starting ZW25 Q3W dose, and standardize the number of step-down doses across all chemotherapy combinations.
Section 5.1.3	Added text specifying the lower limit of step-down doses for ZW25.	To specify that the lowest doses of ZW25 will not be lower than [redacted].
Section 5.1.8	Deleted “All concomitant medications and blood products received within 4 weeks prior to and during the study must be documented in the subject CRF.”	To eliminate redundancy with CRF instructions.
Section 5.1.8.1	Deleted “consistent with institutional standards” regarding premedication and ZW25 dosing.	To standardize across sites by having them follow protocol instructions rather than local practice.
Section 5.1.8.2	Deleted “After enrollment, radiotherapy (RT) is allowed for symptom control at a previously documented site of disease (non-target lesions) with no evidence of progression.”	To align with current sponsor position.

Section(s)	Change	Rationale
Sections 5.2, 5.4, and 5.5	The chemotherapy combination was added to the ends of the subheadings in these sections about the 4 physician's choice chemotherapy combinations. Changed the maximum number of chemotherapy cycles to 6 and specified that after the maximum number of cycles, the subjects would continue on ZW25 monotherapy alone. Added instructions to follow the chemotherapies' prescribing information if there is a conflict between dose modification recommendations in the protocol and in the prescribing information. Deleted references to local or institutional standards or practice for dose modifications. Drug interactions subsections were added.	To avoid having a lot of identical subheadings in the 4 sections (i.e., for clarity). To be consistent with other sections of the protocol. To provide clarity and facilitate standardization across sites as well as to ensure compliance with current labelling for the chemotherapy drugs. To comply with an agreement with the FDA.
Table 8	Specific dose levels (in terms of % of starting dose) were added to the Recommended Dose Modifications for Cisplatin Neurologic Toxicities.	To provide clarity because, previously, the table referred to decrease 1 level without defining the decreased level.
Section 5.3	Section on XELOX (description, dose administration, dose modifications, precautions, etc.) was added.	To accommodate addition of the 4th physician's choice chemotherapy combination.
Section 6 and Appendices A, B, C, and D	Made changes to ECG time points. ECGs will be done 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 done predose, at 1 hour after the end of ZW25 infusion, and 4 hours after the end of ZW25 infusion. No predose ECGs on Day 1 of other cycles.	To align with time points agreed upon with the FDA.
Section 6.1 and Appendices A, B, C, and D	Deleted fine needle aspiration.	To align with current sponsor position.

Section(s)	Change	Rationale
Sections 6.2, 6.3, 6.4, and 6.5	Visit procedures for the treatment cycle (for 3 chemotherapy combinations) were previously in Section 6.2 (in Amendment 2 of the protocol). In Amendment 3, this section was re-organized into 4 sections (one for each of the 4 chemotherapy combinations). Changes were also made to align with the changes in the Schedules of Assessments.	To provide clarity and accommodate the addition of a 4th chemotherapy combination, incorporate changes in the planned dosing frequency of ZW25 from Q2W to Q3W (for all regimens except ZW25+mFOLFOX6), and incorporate changes caused by changes in cycle length for the ZW25+XP and ZW24+FP combinations. To accommodate a schedule change regarding physical examinations and weight and weight-based dosing as requested by Health Canada. To accommodate schedule changes in ECGs as requested by the FDA.
Section 6.7 and Appendices A, B, C, and D	Changed first post-baseline echocardiogram/MUGA time point from 8 weeks after Cycle 1 Day 1 to 6 weeks after Cycle 1 Day 1.	To align first post-baseline echocardiogram/MUGA with first post-baseline disease assessment.
Section 6.8 and Appendices A, B, C, and D	Added physical examination and vital signs.	To correct oversight in previous versions of the protocol.
Section 6.9 and Appendices A, B, C, and D	Added vital signs.	To correct oversight in previous versions of the protocol.
Section 6.9	Added “Disease assessment per RECIST 1.1 (CT/MRI scans, not required if done at EOT visit and/or ≤ 4 weeks since previous scan).”	To provide clarity and consistency with the Schedules of Assessments.
Section 6.12	Added text stating that subjects who do not take ZW25 for >4 weeks will be withdrawn from study treatment unless medical monitor agrees to allow continued study treatment.	To provide consistency with other sections of the protocol.
Section 7.1.2	Deleted “Fine needle aspirations (cell blocks) may be allowed with medical monitor approval.” Added “No genomic testing of germ-line DNA will performed in this study.”	To align with current sponsor position. To provide clarification.

Section(s)	Change	Rationale
Section 7.1.5	Added "Blood samples for ADAs will be taken before the start of the ZW25 infusion. All ADA blood sample collection time points coincide with a pre-dose PK sample time point."	To show that the study is following an FDA recommendation.
Section 7.2.4	Added details to the definition of LVEF as an AESI.	To clarify which LVEF changes will be considered AESIs.
Section 8.4.3.6	Added a summary of LVEF changes considered to be AESIs.	To align with Section 7.2.4.
Section 8.4.5	Added "and Q3W."	To specify that PK parameters will be derived for both ZW25 Q2W and Q3W.
Section 9.2	The clinical monitoring plan items were updated.	To reflect the clinical monitoring plan.
Section 12.3.1	Text was updated to accommodate consent for prescreening before consent for the rest of the study.	To align with revised inclusion criterion 13.
Schedule of Assessments for ZW25+XP and ZW25+FP	Tables were updated to align with changes in the rest of the protocol.	To accommodate changes in cycle length and change in ZW25 dosing from Q2W to Q3W as well as to align with changes made elsewhere in the protocol.
Schedule of Assessments for ZW25+XELOX	Table was added.	To accommodate the addition of the 4th physician's choice chemotherapy combination.
Schedule of Assessments for ZW25+ mFOLFOX6	Added physical examinations including weight on Day 15 of each cycle.	To comply with a request from Health Canada related to weight-based dosing of ZW25.
Footnotes for Schedules of Assessments for ZW25+XP, ZW25+FP, and ZW25+ mFOLFOX6	Added text regarding the maximum number of cycles of chemotherapy and that the subjects would continue on ZW25 monotherapy alone after receiving the maximum number of chemotherapy cycles, clarified that pregnancy testing was only for women of childbearing potential, specified that the physical examination on ZW25 dosing days would be done before dosing and the body weight would be used to adjust the weight based dose of ZW25, and adjusted the number and timing of ECGs.	To provide clarity and/or consistency with other sections of the protocol, accommodate a schedule change regarding physical examinations and weight and weight-based dosing as requested by Health Canada, and accommodate schedule changes in ECGs as requested by the FDA.

Section(s)	Change	Rationale
Pharmacokinetic Extensive Sampling Schedules	In Amendment 2, there was one extensive PK sampling schedule for all chemotherapy combinations. In Amendment 3, there are two such schedules: one for ZW25+mFOLFOX6 and another for the other 3 combinations. The one for the mFOLFOX6 combination is the same as in Amendment 2 except that the window for end of infusion (except for Cycle 1 Day 1) has been expanded from 15 minutes to 30 minutes. A footnote explaining that dates/times for ZW25 infusion and dates/times for PK sampling must be recorded was added to both extensive PK sampling schedules in Amendment 3. Changed post-dose time points from relative to the start of ZW25 administration to relative to the end of ZW25 administration.	To accommodate the changes in cycle length and change in ZW25 dosing from Q2W to Q3W for the non-mFOLFOX6 regimens. To provide clarity and allow the use of actual times rather than nominal times in the PK analyses. To clarify post-dose time points and to prevent the end of infusion and 2 hour post-dose time points from coinciding.
Pharmacokinetic Sparse Sampling Schedules	In Amendment 2, there was one sparse PK sampling schedule for all chemotherapy combinations. In Amendment 3, there are two such schedules: one for ZW25+mFOLFOX6 and another for the other 3 combinations. The one for the mFOLFOX6 combination is the same as in Amendment 2 except that the window for end of infusion has been expanded from 15 minutes to 30 minutes. A footnote explaining that dates/times for ZW25 infusion and dates/times for PK sampling must be recorded was added to both extensive PK sampling schedules in Amendment 3.	To accommodate the changes in cycle length and change in ZW25 dosing from Q2W to Q3W for the non-mFOLFOX6 regimens. To provide clarity and allow the use of actual times rather than nominal times in the PK analyses.

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Synopsis and Sections 3.1.1, 3.1.1.1, and 3.2	Revised the definition of DLT as related to study treatment, which includes the evaluated dose level of ZW25, any component or combination of the components of a chemotherapy regimen, or the combination of ZW25 plus a chemotherapy regimen using the definition of NCI-CTCAE v5.0.	Per FDA request
Synopsis and Section 4.1.1	Changed inclusion criterion #8 8. Hematological function, as follows: b. Platelet count > 100 x 10^9/L	Per FDA request
Section 3.1.1.1	Deleted antimicrobial agents as part of the DLT definition criterion regarding rash	Per FDA request
Section 3.1.1.1	Revised the DLT criteria to specify that Grade 3 symptomatic lab abnormalities or those that require medical treatment are DLTs if not corrected within 72 hours of onset.	Per FDA request
Section 3.1.1.1	Revised the DLT criteria to specify that concomitant Grade 3 ALT/AST and Grade 2 or greater bilirubin increases are DLTs (Hy's law).	Per FDA request
Section 3.1.1.1	Revised the DLT criteria to state that An AE will be considered to be a DLT if a ZW25 dose reduction is needed due to toxicity during the DLT period.	Per FDA request
Section 5.1.3	Removed that decisions regarding dose reduction of ZW25 for occurrence of Grade 3 nausea, vomiting, diarrhea, or rash is contingent on the adequacy of the supportive therapy received. Revised recommended management and potential dose modifications for common ZW25-associated toxicity to provide standard guidelines for management of these toxicities and a consistent approach to dose modification for these Grade 3 events. Additionally, revised the protocol to include instructions for permanent discontinuation of study treatment for recurrence of Grade 3 nausea, vomiting, diarrhea, or rash for which the subject did not receive maximal treatment or refused supportive treatment. If necessary, the protocol should include provisions for site-specific interventions for recurring issues with Grade 3 adverse events that would be preventable with appropriate supportive care	Per FDA request
Sections 7.2.1.1	Updated the assessment of causality to state that related AEs will include those related to study drugs	To include possible relationship to chemotherapies
Section 7.2.3.1	Updated the definition of an unexpected adverse reaction as any untoward and unintended response that is related to the administration of the study drugs	To include possible relationship to chemotherapies

Summary of Changes in Amendment 1

Section(s)	Change	Rationale
Cover page	Upated the IND number.	Per FDA request
Cover page and headers and footers and Appendix J: Document History	Change the dates and amendment number	To reflect current dates and amendment number

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