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

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26 May 2023

CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	Phase 1b/2 Study Investigating Safety, Tolerability, Pharmacokinetics and Preliminary Antitumor Activity of Anti-HER2 Bispecific Antibody ZW25 in Combination With Chemotherapy With/Without Tislelizumab in Patients With Advanced HER2-positive Breast Cancer or Gastric/Gastroesophageal Junction Adenocarcinoma
Protocol Identifier:	BGB-A317-ZW25-101
Phase:	1b/2
Investigational Product(s):	Zanidatamab (ZW25) and Tislelizumab (BGB-A317) injections
Indication(s):	Breast Cancer and Gastric/Gastroesophageal Junction Adenocarcinoma
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 1840 Gateway Drive, 3rd Floor San Mateo, California 94404 USA
Sponsor Medical Monitor:	[redacted]
Original Protocol Version 0.0:	05 September 2019
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Amendment 3.0:	26 May 2023

Approved Date 2023年05月26日

[redacted]

Confidentiality Statement

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FINAL PROTOCOL APPROVAL SHEET

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

BeiGene, Ltd., Approval:

See electronic signature	*See electronic signature*
Sponsor Medical Monitor	Date

INVESTIGATOR SIGNATURE PAGE

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Protocol Identifier: BGB-A317-ZW25-101

This protocol is a confidential communication of BeiGene, Ltd., and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name and address of the center in which the study will be conducted. Return the signed copy to BeiGene or its designee.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

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_____

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SYNOPSIS

Name of Sponsor/Company:	BeiGene, Ltd.
Investigational Product(s):	Zanidatamab (ZW25) and Tislelizumab (BGB-A317) injections
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Protocol Identifier:	BGB-A317-ZW25-101
Phase of Development:	1b/2
Number of Patients:	Approximately 80 patients in total
Study Centers:	Approximately 20 centers in Asian countries

Study Objectives:

Primary:

- To assess the safety and tolerability of zanidatamab (also known as ZW25) in combination with docetaxel in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, and ZW25 in combination with tislelizumab and chemotherapy in patients with HER2-positive gastric/gastroesophageal Junction (GEJ) adenocarcinoma
- To evaluate the preliminary antitumor activity of ZW25 in combination with docetaxel in patients with HER2-positive breast cancer, and ZW25 in combination with tislelizumab and chemotherapy in patients with HER2-positive gastric/GEJ adenocarcinoma as measured by objective response rate (ORR)

Secondary:

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

[redacted]

Study Endpoints:

Primary:

- Adverse events (AEs) and serious adverse events (SAEs) as characterized by type, frequency, severity (as graded by National Cancer Institute-Common Terminology Criteria for Adverse

Events [NCI-CTCAE] Version 5.0), timing, seriousness, and relationship to study therapy, discontinuation of investigational product(s) due to toxicity, and changes from baseline in laboratory, electrocardiograms (ECG), echocardiogram or multiple gated acquisition scan (MUGA) and vital signs as needed

- Objective response rate assessed by investigator per Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Secondary:

- Duration of response by investigator per RECIST Version 1.1
- Time to response by investigator per RECIST Version 1.1
- Progression-free survival by investigator per RECIST Version 1.1
- Disease control rate by investigator per RECIST Version 1.1
- Overall survival
- ZW25 PK and immunogenicity:
  - Serum concentrations of ZW25 as a function of time
  - PK parameters for single (first) dose and multiple doses if data permit
  - Frequency, duration and time of onset of anti-ZW25 antibodies and neutralizing antibodies
- AEs and SAEs during the long-term extension period

[redacted]

Study Design

This is an open-label, multicenter, Phase 1b/2 study to investigate safety, tolerability, PK and preliminary antitumor activity of ZW25 in combination with chemotherapy with or without tislelizumab in patients with histologically or cytologically confirmed unresectable locally advanced or metastatic HER2-positive breast cancer or gastric/GEJ adenocarcinoma.

After providing written informed consent, patient will complete all screening assessments. Patients must have documented HER2-positive disease by overexpression and/or gene amplification as determined by investigator or central laboratory, using the archival tumor tissue or fresh biopsy sample. The most recently collected tissues are required if applicable. Archival tumor tissue must be provided for retrospective confirmation of HER2 status and/or other biomarker analyses. A fresh biopsy of an accessible tumor lesion is required at baseline in the absence of archival tumor tissue, unless previously discussed with sponsor's medical monitor. After being confirmed as eligible, approximately 80 patients will be enrolled into the 2 cohorts in total. Patients enrolled under the original protocol and had been assigned to Cohort 1a or 2a will continuously be treated with ZW25 30 mg/kg. Patients enrolled under Protocol Amendment 1.0 or later will be assigned to Cohort 1b or 2b and receive a flat dosing of ZW25.

- **Cohort 1** (approximately 50 patients)**:** patients who have unresectable, locally advanced, recurrent or metastatic HER2-positive (HER2 immunohistochemistry [IHC] 3+ or in situ

hybridization positive) breast cancer and have not received previous systemic chemotherapy or biologic therapy (including approved or investigational tyrosine kinase/HER inhibitors, checkpoint inhibitors or vaccines) for their advanced or metastatic disease are eligible, and will be treated with ZW25 followed by docetaxel as the first-line therapy. On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity, or another criterion for treatment discontinuation is met. After Cycle 6, continuation of docetaxel treatment is at the discretion of the investigator. ZW25 will be administered until disease progression, intolerable toxicity, or another criterion for treatment discontinuation is met. Detailed dosing schedule and administration is described below:

- **Cohort 1a:** ZW25 30 mg/kg intravenously (IV), docetaxel 75 mg/m^2 IV once every 3 weeks (Q3W)
- **Cohort 1b:** ZW25 1800 mg IV, docetaxel 75 mg/m^2 IV Q3W

- **Cohort 2** (approximately 30 patients)**:** patients who have unresectable, locally advanced, recurrent or metastatic HER2-positive (HER2 IHC 3+ or HER2 IHC 2+ together with in situ hybridization positive) gastric/GEJ adenocarcinoma and who have not received previous systemic therapy for locally advanced unresectable or metastatic disease are eligible, and will be treated with ZW25, tislelizumab and chemotherapy at the beginning of each 21-day cycle (once every 3 weeks) as the first-line therapy. The chemotherapy regimen will be CAPOX (1000 mg/m^2 capecitabine and 130 mg/m^2 oxaliplatin) and will be administered up to 6 cycles. On or prior to Cycle 6, capecitabine or oxaliplatin should only be discontinued for progressive disease or unacceptable toxicity, or another criterion for treatment discontinuation is met. After Cycle 6, oxaliplatin will be discontinued and continuation of capecitabine as maintenance treatment is at the discretion of the investigator. ZW25 and tislelizumab will be administered until disease progression, intolerable toxicity, or another criterion for treatment discontinuation is met. Detailed dosing schedule and administration of ZW25 and tislelizumab is described below:
  - **Cohort 2a:** ZW25 30 mg/kg IV, tislelizumab 200 mg IV, CAPOX (1000 mg/m^2 capecitabine and 130 mg/m^2 oxaliplatin) Q3W
  - **Cohort 2b:** ZW25 1800 mg (subject's body weight < 70 kg) or 2400 mg (subject's body weight ≥ 70 kg) IV, tislelizumab 200 mg IV, CAPOX (1000 mg/m^2 capecitabine and 130 mg/m^2 oxaliplatin) Q3W

  For patients treated with tislelizumab in Cohort 2, treatment beyond initial RECIST Version 1.1 defined disease progression is permitted if the patient has evidence of "pseudoprogression" and after discussion with sponsor and re-consent of patient.

  For Cohort 2, a safety lead-in phase is designed, during which 6 patients will be enrolled. After the first 6 patients have completed at least 1 cycle (21 days) of treatment, safety data will be reviewed by Safety Monitoring Committee to ensure the tolerability before the whole cohort is fully open to enrollment. If there are no new significant or severe safety signals detected, the enrollment of dose expansion will be expanded up to approximately 30 patients in total for Cohort 2.

Study Assessments:

Study Period Through the Data Cutoff Date of the Final Analysis:

Patients will be monitored for safety, tolerability, PK, and preliminary antitumor activity within this period.

Safety will be assessed within this period by monitoring AEs/SAEs, and laboratory results. Vital signs, physical examinations, Eastern Cooperative Oncology Group (ECOG) performance status change, ECG results, echocardiogram/MUGA, and other examinations will also be used for safety assessment.

Preliminary anticancer activity will be evaluated by the investigator using RECIST Version 1.1. Radiological assessment of tumor response status will be performed every 6 weeks (± 7 days) from Cycle 1 Day 1 for the first 36 weeks and every 12 weeks (± 7 days) thereafter until disease progression, withdrawal of consent, death, or start of a new anticancer therapy, whichever occurs first.

PK and immunogenicity analysis will be performed for ZW25 and tislelizumab. Biomarker analysis will also be performed.

Long-term Extension Period:

After the data cutoff (DCO) date of the final analysis (FA), the patients who remain on treatment will continue their treatments according to their previous schedule and will be monitored for safety, tolerability, and antitumor activity within this period.

Safety will be assessed within this period by monitoring AEs/SAEs and laboratory results. Vital signs, physical examinations, ECOG performance status change, ECG results, echocardiogram/MUGA, and other examinations will also be used for safety assessment.

Anticancer activity will also be evaluated by the investigator using RECIST Version 1.1. Radiological assessment of tumor response status will be performed every 12 weeks (± 7 days) according to their previous schedule until disease progression, withdrawal of consent, death, or end of treatment, whichever occurs first.

The samples for the PK and immunogenicity analysis of ZW25 and tislelizumab, as well as the samples for biomarker analysis, will not be required within this period.

Duration of Patient Participation:

Screening Period: Within 28 days prior to the first dose of study drug.

Treatment Period: Starts with the first dose of study drug administration and ends when the patient is discontinued for study treatment when they are no longer considered to be achieving clinical benefit, due to unacceptable toxicity, death, or withdrawal of consent.

End of Treatment/Safety Follow-up: Patients who discontinue treatment for any reason will be asked to return to the clinic for the End of Treatment (EOT)/Safety Follow-up Visit (to occur approximately 30 days [± 7 days] after the last dose of study drug(s), or before the initiation of a new anticancer treatment, whichever occurs first). In addition, safety follow-up also includes telephone contacts with patients treated with tislelizumab in Cohort 2, which should be conducted to assess immune-mediated AEs and concomitant medications (if appropriate, ie, associated with an immune-mediated AE or is a new anticancer therapy) at 60 (±14 days) and 90 days (±14 days) after the last dose of study drug(s) regardless of whether or not the patient starts a new anticancer therapy.

Survival Follow-up: Patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (±14 days) after the EOT/Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor through the DCO date of the FA.

Long-term Extension Period: After the DCO date of the FA, Protocol Amendment 3.0 will be implemented and only the patients who remain on treatment or are in the safety follow-up period will enter the long-term extension period. Patients will be continually monitored for long-term safety and antitumor activity, while the samples for the PK and immunogenicity analysis of ZW25 and tislelizumab, as well as biomarker analysis, will not be required within this period. Within the long-term extension period, long-term survival follow-up and further anticancer therapy information will not be required.

Study Population:

Patients with unresectable, locally advanced, recurrent or metastatic HER2-positive breast cancer or gastric/GEJ adenocarcinoma.

Key Eligibility Criteria:

Adult patients (≥ 18 years of age or the legal age of consent in the jurisdiction in which the study is taking place) on the day of signing the informed consent form (ICF) with histologically or cytologically confirmed unresectable, locally advanced, recurrent or metastatic HER2-positive breast cancer (Cohort 1) or gastric/GEJ adenocarcinoma (Cohort 2) who have not received previous systemic anticancer therapy for locally advanced unresectable or metastatic disease. All patients are also required to have ≥ 1 measurable lesion per RECIST Version 1.1, an ECOG Performance Status score of ≤ 1, adequate organ function and left ventricular ejection fraction ≥ 50% at baseline as determined by either echocardiogram or MUGA.

Investigational Product, Dose, and Mode of Administration:

ZW25 will be administered at a dose of 30 mg/kg IV (Cohorts 1a and 2a) or 1800 mg IV (Cohort 1b) or 1800mg/2400mg (Cohort 2b) on Day 1 of every 21-day cycle.

Tislelizumab will be administered at a dose of 200 mg IV at the beginning (Day 2 for the first 2 cycles and Day 1 for Cycle 3 onwards) of every 21-day cycle.

Reference Therapy, Dose, and Mode of Administration:

Not applicable

Statistical Methods:

Analysis Sets:

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

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

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

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

Safety Analyses:

Descriptive statistical analyses will be performed for all patients in the Safety Analysis Set. Safety data will be presented by cohort.

Safety will be assessed by monitoring and recording of all AEs graded by NCI-CTCAE Version 5.0, and laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, ECGs findings and echocardiogram or MUGA will also be used in determining the safety profile. The incidence of treatment-emergent AEs (TEAEs) will be reported as the number (percentage) of patients with TEAEs by Medical Dictionary for Regulatory Activities system organ class and preferred term.

Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

Efficacy Analyses:

No formal hypotheses testing is planned for efficacy. Descriptive statistical analyses will be based on the Efficacy Evaluable Analysis Set and the Safety Analysis Set. Efficacy results will be presented by cohort.

Objective response rate

The ORR is the proportion of patients who had a best overall response of confirmed complete response (CR) or partial response (PR) assessed by investigator per RECIST Version 1.1. The 2-sided Clopper-Pearson 95% CIs for ORR will be calculated for each cohort. ORR will be estimated on the Efficacy Evaluable Analysis Set.

Duration of response

Duration of response is defined as the time from the first determination of an objective response by investigator per RECIST Version 1.1, until the first documentation of progression or death, whichever occurs first. Duration of response will be estimated using Kaplan-Meier method and will be estimated on the Efficacy Evaluable Analysis Set.

Time to response

Time to response (TTR) is defined as the time from the start date of study drug to the first determination of an objective response by investigator per RECIST Version 1.1. Only the subset of patients who achieved a CR or PR will be included in the TTR analysis. TTR will be summarized for descriptive purpose on the Efficacy Evaluable Analysis Set; the mean, SD, median, and range of TTR will be provided.

Progression-free survival

Progression-free survival is defined as the time from the start date of study drug to the date of the first objectively documented tumor progression, assessed by investigator per RECIST Version 1.1, or death, whichever occurs first. Kaplan-Meier method will be applied for analyses. Progression-free survival will be estimated on the Efficacy Evaluable Analysis Set.

Disease control rate

Disease control rate is defined as the proportion of patients with best overall response of CR, PR, and stable disease by investigator per RECIST Version 1.1. Disease control rate will be analyzed similarly to ORR, and DCR will be estimated on the Efficacy Evaluable Analysis Set.

Overall survival

Overall survival is defined as the time from the start date of study drug to the date of death due to any cause. Kaplan-Meier method will be applied for analyses. Overall survival will be estimated on the Safety Analysis Set.

Pharmacokinetic Analyses:

Serial PK samples from up to 28 patients are planned to characterize the PK profiles of ZW25 in the targeted patient population. Serum concentration-time data of each patient will be tabulated and graphically presented on linear semi-logarithmic scales. Pharmacokinetic parameters will be determined using a standard noncompartmental method. A listing of patients excluded from the analysis set and individual data points excluded from the analysis will be provided. The parameters will be summarized with descriptive statistics (N, arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation [CV] % associated to the geometric mean). PK parameters will include, but are not limited to, the following as allowed by data: C_{max} (ng/mL), t_{max} (hour), $t_{½}$ (hour), $AUC_{(0\text{-}t)}$ (ng·h/mL), CL (L/hr).

The ZW25 and tislelizumab PK concentration data collected sparsely at predose and postdose (end of infusion) will be tabulated and summarized by visit/cycle. Descriptive statistics will include means, standard deviations, medians, and ranges as appropriate.

Immunogenicity Analyses:

Samples to assess anti-ZW25 antibodies and anti-tislelizumab antibodies will be collected only in patients who receive study drug(s) and at sites that are able to adequately perform sampling, handling, and processing as outlined in the laboratory manual.

The ADA results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive ADAs and neutralizing ADAs will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allow.

[redacted]

Sample Size Consideration:

Approximately 50 patients will be enrolled in Cohort 1 and approximately 30 patients will be enrolled in Cohort 2.

For an event of 1% incidence rate, the chance of detecting any safety signal is about 26% to 39% in 30 to 50 patients. The probability of observing a safety event of interest goes up to 79% to 92% in 30 to 50 patients when the underlying rate is 5%. The current sample size is considered adequate for an initial safety evaluation for each combination.

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

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	antidrug antibody
ADC	antibody drug conjugate
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BGB-A317	tislelizumab
CR	complete response
CT	computed tomography
DCO	data cutoff
DCR	disease control rate
ECD	extracellular domain
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOT	End of Treatment (Visit)
FA	final analysis
FDG	fluorine-18 [F-18] fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GEA	gastroesophageal adenocarcinoma
GEJ	gastroesophageal junction
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
ICF	informed consent form
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IV	intravenous(ly)

Abbreviation	Definition
imAE	immune-mediated adverse event
IRB	Institutional Review Board
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MUGA	multiple gated acquisition scan
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death protein-1
PD-L1	programmed cell death protein ligand-1
PET	positron-emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
Q3W	once every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SMC	Safety Monitoring Committee
TEF	Treatment Eligibility Form
T-DM1	antibody drug conjugate ado-trastuzumab emtansine
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
ZW25	zanidatamab

1. INTRODUCTION

1.1. Metastatic Breast Cancer

1.1.1. Background Information on Metastatic Breast Cancer

Globally, breast cancer is the second most common invasive malignancy. Among females, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death. There were about 2,088,849 newly diagnosed female breast cancer cases in 2018, accounting for almost 1 in 4 cancer cases among women, and about 626,679 death cases worldwide (Bray et al 2018). In Asia, breast cancer is the most common cancer in women and is the second leading cause of cancer death after lung cancer (Kwong et al 2015). In 2012, a total of 639,824 new cases of breast cancer were recorded in Asian countries, and 228,926 deaths occurred due to breast cancer in Asia (Ghoncheh et al 2016).

Approximately one-third of women with primary breast cancer will develop metastatic disease, which remains incurable. About 50% of patients have disease progression within 1 year of treatment for advanced disease (Marty et al 2005; Andersson et al 2011) and the 5-year survival rate following metastatic diagnosis is approximately 15% (Jemal et al 2011; Ferlay et al 2013).

1.1.2. Current Anti-HER2 Treatment for Metastatic Breast Cancer

The human epidermal growth factor receptor 2 (HER2), also known as Neu, HER2/neu, and ErbB-2, has emerged as one of the most important targets for the treatment of breast cancer. HER2 is a transmembrane spanning receptor-like protein and is a member of the epidermal growth factor receptor (EGFR)/ErbB family that includes 4 structurally related HER receptors: HER1 (EGFR), HER2, HER3, and HER4. Expression of HER2, which may or may not involve HER2 overexpression or gene amplification, results in proliferative pathway activation and an increase in tumor growth (Alajati et al 2015).

HER-mediated tumorigenic signaling may involve homodimerization or heterodimerization. HER2 exists in a conformation that allows dimerization without ligand binding whereas HER1, HER3, and HER4 are activated by binding of epidermal growth factor ligands. Ligand binding changes the conformation of these other receptors to expose the dimerization extracellular domain (ECD) 2 and permit homo- or heterodimerization with EGFR/ErbB family members. HER2 is the preferred dimerization partner with other HER family members. Receptor dimerization leads to autophosphorylation of specific tyrosine residues and activation of intracellular signaling pathways, notably the mitogen-activated protein kinases and PI3K/Akt (phosphatidylinositol 3 kinase/protein kinase B) pathways that mediate cell proliferation and cell survival, respectively (Moasser 2007). HER2 may also crosstalk synergistically with other receptor tyrosine kinase cell growth pathways and thus effective blockade of HER2 may be therapeutically beneficial in inhibiting tumor growth.

Breast cancers with very high expression of HER2 on their cell surface are considered highly aggressive neoplasm characterized by HER2-mediated activation of oncogenic pathways (Harbeck and Gnant 2017; Vernieri et al 2019). HER2 expression is typically determined by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH), although some other methodologies are available. Per the American Society of Clinical Oncology

(ASCO)/College of American Pathologists guidelines (Wolff et al 2013), HER2 expression levels may be classified as 0, 1+, 2+ or 3+ by IHC depending upon the extent and pattern of staining or HER2 gene amplified as determined by FISH or other alternative in situ hybridization method. HER2-positive breast cancer is defined globally as HER2 IHC 3+ or in situ hybridization positive. The frequency of HER2-positive breast cancer ranges from about 10% to 30% of metastatic breast cancer (Vogel et al 2010; Giordano et al 2014; Varga and Noske 2015) Available data suggest that the incidence of HER2-positive breast cancers is similar for Chinese and US women; up to 25% of Asian patients could therefore potentially benefit from HER2-targeted treatment (Li et al 2011; Liu et al 2008; Tan et al 2010).

Before the introduction of HER2-targeted therapies, the prognosis of patients with HER2-positive metastatic breast cancer was especially poor as a result of fast tumor growth and lack of response to cytotoxic chemotherapy (Ross et al 2009). In recent years, the availability of effective anti-HER2 agents has dramatically improved clinical outcomes in all disease stages. The introduction of HER2-targeted therapies in neoadjuvant/adjuvant and metastatic treatment of HER2-overexpressing breast cancer has led to marked improvements in disease-free survival, progression-free survival (PFS), and overall survival (OS) (Schramm et al 2015).

There are currently multiple approved HER2-targeted therapies worldwide, including the antibodies trastuzumab, pertuzumab and margetuximab, the antibody drug conjugate ado-trastuzumab emtansine (T-DM1), fam-trastuzumab deruxtecan-nxki (DS-8201a), and the small molecule inhibitors lapatinib, neratinib, tucatinib, and pyrotinib (approved in China only). Trastuzumab binds to the ECD4 subdomain of HER2 while pertuzumab binds to the ECD2 dimerization domain to block HER2 mediated tumorigenesis. The combination of trastuzumab and pertuzumab has also been shown to increase degradation of HER2 and thereby turn off HER2 signaling (Bertelsen and Stang 2014). A drug conjugate of trastuzumab, T-DM1, acting by inhibiting tubulin and promoting tumor cell death, has been shown to improve both PFS and OS in second-line and third-line setting; T-DM1 has been approved in China as adjuvant therapy of HER2-positive early breast cancer in patients who had residual invasive disease after completion of neoadjuvant therapy in 2020 and as the second-line therapy for HER2-positive metastatic breast cancer most recently. Lapatinib is a dual tyrosine kinase inhibitor (TKI), which interrupts the HER2/neu and EGFR pathways. Neratinib is another TKI, which interacts with the catalytic domain of several EGFR family members (EGFR, HER2 and HER4) and blocks their downstream signaling pathways. In 2018, pyrotinib was approved as the second-line treatment in China for metastatic breast cancer by the National Medical Products Administration (NMPA). Pyrotinib is a small molecule irreversible inhibitor of receptor tyrosine kinase targeting EGFR, HER2, and HER4.

The addition of trastuzumab to chemotherapy increases response rates, PFS, and OS in patients with HER2-positive metastatic breast cancer, and the regimen of a taxane in combination with trastuzumab was historically considered standard-of-care first-line therapy (Slamon et al 2001; Andersson et al 2011). Subsequently, with preclinical studies demonstrating that blockade of both HER2 and HER3 could have synergistic antitumor effects, pertuzumab, with the mechanism of action by blocking the association of HER2 with other HER family members, was developed (Nahta et al 2004). In the randomized, double-blind Phase 3 CLEOPATRA trial, patients treated with docetaxel, trastuzumab, and pertuzumab had a median PFS duration of 18.5 months; in comparison, patients randomized to placebo, docetaxel, and trastuzumab, a previous

standard-of-care for first-line therapy, had a median PFS of 12.4 months. The hazard ratio (HR) was 0.62 (95% CI: 0.51 to 0.75; p < 0.001) (Baselga et al 2012). The median OS in placebo group was 40.8 months, compared with 56.5 months in the pertuzumab treatment group (Swain et al 2015). The safety profile was generally similar between the 2 groups, the rates of febrile neutropenia (13.8% versus 7.6%) and diarrhea of Grade 3 or above (7.9% versus 5.0%) were higher in the pertuzumab group than in the control group. Left ventricular systolic dysfunction occurred in 4.4% of the pertuzumab group and 8.3% of the placebo group. Based on the promising PFS improvement, pertuzumab was approved by United States Food and Drug Administration (FDA) as the first-line treatment of HER2-positive metastatic breast cancer in 2012 and approved by the NMPA in 2019 for the same indication. Of note, one limitation of CLEOPATRA study is that mainly due to the historical context, most patients included in the trial were trastuzumab naive. Among the 47 patients in the pertuzumab group and 41 patients in the placebo group who had previously been treated with trastuzumab, the median PFS for pertuzumab group was 16.9 months and for placebo group was 10.4 months with the HR of 0.62; and the HR for OS was 0.80. The efficacy of pertuzumab plus trastuzumab in patients who have been treated with trastuzumab in (neo)adjuvant setting is to be further demonstrated.

For patients who subsequently develops disease progression on the first-line anti-HER2 treatment, T-DM1 has been shown to significantly improve both PFS and OS compared with lapatinib plus capecitabine as a second-line treatment (Verma et al 2012; Diéras et al 2017) and as a later line in patients with advanced HER2-positive breast cancer previously treated with trastuzumab (Krop et al 2014; Krop et al 2017). Based on those results, T-DM1 was previously the standard second-line therapy for advanced HER2-positive breast cancer, but it is now currently recommended by National Comprehensive Cancer Network 2023 version 3.0 as one regimen of third-line therapies after the emergence of new standard second-line therapy.

In December 2019, ENHERTU® (fam-trastuzumab deruxtecan-nxki), a HER2 directed antibody drug conjugate (ADC), was approved by FDA for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens in the metastatic setting. The approval is based on the results of the single-arm, pivotal phase 2 DESTINY-Breast01 trial of trastuzumab deruxtecan (5.4 mg/kg) monotherapy in 184 female patients with HER2-positive metastatic breast cancer. Trial results showed a confirmed objective response rate (ORR) of 60.3% (n=111; 95% confidence interval [CI]: 52.9 to 67.4). Median progression free survival is 16.4 months (95% CI: 12.7 to Not Estimable) (Modi et al 2020). In May 2022, ENHERTU was also approved by the FDA for adult patients with HER2-positive unresectable or metastatic breast cancer who have received an anti-HER2-based regimen either in the metastatic setting or in the (neo)adjuvant setting, and have developed disease recurrence at ≤ 6 months. This approval was based on the Phase 3 DESTINY-Breast03 study, which compared the efficacy and safety of trastuzumab deruxtecan with those of trastuzumab emtansine in patients with HER2-positive metastatic breast cancer who were previously treated with trastuzumab and a taxane. Among 524 randomly assigned patients, the percentage of those who were alive without disease progression at 12 months was 75.8% (95% CI, 69.8 to 80.7) with trastuzumab deruxtecan and 34.1% (95% CI, 27.7 to 40.5) with trastuzumab emtansine (HR for progression or death from any cause, 0.28; 95% CI, 0.22 to 0.37; P<0.001). (Cortés et al 2022). ENHERTU is currently the standard second-line therapy for advanced HER2-positive breast cancer. Recently in February 2023, ENHERTU was approved by NMPA for the same indication.

1.1.3. Unmet Medical Needs for First-Line HER2-positive Metastatic Breast Cancer

Despite all these advances, most patients presenting with HER2-positive metastatic breast cancer will ultimately become resistant to these agents and die of their disease. HER2-positive metastatic breast cancer remains an aggressive disease, and the efficacy of individual anti-HER2 therapies is short-lived, especially for patients recurring after previous trastuzumab-containing (neo)adjuvant treatment, with median PFS of about 1 year and less than 1 year in the first- and second-line settings, respectively (Ponde et al 2018). In recent years, trastuzumab is more and more widely used in (neo)adjuvant setting for HER2-positive early stage breast cancer. For those who have recurrent and metastatic disease after prior exposure to perioperative trastuzumab, the first-line treatment option is still trastuzumab based regimen, whether the regimen includes pertuzumab depends on its availability in different countries/regions. However, first-line trastuzumab-containing treatment regimens had been reported to be less effective in patients with the failure of adjuvant trastuzumab compared with trastuzumab-naive patients (Láng et al 2014; Xu et al 2016; Rier et al 2017). Therefore, there remain large unmet medical needs for more effective treatment and new treatment options with tolerable toxicity for patients with HER2-positive breast cancer.

1.2. Metastatic Gastric/Gastroesophageal Junction Adenocarcinoma

1.2.1. Background Information on Metastatic Gastric/Gastroesophageal Junction Adenocarcinoma

Gastric cancer, including gastroesophageal junction (GEJ) cancer, represents a challenging global health problem. In worldwide, gastric cancer alone contributed about 1.3 million cases with 800,000 deaths in 2015. It is the fifth most common cancer worldwide and the second leading cause of cancer death together with colorectal and liver cancer (Global Burden of Disease Cancer Collaboration 2017). Notably, gastric/GEJ adenocarcinoma is considered approximately 20 times more prevalent in Eastern Asia than in North America (WHO 2018a; WHO 2018b).

The high mortality rate indicates that most patients diagnosed with gastric/GEJ adenocarcinoma are primarily diagnosed in stage IV or eventually recur with metastases (Obermannova et al 2017). Patients with newly diagnosed inoperable locally advanced or metastatic disease generally receive chemotherapy regimens containing a platinum and a fluoropyrimidine (Smyth et al 2016; NCCN 2019). Triplet regimens may provide additional clinical benefit (Okines et al 2009), however, because of their added toxicities, they have not been uniformly adopted and are recommended only for medically fit patients with good performance status and access to frequent toxicity evaluations. Response rates for first-line chemotherapy regimens are around 30% to 50% with median PFS ranging from 5 to 7 months. Median OS is less than 12 months, and less than 10% of patients are still alive after 5 years (Cunningham et al 2008; Kang et al 2009; Van Cutsem et al 2006; Wagner et al 2006; Fock et al 2008).

1.2.2. Current Anti-HER2 Treatment for Metastatic Gastric/Gastroesophageal Junction Adenocarcinoma

The biology of HER2-positive gastric/GEJ adenocarcinoma may be not completely the same with breast cancer (Ruschoff et al 2012). HER2 overexpression or "positivity" in gastric/GEJ adenocarcinoma is currently defined as IHC 3+, or IHC 2+ and in situ hybridization positive (ISH+) with the guidelines established by the ToGA trial (Bang et al 2010). Considering the heterogeneous nature of HER2 overexpression/amplification in gastric cancer, and gastric tumor cells may only show HER2 staining at the basolateral or lateral membrane regions, complete membranous staining is not a prerequisite for IHC 2+ or IHC 3+ scores in gastric cancer as it is for breast cancer (Bang et al 2012). HER2-positivity is seen in about 21% to 32% gastric/GEJ cancers (VanCutsem 2015), and it is associated with GEJ tumors more than with adenocarcinoma in gastric body; 20% of intestinal-type cancers have HER2 overexpression/amplification compared with 5% of diffuse-type cancers (Albarello et al 2011). The impact of HER2 expression on prognosis of gastric cancer is controversial, and not as straightforward as it is for breast cancer (Boku N 2014).

Given the success in breast cancer in both metastatic and adjuvant settings, evaluation of trastuzumab in HER2-positive gastric cancer was inevitable. The randomized phase 3 ToGA trial evaluated trastuzumab in combination with standard platinum/fluoropyrimidine combination versus platinum/fluoropyrimdine chemotherapy alone in treatment-naive HER2-positive metastatic gastric/GEJ adenocarcinoma. Patients were considered eligible for enrollment if they had either HER2 overexpression by IHC or gene amplification by FISH. The addition of trastuzumab to chemotherapy improved median OS (13.8 months with the combination versus 11.1 months for chemotherapy alone, HR = 0.74; p = 0.0046). An exploratory analysis limited to patients with classic higher HER2 positivity (IHC 3+ or IHC 2+ and FISH+) demonstrated an even greater survival advantage (16.0 months versus 11.8 months; HR = 0.65) (Bang et al 2010). Trastuzumab plus chemotherapy with capecitabine or fluorouracil plus a platinum-based drug, such as cisplatin, is now the first-line standard-of-care treatment in patients with HER2-positive metastatic gastric/GEJ adenocarcinoma. In May 2021, the US FDA granted accelerated approval to the experimental regimen tested in the KEYNOTE-811 study based on the results of a prespecified interim analysis of ORR as assessed by the blinded independent central review (BICR). The ORR was 74% (95% CI, 66 to 82) in the Pembrolizumab Arm and 52% (95% CI, 43 to 61) in the Placebo Arm. The median duration of response was 10.6 months in the Pembrolizumab Arm compared to 9.5 months in the Placebo Arm (Keytruda [pembrolizumab] 2021).

Exploration of other anti-HER2 treatment in gastric/GEJ adenocarcinoma, however, has not being able to repeat the success as in breast cancer. The double-blind phase 3 JACOB trial (BO25114) was designed to assess whether the addition of pertuzumab to cisplatin, 5-Fluorouracil and trastuzumab may further improve the survival of HER2-positive gastric/GEJ adenocarcinoma patients with an acceptable safety profile. A total of 780 eligible patients randomly assigned to receive either pertuzumab plus trastuzumab and chemotherapy (pertuzumab group, n = 388) or placebo plus trastuzumab and chemotherapy. Unfortunately, this trial narrowly missed the primary endpoint of OS, but a treatment effect trend with pertuzumab + trastuzumab + chemotherapy was observed (median OS 17.5 months [95% CI: 16.2 to 19.3] in the pertuzumab group and 14.2 months [95% CI: 12.9 to 15.5] in the control group; HR = 0.84

[95% CI: 0.71 to 1.00]; p = 0.057). Although there was a significant increase in median PFS (8.5 months versus 7.0 months, HR = 0.73, 95% CI: 0.62 to 0.86) as the key secondary endpoint, the statistical significance could not be concluded due to hierarchical testing (Tabernero et al 2018) As the JACOB trial did not meet its primary endpoint, pertuzumab is not recommended for metastatic gastric/GEJ adenocarcinoma as it had for breast cancer.

The phase 2/3 GATSBY trial was designed to assess the efficacy of trastuzumab emtansine in the advanced HER2-positive gastric/GEJ adenocarcinoma patients who progressed after the first-line treatment. The patients were randomized into three arms: T-DM1 3.6 mg/kg once every 3 weeks, T-DM1 2.4 mg/kg every week, or physician's choice of a taxane. The results did not show the OS benefit of trastuzumab emtansine 2.4 mg/kg every week over taxanes (7.9 months versus 8.6 months), failing to be approved as second-line regimen in HER2-positive gastric/GEJ adenocarcinoma (Thuss-Patience et al 2017).

Lapatinib was tested in the first-line as well as second-line setting in 2 pivotal studies in gastric cancer respectively. However, both studies (TRiO-013 LOGiC trial and the TyTAN trial) did not demonstrate a significant improved efficacy with lapatinib treatment in OS as the primary endpoints (Hecht et al 2016; Satoh et al 2014).

With several failure attempts in clinical trials, there has been no recommended anti-HER2 agent in second-line setting, hence the treatment options for gastric/GEJ adenocarcinoma patients who subsequently progress the first-line treatment are following the same treatment options regardless of HER2 status. Second-line treatment usually consists of single-agent chemotherapy, including paclitaxel, docetaxel, or irinotecan, showing a modest survival benefit in gastric/GEJ adenocarcinoma, with median OS averaging approximately 8 to 9 months (Ghosn et al 2016; Takahari 2017; Ter Veer et al 2016). Other available treatment options include ramucirumab as monotherapy, or in combination with paclitaxel, and apatinib as monotherapy. Ramucirumab, a monoclonal antibody targeting vascular endothelial growth factor 2, as a single agent or in combination with paclitaxel since it has shown a survival benefit comparable with chemotherapy (Fuchs et al 2014; Wilke et al 2014). When used in combination with paclitaxel versus paclitaxel alone, median OS was 9.6 months versus 7.4 months; and median PFS was 4.4 months versus 2.9 months, respectively (Wilke et al 2014).

For patients who had progressed after 2 or more lines of systemic treatments, apatinib, a small-molecule TKI that binds to and inhibits vascular endothelial growth factor receptor 2 (VEGFR-2), as monotherapy, is approved for third-line treatment in China, with moderately improved survival benefit (Li et al 2016). More recently, immunotherapy with anti-programmed cell death protein-1 (PD-1) antibodies pembrolizumab and nivolumab has resulted in durable remissions for a subset of patients (Muro et al 2016; Le et al 2016). Pembrolizumab has been approved by FDA for the treatment of patients with programmed cell death protein ligand-1 (PD-L1)-positive recurrent or advanced gastric/GEJ adenocarcinoma who have received 2 or more lines of chemotherapy (Keytruda [pembrolizumab] 2021). Among the 259 patients enrolled in Cohort 1 of KEYNOTE-059 study, ORR was 11.6% with a complete response (CR) rate of 2.3% (Fuchs et al 2018). ATTRACTION-2 is a randomized, double-blind, Phase 3 study conducted in Japan, South Korea, and Taiwan to evaluate safety and efficacy of nivolumab in patients with advanced gastric/GEJ adenocarcinoma refractory to, or intolerant of, at least 2 previous chemotherapy regimens (Kang et al 2017). The study met its primary endpoint: median OS was 5.26 months (95% CI: 4.60 to 6.37) in the nivolumab group, which is statistically longer

than 4.14 months (95% CI: 3.42 to 4.86) in the placebo group. Based on the positive readout, nivolumab was approved for third-line treatment of advanced gastric cancer in Japan, China and other Asian countries/regions.

Most recently, the ADC trastuzumab deruxtecan was shown to improve responses and increase OS (median OS 12.5 vs. 8.4 months) compared to chemotherapy in subjects with gastroesophageal adenocarcinomas (GEAs) arising from the stomach and/or GEJ who had previously received treatment with 2 prior regimens, including a trastuzumab-based regimen (Shitara et al 2020). Based on this data, trastuzumab deruxtecan (ENHERTU®) was approved by the Pharmaceuticals and Medical Devices Agency for third-line HER2-positive G/GEJ cancer in September 2020 and approved by the FDA for G/GEJ cancer in January 2021. Breakthrough Therapy Designation and Orphan Drug Designation was granted to this agent in May 2020. Furthermore, another ADC disitamab vedotin (RC48) was approved in China by the NMPA in June 2021 as the third-line therapy for HER2-overexpressing (IHC 2+ or 3+) G/GEJ cancer. In the Phase 2 single-arm study, RC48 demonstrated a clinical response and survival benefit (median overall survival of 7.6 months) in the heavily treated patients with HER2-overexpressing G/GEJ cancers (Peng et al 2020).

1.2.3. Unmet Medical Needs for First-Line HER2-positive Metastatic Gastric/Gastroesophageal Junction Adenocarcinoma

Patients with HER2-positivity constitute about 20-25% of all gastric/GEJ adenocarcinoma patients, which is of high incidence and mortality, especially in Asian countries. The treatment outcome remains poor and the treatment options are quite limited for HER2-positive gastric/GEJ adenocarcinoma patients. Trastuzumab is only recommended anti-HER2 agent in gastric/GEJ adenocarcinoma, with a moderate survival improvement as demonstrated in ToGA trial (13.8 months versus 11.1 months). Multiple failed trials in HER2-positive gastric cancer indicate the need to further explore the disease biological behavior and develop more effective therapies. It exists huge unmet medical needs to explore new treatment options for HER2-positive metastatic gastric/GEJ adenocarcinoma patients.

1.3. Background Information on Zanidatamab

Zanidatamab (also known as ZW25) is a novel humanized, bispecific immunoglobulin G antibody isotype 1 (IgG1)-like antibody engineered using the Azymetric™ platform. ZW25 binds to both ECD4 and ECD2 domains of HER2, the same domains bound by trastuzumab and pertuzumab, respectively. The unique binding geometry of ZW25 drives multiple mechanisms of action, including increased tumor cell binding, receptor clustering, and enhanced internalization relative to trastuzumab, as well as inhibition of growth factor dependent and independent cell growth and potent antibody dependent cytotoxicity.

1.3.1. Pharmacology

In preclinical studies in tumor cell lines and xenograft tumor models, ZW25 demonstrated antitumor activity that was superior to trastuzumab across a range of tumor types, including gastric cancer. In the HER2 IHC 3+ NCI-N87 gastric epithelial carcinoma cell line (Yamashita-Kashima et al 2014), ZW25 inhibited cell growth and bound with a maximal binding (B_{max}) 1.5 fold higher than trastuzumab. ZW25 also demonstrated greater inhibition of epidermal

growth factor induced proliferation compared to trastuzumab. In a patient-derived HER2 IHC 3+ gastric cancer xenograft nude-mouse model (GXA 3054), ZW25 significantly inhibited the growth rate and debulked established tumors compared to either human IgG control or trastuzumab. Based on these results, ZW25 was granted Orphan Drug Designation from the FDA as a potential treatment for patients with HER2-expressing gastric carcinomas.

Please refer to the ZW25 Investigator's Brochure for additional details regarding nonclinical studies of ZW25.

1.3.2. Toxicology

The toxicity and safety profile of ZW25 was characterized in single-dose toxicology studies and a 13-week, Good Laboratory Practice (GLP) repeat-dose toxicology study in cynomolgus monkeys.

In the GLP repeat-dose cynomolgus monkey study, ZW25 was well tolerated with no adverse effects observed at doses up through 150 mg/kg when administered as weekly intravenous (IV) infusions for up through 13 weeks. The non-adverse effects associated with the administration of ZW25 at all dose levels included a non-dose dependent increase in the incidence of watery/soft feces. In some animals, this finding correlated with a mild increase in urea nitrogen concentration at all dose levels, which may have been secondary to mild subclinical dehydration associated with watery/soft feces. Based on the lack of adverse effects observed in the GLP study, the No Observed Adverse Effect Level (NOAEL) of ZW25 in the 13-week monkey toxicity study was considered to be 150 mg/kg.

Overall, no apparent toxicity was noted in monkey toxicity studies. The toxicokinetic profile was well characterized and demonstrated confirmed systemic exposure in all ZW25-treated animals. There was also no evidence of immunotoxicity.

Please refer to the ZW25 Investigator's Brochure for more detailed information on the toxicology of ZW25.

1.3.3. Clinical Pharmacology and Prior Clinical Experience

A summary of ongoing clinical studies with zanidatamab as of 28 July 2022 is presented in Table 1. Please refer to the ZW25 Investigator's Brochure for more detailed information on the safety and efficacy of zanidatamab when given as monotherapy or in combination with chemotherapy.

Table 1: Summary of Ongoing Clinical Studies in the Zanidatamab Clinical Development Program

Study No. Phase	Study Objectives	Trial Design	Zanidatamab: Dose, Regimen, Route of Administration	Study Population	Planned Enrollment/ Actual [a]	Region	Study Status/ First Subject First Dose
ZWI-ZW25-101 Phase 1	Safety, tolerability, PK, ZW25 immunogenicity, antitumor activity Primary endpoint: identify MTD, OBD, or RD characterize the safety and tolerability of zanidatamab as monotherapy and in combination with selected antineoplastic agents	Open-label, 3-part trial **Part 1:** monotherapy 3+3 dose escalation and DLT evaluation **Part 2:** monotherapy dose expansion cohorts at MTD, OBD, or RD **Part 3:** combination therapy dose expansion cohorts of subjects with breast cancer or GEA treated at MTD, OBD, or RD plus selected antineoplastic agents (paclitaxel; capecitabine; vinorelbine; capecitabine plus tucatinib; tucatinib)	**Part 1** (monotherapy): • 5, 10, and 15 mg/kg IV QW • 20, 25, and 30 mg/kg IV Q2W • 30 mg/kg IV Q3W **Part 2** (monotherapy): • 10 mg/kg IV QW or 20 mg/kg IV Q2W, the RDs identified in Part 1 **Part 3** (in combination therapy): • 10 mg/kg IV QW, 20 mg/kg IV Q2W, or 30 mg/kg IV Q3W – the RDs identified in Part 1	Locally advanced (unresectable) and/or metastatic HER2-expressing cancer that has progressed after receipt of all therapies known to confer clinical benefit	Monotherapy (Part 1 and Part 2): 272/192 Combination Therapy (Part 3): 146/87	US, Canada, S Korea	Ongoing/ September 2016
ZWI-ZW25-102 Phase 1	Safety, tolerability, PK, ZW25 immunogenicity, antitumor activity Primary endpoint: characterize the safety and tolerability of zanidatamab monotherapy	Open-label, 2-part trial **Part A:** dose escalation by the mTPI method to identify the HSD; and evaluate flat dosing **Part B:** dose expansion to ensure at least 6 PK-evaluable GEA subjects and 6 PK-evaluable non-GEA subjects are treated at the 2 highest weight-based doses determined to be safe	Monotherapy. Weight-based dose: • 20 mg/kg IV Q2W • 30 mg/kg IV Q3W • 15 mg/kg IV Q2W (as step-down dose level, if needed) Flat dose by subject weight: < 70 kg: 1,800 mg IV Q3W, or ≥ 70 kg: 2,400 mg IV Q3W	Japanese subjects with locally advanced (unresectable) and/or metastatic HER2-expressing cancer that has progressed after receipt of all therapies known to confer clinical benefit	48/7	Japan	Ongoing/ August 2021

Study No. Phase	Study Objectives	Trial Design	Zanidatamab: Dose, Regimen, Route of Administration	Study Population	Planned Enrollment/ Actual [a]	Region	Study Status/ First Subject First Dose
ZWI-ZW25-201 Phase 2	**Part 1:** Safety, tolerability, PK, ZW25 immunogenicity **Part 2:** Antitumor activity Primary endpoint: ORR	Open-label, first-line, 2-part, global, combination therapy trial **Part 1:** DLT evaluation and RD confirmation in combination with antineoplastic agents (CAPOX, FP, or mFOLFOX6 for GEA; mFOLFOX6 [with and without bevacizumab] for CRC; CisGem for BTC) **Part 2:** Further evaluation of each combination therapy for which an RD of ZW25 has been confirmed in Part 1	In combination therapy. **Part 1:** Q3W regimen: • 30 mg/kg IV Q3W • < 70 kg: 1,800 mg IV Q3W, or ≥ 70 kg: 2,400 mg IV Q3W Q2W regimen: • 20 mg/kg IV Q2W • < 70 kg: 1,200 mg IV Q2W, or ≥ 70 kg: 1,600 mg IV Q2W **Part 2:** RDs of ZW25 as confirmed in Part 1 for each of the combination therapy regimens.	Unresectable, locally advanced, recurrent or metastatic HER2-expressing GEA, BTC, or CRC	362/56	US, Canada, S Korea, Chile	Ongoing/ August 2019
ZWI-ZW25-202 Phase 2a	**Part 1:** Safety, tolerability, PK, ZW25 immunogenicity **Part 2:** Antitumor activity Primary endpoint: PFS6	Open-label, 2-part, single-arm, combination therapy trial **Part 1:** DLT evaluation and RD confirmation of each of ZW25, palbociclib, and fulvestrant when administered in combination **Part 2:** PFS6	In combination therapy. **Part 1:** • 20 mg/kg IV Q2W **Part 2:** RD of 20 mg/kg IV Q2W as confirmed in Part 1	Locally advanced (unresectable) and/or metastatic HER2-positive, HR positive breast cancer	86/44	US, Canada, Spain	Ongoing/ June 2020
ZWI-ZW25-203 Phase 2b	Antitumor activity, safety, PK, ZW25 immunogenicity Primary endpoint: Confirmed ORR per RECIST v1.1 by ICR	Pivotal, open-label, single-arm, 2-cohort, global, monotherapy trial	Monotherapy. • 20 mg/kg IV Q2W	HER2 gene-amplified, inoperable and advanced or metastatic BTC, including ICC, ECC, and GBC **Cohort 1:** HER2 expression of IHC 2+ or 3+ and ISH+ **Cohort 2:** HER2 expression of IHC 0 or 1+ and ISH+	100/87	US, Canada, UK, EU, China, S Korea, Chile	Ongoing/ October 2020

Study No. Phase	Study Objectives	Trial Design	Zanidatamab: Dose, Regimen, Route of Administration	Study Population	Planned Enrollment/ Actual [a]	Region	Study Status/ First Subject First Dose
ZWI-ZW25-204 Phase 1b/2	**Part 1:** Safety, tolerability **Part 2:** Antitumor activity, PK, immunogenicity Primary endpoint: confirmed ORR per RECIST v1.1	Open-label, 2-part, combination therapy trial **Part 1:** DLT evaluation and RD confirmation of each of ZW25 and ALX148 when administered in combination **Part 2:** ORR by RECIST v1.1	In combination therapy. **Part 1:** • < 70 kg: 1,200 mg IV Q2W, or ≥ 70 kg: 1,600 mg IV Q2W **Part 2:** RD of ZW25 and ALX148 as confirmed in Part 1	Advanced HER2-expressing cancer **Cohort 1:** HER2-positive breast cancer **Cohort 2:** HER2-low expressing breast cancer **Cohort 3:** HER2-overexpressing non-breast cancers	93/11	US	Ongoing/ September 2021
ZWI-ZW25-301 Phase 3	Efficacy, safety, PK, ZW25 immunogenicity, HRQoL Dual primary endpoint: PFS per RECIST v1.1 assessed by BICR, and OS	Randomized, open-label, 3-arm, active-comparator, multicenter study of zanidatamab in combination with chemotherapy with or without tislelizumab	In combination therapy: • < 70 kg: 1,800 mg IV Q3W, or ≥ 70 kg: 2,400 mg IV Q3W (flat dose by subject weight)	HER2-positive unresectable locally advanced or metastatic GEA	714/84	Global	Ongoing/ December 2021
BGB-A317-ZW25-101[b] Phase 1b/2	Safety, tolerability, preliminary antitumor activity, PK Primary endpoint: safety and tolerability, confirmed ORR per RECIST v1.1	Open-label, multicenter study of zanidatamab in combination with standard first-line chemotherapy with (Cohort 2) or without (Cohort 1) tislelizumab	In combination therapy. Cohorts 1a and 2a: • 30 mg/kg IV Q3W Cohort 1b: • 1,800 mg IV (flat dose) Cohort 2b: • < 70 kg: 1,800 mg IV Q3W, or ≥ 70 kg: 2,400 mg IV Q3W (flat dose by subject weight)	**Cohort 1:** Locally advanced [unresectable] and/or recurrent or metastatic HER2-positive (IHC 3+ or ISH +) breast cancer **Cohort 2:** Unresectable, locally advanced, recurrent or metastatic HER2-positive (IHC 3+ or IHC 2+ and ISH positive) gastric/GEJ adenocarcinoma	80/71	China mainland S Korea, Taiwan	Ongoing/ March 2020

Study No. Phase	Study Objectives	Trial Design	Zanidatamab: Dose, Regimen, Route of Administration	Study Population	Planned Enrollment/ Actual[a]	Region	Study Status/ First Subject First Dose
ZWI-ZW25-EAP NA	Safety	Expanded access/ compassionate use protocol	Monotherapy. • 20 mg/kg IV Q2W	HER2-positive advanced solid tumors (in subjects who do not qualify for participation in, or who are otherwise unable to access an ongoing ZW25 clinical trial)	200/19	US, Canada	Ongoing/ June 2021

Abbreviations: BICR = blinded independent central review; BTC = biliary tract cancer; CAPOX = capecitabine plus oxaliplatin (also known as XELOX); CisGem = cisplatin plus gemcitabine; CRC = colorectal cancer; DLT = dose-limiting toxicity; ECC = extrahepatic cholangiocarcinoma; EAP = expanded access program; EU = European Union; FISH = fluorescent *in situ* hybridization; FP = fluorouracil (5-FU) plus cisplatin; GBC = gallbladder cancer; GEA = gastroesophageal adenocarcinoma; GEJ = gastroesophageal junction; HER2 = human epidermal growth factor receptor 2; HER2-positive = immunohistochemistry (IHC) 3+, or IHC 2+ and fluorescence *in situ* hybridization (FISH)+; HER2-low = IHC 1+ or IHC 2+; and not HER2-positive per the ASCO/CAP guideline; HR = hormone receptor; HRQoL = health-related quality of life; ICC = intrahepatic cholangiocarcinoma; ICR = independent central review; IHC = immunohistochemistry; ISH +, *in situ* hybridization positive; IV = intravenous; mFOLFOX6 = fluorouracil (5FU) and leucovorin plus oxaliplatin; MTD = maximum tolerated dose; mTPI = modified toxicity probability interval; NA = not applicable; OBD = optimum biological dose; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS6 = percent of evaluable subjects with PFS ≥ 24 weeks; PK = pharmacokinetic; QW = weekly; Q2W = once every 2 weeks; Q3W = once every 3 weeks; RD = recommended dose; RECIST = Response Evaluation Criteria in Solid Tumors; S Korea = South Korea; UK = United Kingdom; US = United States; ZW25 = zanidatamab.

[a] Actual enrollment as of 28 July 2022.

[b] Sponsored by BeiGene.

1.3.3.1. Zanidatamab Monotherapy

Zanidatamab monotherapy is being assessed in 3 studies: ZWI-ZW25-101 (Parts 1 and 2), ZWI-ZW25-102, and ZWI-ZW25-203.

Please refer to the ZW25 Investigator's Brochure for detailed study design, demographics and baseline characteristics, and efficacy information.

1.3.3.2. Zanidatamab in Combination With Antineoplastic Agents

Zanidatamab in combination with antineoplastic agents is being assessed in 6 ongoing studies: ZWI-ZW25-101 (Part 3), ZWI-ZW25-201, ZWI-ZW25-202, ZWI-ZW25-204, BGB-A317-ZW25-101, ZWI-ZW25-301.

Please refer to the ZW25 Investigator's Brochure for detailed study design, demographics and baseline characteristics, and efficacy information.

1.3.4. Preliminary Zanidatamab Safety Profile

Zanidatamab Monotherapy

Safety data from the 3 ongoing studies of zanidatamab monotherapy as of the data cutoff (DCO) date (28 July 2022) are presented in this section.

With zanidatamab monotherapy, 286 subjects have been exposed to the following dose regimens: 3 subjects to 5 mg/kg once weekly, 13 subjects to 10 mg/kg once weekly, 7 subjects to 15 mg/kg once weekly, 235 subjects to 20 mg/kg once every 2 weeks, 6 subjects to 25 mg/kg once every 2 weeks, 6 subjects to 30 mg/kg once every 2 weeks, and 16 subjects to 30 mg/kg once every 3 weeks. Eighty-two percent of subjects (235/286) receiving monotherapy have been treated with the 20 mg/kg once-every-2-weeks dose regimen. The median duration of exposure for all dose regimens was 15.4 weeks (range, 0.1 to 221.1 weeks).

In the 286 subjects receiving zanidatamab monotherapy, treatment-emergent adverse events (TEAEs) occurring in ≥ 25% of subjects included diarrhea (47%) and infusion related reaction (IRR; 31%). TEAEs related to zanidatamab treatment occurring in ≥ 25% of subjects included diarrhea (41%) and IRR (31%). Grade 3 or higher TEAEs occurring in more than 5 subjects included anemia (8%), hypertension (5%), diarrhea (4%), pneumonia (3%), decreased appetite (2%), blood bilirubin increased (2%), fatigue (2%), and sepsis (2%). Twenty-one subjects (7%) experienced Grade 3 TEAEs that were assessed by the investigator to be related to zanidatamab treatment: diarrhea (8 subjects, 3%), anemia (3 subjects, 1%), fatigue (2 subjects, 1%), stomatitis (2 subjects, 1%), and arthralgia, aspartate aminotransferase (AST) increased, decreased appetite, ejection fraction decreased, enteritis, hypertension, hypokalemia, hypophosphatemia, IRR, nausea, oral candidiasis, platelet count decreased, and pneumonitis (1 subject each). No subject experienced treatment-related Grade 4 or Grade 5 TEAEs.

Of the 286 subjects receiving zanidatamab monotherapy, 80 (26%) experienced a treatment-emergent serious adverse event (SAE). Treatment-emergent SAEs occurring in more than 2 subjects included pneumonia (4%), sepsis (2%), cholangitis (2%), and diarrhea, jaundice cholestatic, obstruction gastric, and small intestinal obstruction (each in 1%). SAEs assessed by the investigator as related to zanidatamab treatment included diarrhea (2 subjects, < 1%), and

anemia, ejection fraction decreased, enteritis, fatigue, IRR, oral candidiasis, and pneumonitis (1 subject each, < 1%).

Seven of 286 subjects (2%) had a TEAE that led to discontinuation of zanidatamab monotherapy, including brain edema, ejection fraction decreased, IRR, pneumonitis, pulmonary embolism, small intestinal obstruction, and sudden death (1 subject each). The events of IRR, ejection fraction decreased, and pneumonitis were assessed by the investigator to be related to zanidatamab.

As of 28 July 2022, there have been 39 deaths in zanidatamab monotherapy studies; the majority (22 subjects, 56%) were due to disease progression. Seven subjects (18%) have died due to adverse events (AEs) assessed by the investigator as unrelated to zanidatamab, including sudden death (2 subjects), cardiac arrest, hepatic failure, cholangiocarcinoma, multiple organ dysfunction syndrome, and jaundice cholestatic.

Please refer to the ZW25 Investigator's Brochure for additional details on the safety profile of zanidatamab monotherapy, including summaries of TEAEs across dose escalation groups.

Zanidatamab Combination Therapy

Safety data from the zanidatamab plus tislelizumab combination study BGB-A317-ZW25-101 as of the DCO date (28 July 2022) are presented in this section. Refer to the ZW25 Investigator's Brochure for additional details on the safety profile of zanidatamab in this study, as well as the safety profile of zanidatamab in other ongoing combination trials.

A total of 38 subjects were treated with zanidatamab plus chemotherapy in the breast cancer cohort (Cohort 1) of Study BGB-A317-ZW25-101; however, 1 subject with a history of breast cancer was enrolled that had a subsequent biopsy that showed "pulmonary sarcomatoid carcinoma, spindle cell carcinoma," and this subject was excluded from the analyses. In the remaining 37 subjects with breast cancer, the most common TEAEs across treatment groups were neutrophil count decreased (60%), diarrhea (51%), anemia (46%), and white blood cell count decreased (43%). The only zanidatamab-related TEAE occurring in ≥ 25% of subjects was diarrhea (49%). The most common ≥ Grade 3 TEAEs were neutrophil count decreased (49%), white blood cell count decreased (19%), diarrhea (8%), alanine aminotransferase (ALT) increased (5%), febrile neutropenia (5%), and hypokalemia (5%). Grade 3 or higher TEAEs observed in > 1 subject and considered by the investigator to be related to zanidatamab treatment included diarrhea (8%), neutrophil count decreased (8%), hypokalemia (5%), and white blood cell count decreased (5%). The only SAE that occurred in more than 1 subject was blood bilirubin increased (2 subjects, 5%). Four subjects (11%) experienced SAEs assessed by the investigator to be related to zanidatamab treatment including blood bilirubin increased (2 subjects, 5%), and ALT increased, cholangitis, diarrhea, febrile neutropenia, heart rate decreased, and hypokalemia (each in 1 subject, 3%).

One subject (3%) discontinued study treatment (zanidatamab and docetaxel) due to TEAEs. One subject with breast cancer died during the study; the cause of death was the disease under study.

Of the 33 subjects with gastric/GEJ adenocarcinoma treated with zanidatamab plus chemotherapy and tislelizumab in Study BGB-A317-ZW25-101 (Cohort 2), the most common TEAEs included diarrhea (100%), nausea (67%), decreased appetite (49%), pyrexia (49%), vomiting (45%), and hypokalemia (42%).

Zanidatamab-related TEAEs occurring in ≥ 25% of subjects included diarrhea (88%), nausea (42%), pyrexia (36%), and hypokalemia (27%). The most common ≥ Grade 3 TEAEs included diarrhea (27%), anemia (18%), and lipase increased (15%). Grade 3 or higher TEAEs that were assessed by the investigator as related to zanidatamab and occurred in > 1 subject included diarrhea (27%), and ejection fraction decreased, fatigue, hypokalemia, lipase increased, and platelet count decreased (in 6% each). Serious TEAEs occurring in 2 or more subjects included COVID-19 (9%), diarrhea (9%), blood creatinine increased (6%), and obstruction gastric (6%). Seven subjects (21%) experienced SAEs assessed by the investigator to be related to zanidatamab treatment, including diarrhea (3 subjects, 9%), and abdominal pain, blood creatine phosphokinase increased, blood creatinine increased, pneumonia, pneumonitis, and transient ischemic attack (each in 1 subject, 3%). Four subjects (12%) discontinued study treatment (zanidatamab, tislelizumab, and CAPOX [capecitabine plus oxaliplatin]) due to TEAEs. Ten subjects with GEA died during the study; 5 due to the disease under study, 4 due to AEs, and 1 cause of death was indeterminate.

Please refer to the ZW25 Investigator's Brochure for a full description of all available safety data on the toxicology of ZW25.

1.3.5. Preliminary Zanidatamab Efficacy

Preliminary efficacy data of zanidatamab monotherapy are available from Study ZWI-ZW25-101 Part 1 and Part 2 and preliminary efficacy data of zanidatamab in combination with antineoplastic agents are available from 3 combination therapy studies (Study ZWI-ZW25-101 Part 3, Study ZWI-ZW25-201, and Study BGB-A317-ZW25-101).

Please refer to the ZW25 Investigator's Brochure for a full description of all available efficacy data.

1.4. Background Information on Tislelizumab

1.4.1. Pharmacology

Tislelizumab (also known as BGB-A317) is a humanized, immunoglobulin G4 (IgG4)-variant monoclonal antibody against PD-1 under clinical development for the treatment of several human malignancies.

Tislelizumab acts by binding to the extracellular domain of human PD-1 with high specificity as well as high affinity (dissociation constant [K_D] = 0.15 nM). It competitively blocks binding efforts by both PD-L1 and programmed cell death protein ligand-2 (PD-L2), thus inhibiting PD-1-mediated negative signaling in T cells. In in vitro cell-based assays, tislelizumab was observed to enhance the functional activity of human T-cells and pre-activated, primary peripheral blood mononuclear cells consistently and dose-dependently. In addition, tislelizumab has demonstrated antitumor activity in several allogeneic xenograft models, in which peripheral blood mononuclear cells were co-injected with human cancer cells (A431 [epidermoid carcinoma]) or tumor fragments (BCCO-028 [colon cancer]) into immunocompromised mice.

In addition, tislelizumab is an IgG4 variant antibody to gamma fragment crystallizable region (Fc) receptors (FcγR) such as FcγRI and FcγRIIIA, and it has very low binding affinity to Complement 1q (C1q), a subunit of complement 1. In vitro assays with tislelizumab suggest

either low or no antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, or complement-dependent cytotoxicity effects in humans (Labrijn et al 2009; Zhang et al 2018). Tislelizumab was specifically engineered to abrogate these potential mechanisms of T-cell clearance and potential resistance to anti-PD-1 therapy.

Please refer to the Tislelizumab Investigator's Brochure for additional details regarding nonclinical studies of tislelizumab.

1.4.2. Toxicology

The toxicity and safety profile of tislelizumab was characterized in single-dose toxicology studies in mice and monkeys and in a 13-week, repeat-dose toxicology study in cynomolgus monkeys. The tissue cross-reactivity was evaluated in the normal frozen tissues from both humans and monkeys. The cytokine release assays were also evaluated using fresh human whole blood cells. The single-dosing regimens spanned from the intended human doses to 10-fold higher than the maximum of the intended human doses, and the repeat-dosing regimens spanned to 3-fold higher than the maximum of the intended human doses. Cynomolgus monkey was the only relevant species based on the target sequence homology and binding activity.

Overall, no apparent toxicity was noted in mice or monkey toxicity studies. No tissue cross-reactivity was found in either human or monkey tissues, nor was any effect on cytokine release observed in human whole-blood assay. The toxicokinetic profile was well characterized, with dose proportional increases in systemic exposure without apparent accumulation or sex difference. Immunogenicity was observed without apparent immunotoxicity or effect on the systemic exposure. The NOAEL of tislelizumab in the 13-week monkey toxicity study was considered to be 30 mg/kg. The safety profile of tislelizumab is considered adequate to support the current study BGB-A317-ZW25-101.

Please refer to the Tislelizumab Investigator's Brochure for more detailed information on the toxicology of tislelizumab.

1.4.3. Clinical Pharmacology

The non-compartmental pharmacokinetics (PK) of tislelizumab was characterized in 129 patients with solid tumors in the Phase 1 studies, BGB-A317_Study_001 study and Study BGB-A317-102, using serum concentrations from patients who received doses of 0.5, 2.0, 5.0, 10 mg/kg every 2 weeks and 2.0 mg/kg, 5.0 mg/kg, 200 mg every 3 weeks (109 patients in BGB-A317_Study_001, 20 patients in Study BGB-A317-102). The drug exposure (maximum observed plasma concentration [C_{max}] and the area under the plasma or serum concentration-time curve [AUC]) increased in a dose-proportional manner from 0.5 mg/kg to 10 mg/kg, following the first dose administration. Combining the data from these 2 Phase 1 studies, the lack of correlation between clearance and body weight indicates that clearance is not dependent on body weight, which supports fixed dosing of tislelizumab.

Population PK analysis was conducted from 2596 patients who received doses of 0.5, 2.0, 5.0, and 10 mg/kg once every 2 weeks, 2.0 and 5.0 mg/kg once every 3 weeks, and 200 mg once every 3 weeks. The PK of tislelizumab was best characterized using a 3-compartmental model with linear clearance mechanism. No time varying clearance was observed in tislelizumab PK. The typical estimates of clearance (CL), central volume of distribution (V_c), and peripheral

volumes 2 and 3 (V_2 and V_3, respectively), were 0.153 L/day, 3.05 L, 1.27 L, and 2.10 L, respectively, with interindividual variability in CL (26.3%), V_c (16.7%), V_2 (74.7%), and V_3 (99.9%). The terminal $t_{½}$ was estimated to be approximately 23.8 days. The accumulation ratios were estimated to be 2.14 and 2.49 for AUC_{ss} and minimum serum concentration at steady state ($C_{min,ss}$), respectively. Steady state is expected to be reached in approximately 12 weeks.

The population PK analyses demonstrated that race, baseline ALT, AST, bilirubin, lactate dehydrogenase, estimated glomerular filtration rate, Eastern Cooperative Oncology Group (ECOG) Performance Status score, and sum of products of perpendicular diameters of classical Hodgkin Lymphoma (cHL) did not have statistically significant influences on tislelizumab PK. Baseline body weight, tumor size of solid tumors, albumin, age, sex, immunogenicity, and tumor type were found to be statistically significant covariates on the PK of tislelizumab; however, the exposure changes by these covariates were small compared to the overall estimated PK exposures range and hence are not considered clinically meaningful.

1.4.4. Prior Clinical Experience

As of 20 July 2022, 7 studies with tislelizumab have been completed and 18 studies are ongoing. Of the ongoing studies, 10 studies have preliminary data available; 5 monotherapy studies and 5 chemotherapy combination therapy studies.

Please refer to the Tislelizumab Investigator's Brochure for more detailed information on safety and efficacy data with tislelizumab when given as monotherapy or in combination with chemotherapy.

1.4.4.1. Pooled Safety Assessment of Monotherapy Studies

For monotherapy, the safety profile is well tolerated in solid tumors and hematological malignancies. Most AEs were Grade 1 or 2 in the pooled solid tumor studies, and most ≥ Grade 3 TEAEs were assessed as unrelated to tislelizumab. AEs were generally reversable and manageable. The percentage of patients with tislelizumab-related TEAEs leading to tislelizumab discontinuation was small. In the hematological malignancies studies, most AEs were Grade 1 or 2, and most ≥ Grade 3 TEAEs were assessed as unrelated to tislelizumab. As with the solid tumor studies, AEs were generally reversable and manageable, and the percentage of patients with tislelizumab-related TEAEs leading to tislelizumab discontinuation was small. The safety profile for single-agent tislelizumab is similar to that observed with other PD-1 inhibitors in solid tumors and hematological malignancies.

For more detailed information on the safety of tislelizumab when given as monotherapy or in combination with chemotherapy, refer to the Tislelizumab Investigator's Brochure.

1.4.4.2. Efficacy Assessment of Tislelizumab

Efficacy data are available from 9 monotherapy studies and 6 combination therapy studies. Among these 15 studies, 13 studies were in patients with solid tumors, and 2 studies were in patients with hematologic malignancies.

The data collected show that tislelizumab monotherapy can result in antitumor activity across a variety of tumor types, and the antitumor activity has been observed across the dose ranges evaluated in patients.

Please refer to the Tislelizumab Investigator's Brochure for detailed efficacy information.

1.5. Study Rationales

1.5.1. Rationale for Combination of ZW25 and Chemotherapy in the Treatment of Breast Cancer

ZW25 has been extensively studied in in vitro and in vivo models of HER2 high- and low-expressing tumors as a single agent and in combination with anticancer therapies. ZW25 has demonstrated subnanomolar affinity to recombinant HER2 that was comparable to the binding affinities of trastuzumab and pertuzumab for HER2, as well as the synergy and additivity with chemotherapeutic agents in inhibiting the growth of human cancer cell lines that express high to low levels of HER2. The results of in vitro and in vivo nonclinical studies suggest that ZW25 combines the mechanisms of action of trastuzumab and pertuzumab synergistically in a single antibody bringing about greater efficacy than trastuzumab or pertuzumab alone or in combination. Based upon mechanism of action, activity in in vitro and in vivo studies as a single agent and in combination with other agents, and tolerability in toxicology studies, ZW25 has the potential to address much of the currently unmet medical need in HER2-expressing cancers.

In the ongoing first-in-human study of ZW25, a multi-part Phase 1 study (ZWI-ZW25-101), antitumor activity of ZW25 either as single agent or in combination with chemotherapy has been observed. At the DCO date of 31 October 2018, 67 patients had been treated with single agent ZW25 at multiple dosage levels. Most patients have received prior HER2-targeted therapies, including trastuzumab in 88.1% of patients, pertuzumab in 53.7%, and T-DM1 in 58.2%. Forty-eight patients had response evaluable disease, including 28 with breast cancer, 9 with GEA, 11 with other cancer types. Most of these patients with measurable disease demonstrated a decrease in target lesions. The overall ORR was 31.3% (n = 15/48, all partial response [PR]) and disease control rate (DCR) (PR+stable disease) was 66.7% (n = 32/48). In breast cancer, the ORR was 28.6% (n = 8/28, all PR) and DCR was 60.7% (n = 17/28). At the DCO date of 31 October 2018, 6 patients had been treated with ZW25 in combination with chemotherapy (4 patients with capecitabine and 2 patients with paclitaxel). Small data set for ZW25 in combination with standard-of-care chemotherapy did not demonstrate any new safety signals in breast cancer or GEA patients, with no dose-limiting toxicity (DLT) observed and no treatment-related SAEs or discontinuations.

Taken together, ZW25's bispecific structure which enables combining the mechanisms of action of trastuzumab and pertuzumab ability, in vivo as well as in vitro preclinical research data, and the Phase 1 study preliminary clinical data suggest the antitumor efficacy of ZW25 in HER2-positive breast cancer and an acceptable safety profile to combine with taxane chemotherapy.

These information supports the rationale to explore the hypothesis of Cohort 1 in this study: ZW25 in combination with chemotherapy has the potential to provide clinical benefit to patients with HER2-positive metastatic breast cancer. The Cohort 1 in this study will evaluate the safety and preliminary antitumor activity of ZW25 in combination with docetaxel as the first-line treatment of HER2-positive metastatic breast cancer.

1.5.2. Rationale for Combination of ZW25, Tislelizumab, and Chemotherapy in the Treatment of Gastric/Gastroesophageal Junction Adenocarcinoma

With the remarkable breakthrough of immunotherapy in multiple tumor types, it has also been explored whether adding blocking HER2 pathway together with PD-1 can achieve synergistic effect in HER2-positive tumor types. Preclinical data have reported that tumor regressions from anti-HER2 therapy in a preclinical mouse model require both effective innate and adaptive immunity. As proof-of-concept, enhancement of T-cell responses in combination with trastuzumab was evaluated in an immunocompetent transgenic HER2 mammary mouse model. In this model, the combination of the anti-HER2 mAb and anti-PD-1 therapy was synergistic and more effective than either monotherapy (Stagg et al 2011). More recent studies also indicated that HER2 targeting ADCs synergized with PD-L1 and/or CTLA-4 antibodies and triggered innate and adaptive immunity in different mouse models (Mueller et al 2015). These data suggest that HER2-overexpressing tumors use immunosuppression as a mechanism to facilitate growth and progression, and these tumors may benefit from anti-PD-1 and anti-HER2 combined therapy.

In a recently reported Phase 2 study, 35 previous untreated HER2-positive metastatic GEA patients received pembrolizumab 200 mg, trastuzumab 6 mg/kg (after 8 mg/kg load), oxaliplatin 130 mg/m^2 every 3 weeks, and capecitabine 850 mg/m^2 dosed 2 weeks on/1 week off (or 5-FU) as first-line treatment. In the 32 patients who were response evaluable, 28 patients achieved the CR or PR as their best response, resulting an ORR of 87% and DCR of 100%. At median follow-up of 6.6 months, the median PFS was 11.4 months (95% CI: 6.0 to 16.4) and median OS was not reached. In the biomarker analysis, it was noted that PD-L1 status is not a predictor of efficacy, with no PFS or OS difference between PD-L1 positive versus PD-L1 negative patients (Janjigian et al 2019a). Though the sample size is small, this study provides encouraging signal to further explore anti-PD-1 and anti-HER2 dual blockade, which led to the initiation of KEYNOTE-811, an ongoing randomized double-blinded Phase 3 study comparing the safety and efficacy of pembrolizumab +trastuzumab in combination with standard-of-care chemotherapy versus trastuzumab alone in combination with standard-of-care chemotherapy in patients with HER2-positive gastric/GEJ adenocarcinoma (NCT03615326; Janjigian et al 2019b). These data were published at ASCO 2021; the ORR was 74% versus 52% ($p<0.0001$) and the median DOR was 10.6 months versus 9.5 months. Based on the ORR and DOR results, the FDA has granted accelerated approval to pembrolizumab + trastuzumab + fluoropyrimidine and platinum-containing chemo (5-FU+Cis or CAPOX) for 1L HER2+ G/GEJ adenocarcinoma (Janjigian et al 2021).

ZW25 has demonstrated synergistic effects when combined with selected chemotherapeutic agents, in in vitro studies in breast cancer and gastric cancer cell lines, including HER2 3+ NCI-N87 (gastric cancer) cells (Weisser et al 2017). In xenograft models in nude mice, ZW25 also demonstrated improved efficacy when combined with chemotherapy. For example, ZW25 in combination with cisplatin showed greater antitumor activity and increased survival of nude mice bearing established tumors with human non-small cell lung cancer and head and neck squamous cell carcinoma cell lines compared with cisplatin or trastuzumab alone. Although ZW25 has not been evaluated in combination with chemotherapy in gastric cancer xenograft models, the improved antitumor activity observed in combination with cisplatin is relevant to gastric/GEJ adenocarcinoma, as cisplatin is considered part of standard-of-care chemotherapy for

these tumors. The efficacy and safety of ZW25 plus first-line chemotherapy is being investigated in a Phase 2 study (ZWI-ZW25-201).

Tislelizumab demonstrated antitumor activity as single agent and/or in combination with chemotherapy for the treatment of advanced gastric/GEJ adenocarcinoma. The preliminary anticancer activity was observed using tislelizumab monotherapy for previously treated unresectable gastric/GEJ adenocarcinoma in two Phase I (Study BGB-A317_Study_001 and Study BGB-A317-102) dose expansion cohorts. While in the HER2-negative gastric/GEJ adenocarcinoma cohort of BGB-A317-205 study, the ORR was 46.7% (95% CI: 21.3% to 73.4%), and the responses were durable, with median duration of response (range 2.99 to 13.11+ months) not yet reached and 4 responders ongoing at the time of the DCO date, and the median OS was also not reached within the median follow up time of 15.38 months (95% CI: 14.69 to 17.22).

In short, these information supports the rationale to explore the hypothesis of Cohort 2 in this study: ZW25 in combination with tislelizumab and chemotherapy has the potential to provide clinical benefit to patients with HER2-positive gastric/GEJ adenocarcinoma.

- preclinical mechanism of action of anti-PD-1 and anti-HER2 dual blockade;
- the external clinical evidence from other anti-PD-1 and anti-HER2 combination treatment in first-line HER2-positive GEA;
- the activity of ZW25 as a single agent and in combination with chemotherapy in cancer cell lines and xenograft models;
- the single-agent antitumor effects and tolerable safety profile of ZW25 in patients with HER2-positive GEA;
- the antitumor activity and tolerable safety profiles of tislelizumab alone or in combination with chemotherapy observed in advanced gastric/GEJ cancer.

The Cohort 2 in this study will evaluate the safety and preliminary antitumor activity of ZW25 combined with tislelizumab and chemotherapy regimens in the first-line treatment of gastric/GEJ adenocarcinoma.

1.5.3. Rationale for Dose Selection

1.5.3.1. ZW25

In the ongoing first-in-human study of ZW25 (ZWI-ZW25-101), the starting dose of 5 mg/kg every week is at least 30-fold lower than the NOAEL and the highest nonseverely toxic dose (HNSTD) in cynomolgus monkeys, which were both considered to be 150 mg/kg based on a GLP toxicology study. As of 31 October 2018, all enrolled patients in the 20 mg/kg biweekly cohort completed the per-protocol DLT evaluation period, with no DLTs reported. In addition, the safety profile was generally consistent among different dose levels. As the maximum tolerated dose was not exceeded at any of the evaluated doses or schedules, the Safety Monitoring Committee (SMC) subsequently recommended that the doses and schedules for further study were 10 mg/kg weekly or 20 mg/kg biweekly.

The regimen of 30 mg/kg once every 3 weeks was further evaluated in Study ZWI-ZW25-101 and Study ZWI-ZW25-201 to pair with the cycle of standard chemotherapy. At this dose level, the weekly dosing amount is equivalent to 10 mg/kg every week or 20 mg/kg once every 2 weeks, and a 4-fold safety margin remains based on monkey HNSTD. A quantitative system pharmacology model has been established, validated, and adopted to predict the potential efficacy. The results suggested that 75% of patients are expected to achieve the targeted human efficacious level at the 30 mg/kg once-every-3-weeks dose level. To date, clinical data suggested that the 30 mg/kg once-every-3-weeks dosing regimen is well tolerated as monotherapy or in combination with chemotherapy. As of the DCO date (01 April 2020), 21 patients in Study ZWI-ZW25-101 have been treated with 30 mg/kg once every 3 weeks (Q3W). No DLTs were observed with this dose regimen, and ≥ Grade 3 or serious drug-related events were rare. Refer to Section 1.3.3 for detail safety information.

In this amendment, flat dosing regimen of ZW25 will be evaluated in Cohort 1b and 2b. The influence of body weight on exposure has been evaluated in a population PK analysis. The results suggest that with flat dosing, the central tendency of the PK profile and its variability are comparable to that achieved with body weight dosing. Considering a typical bodyweight of 60 kg in breast cancer patients (Shin et al 2009), 1800 mg Q3W flat dose is considered to be equivalent to the 30 mg/kg Q3W.

GEA patients are reported to have a wider bodyweight range (Min-Max: 40 to 128 kg, Median = 66.1 kg) compared to breast cancer patients. Additionally, in the GEA population, ZW25 has lower exposure than in other indications, which is consistent with findings in other mAbs, including trastuzumab (Shah et al 2017). Therefore, a two-tiered, flat-dosing regimen (1800 mg Q3W for patients < 70 kg, 2400 mg Q3W for patients ≥ 70 kg) is selected based on population analyses. The purpose is to maintain the targeted trough ZW25 concentration for GEA patients who have a relatively large body weight.

In summary, the above proposed dose schedule is appropriate to be investigated in this study.

1.5.3.2 Tislelizumab

The PK, safety, and efficacy data obtained from the first-in-human study BGB-A317_Study_001, as well as other clinical study data, were analyzed in aggregate to determine the recommended dose for pivotal studies of tislelizumab. The flat dose of 200 mg IV once every 3 weeks was selected for further evaluation.

Rates of treatment-related AEs and SAEs observed in patients receiving 2 mg/kg and 5 mg/kg once every 2 weeks and once every 3 weeks were comparable, suggesting no clear dose-dependence across these regimens. Similarly, confirmed ORRs in patients treated with tislelizumab 2 mg/kg and 5 mg/kg once every 2 weeks ranged between 10% and 15%, compared to a range of 15% to 38% for patients treated at 2 mg/kg and 5 mg/kg once every 3 weeks.

According to PK data from BGB-A317_Study_001, Phase 1A, the clearance of tislelizumab was found to be independent of body weight, ethnicity, and sex, and the observed serum exposure of a 200-mg dose fell between serum exposure observed after 2 mg/kg and 5 mg/kg doses (dose range with comparable safety and efficacy rates).

Additionally, no unexpected treatment-related AEs occurred in the 200-mg fixed dose cohort (BGB-A317_Study_001, Phase 1A, Part 3) when compared to body-weight-based cohorts. Of

the evaluable patients treated (n = 13), 3 patients (23%) had a BOR of PR, 4 patients (31%) had a BOR of stable disease, and 6 patients (46%) had a BOR of progressive disease. Therefore, clinical activity with a manageable and tolerable safety profile is expected to be maintained in patients receiving tislelizumab 200 mg once every 3 weeks.

In conclusion, tislelizumab 200 mg once every 3 weeks is the recommended dose for this study.

1.6. Benefit-Risk Assessment

HER2 has long been widely recognized as the most important target for HER2-positive metastatic breast cancer and gastric cancer. Several anti-HER2 agents have been successfully approved. Available data from other anti-HER2 antibodies, such as trastuzumab and pertuzumab, have demonstrated favorable benefit/risk profiles. The efficacy data with ZW25 in breast cancer or GEA patients are preliminary but are comparable with other anti-HER2 monoclonal antibodies.

Based on the ZW25 mechanism of action, in vivo and in vitro preclinical data, and clinical efficacy observed in the Phase 1 studies ZWI-ZW25-101 and BGB-A317-ZW25-101, and the Phase 2 study ZWI-ZW25-201, ZW25 has the potential to address unmet medical needs in patients with HER2-positive cancers, by combining trastuzumab-like and pertuzumab-like activities in a synergistic manner as a single antibody. In the ongoing first-in-human study ZWI-ZW25-101, antitumor activity of ZW25 either as single agent or in combination with chemotherapy has been observed. The results suggest that ZW25 has the potential to provide clinical benefit to patients with HER2-positive breast cancer or gastric/GEJ adenocarcinoma.

As of 28 July 2022, 286 patients have been treated with ZW25 monotherapy in multiple tumor types. Nonclinical toxicology studies as well as clinical safety data from the Phase 1 study suggest that AEs associated with ZW25 are well tolerated and manageable. For further discussion on the safety profile of ZW25, please refer to the ZW25 Investigator's Brochure.

As of 20 July 2022, > 2000 patients have been treated with tislelizumab monotherapy at clinically relevant doses (≥ 2 mg/kg; most patients received 200 mg) and > 1000 patients have been treated with tislelizumab 200 mg in combination with chemotherapy or other agents. The safety profile is largely consistent with that of other anti-PD-1 antibodies and included mostly mild/moderate AEs. Very few Grade 3/4 immune-mediated adverse events (imAEs) have been observed, and they have been generally reversible and manageable with study drug interruption and/or steroid treatment. For further discussion on the safety profile of tislelizumab, please refer to the Tislelizumab Investigator's Brochure.

When treated with tislelizumab or ZW25 alone, AEs such as diarrhea, nausea, fatigue and infusion-related reactions have been observed. These AEs are non-specific and typical of cancer treatment regimens. There is potential risk of increased toxicities for patients in Study BGB-A317-ZW25-101 Cohort 2 who are treated with ZW25 and tislelizumab. The pulmonary toxicity has been reported in tislelizumab as an imAE and in drugs of similar mechanisms of action to ZW25. Therefore, the AEs related to pulmonary toxicity may potentially increase in severity or in frequency when using tislelizumab and ZW25 in combination.

The Phase 2 study BGB-A317-205 investigates the safety, PK and preliminary antitumor activity of tislelizumab in combination with chemotherapy as first-line treatment in patients with

inoperable, locally advanced or metastatic esophageal, gastric, or GEJ carcinoma. A total of 30 gastric/GEJ adenocarcinoma patients were enrolled. Though the study population is HER2-negative, this study uses the same chemotherapy as backbone as Study BGB-A317-ZW25-101 Cohort 2. The incidence and type of treatment-related AEs were similar to the AEs known to be associated with chemotherapy regimens combined with other PD-1 products. Tislelizumab in combination with oxaliplatin + capecitabine demonstrated manageable safety profiles.

Given the unmet medical need and limited treatment options for these patients, the benefit/risk assessment of this study is considered favorable based on available data from the ZW25 Phase 1 study ZWI-ZW25-101, the tislelizumab Phase 1 study BGB-A317_Study_001, the tislelizumab Phase 2 study BGB-A317-205 in GC, and the publications on other anti-PD-1 agents in combination with anti-HER2 antibodies in gastric/GEJ adenocarcinoma.

1.7. Study Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and in accordance with the International Council for Harmonisation (ICH) Good Clinical Practice (GCP) standards.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

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

2.1.2. Secondary Objective

- To further evaluate the preliminary antitumor activity of ZW25 in combination with docetaxel in patients with HER2-positive breast cancer, and ZW25 in combination with tislelizumab and chemotherapy in patients with HER2-positive gastric/GEJ adenocarcinoma as measured by duration of response, time to response, PFS, DCR, and OS
- To characterize the PK and immunogenicity of ZW25 in both cohorts
- To evaluate the long-term safety of ZW25 in combination with docetaxel in patients with HER2-positive breast cancer, and ZW25 in combination with tislelizumab and chemotherapy in patients with HER2+ G/GEJC during the long-term extension period

2.1.3. Exploratory Objectives

- [redacted]
- [redacted]

2.2. Study Endpoints

2.2.1. Primary Endpoints

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

2.2.2. Secondary Endpoints

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

2.2.3. Exploratory Endpoints

[redacted]

3. STUDY DESIGN

3.1. Summary of Study Design

This is an open-label, multicenter, Phase 1b/2 study to investigate safety, tolerability, PK and preliminary antitumor activity of ZW25 in combination with chemotherapy with or without tislelizumab in patients with histologically or cytologically confirmed unresectable locally advanced or metastatic HER2-positive breast cancer or gastric/GEJ adenocarcinoma. The study design schematic is presented in Figure 1.

After being confirmed as eligible, approximately 80 patients will be enrolled into the 2 cohorts in total: approximately 50 patients for Cohort 1 and approximately 30 patients for Cohort 2. The study will be conducted across approximately 20 sites in Asian countries. This study consists of the 2 cohorts described below.

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

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

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

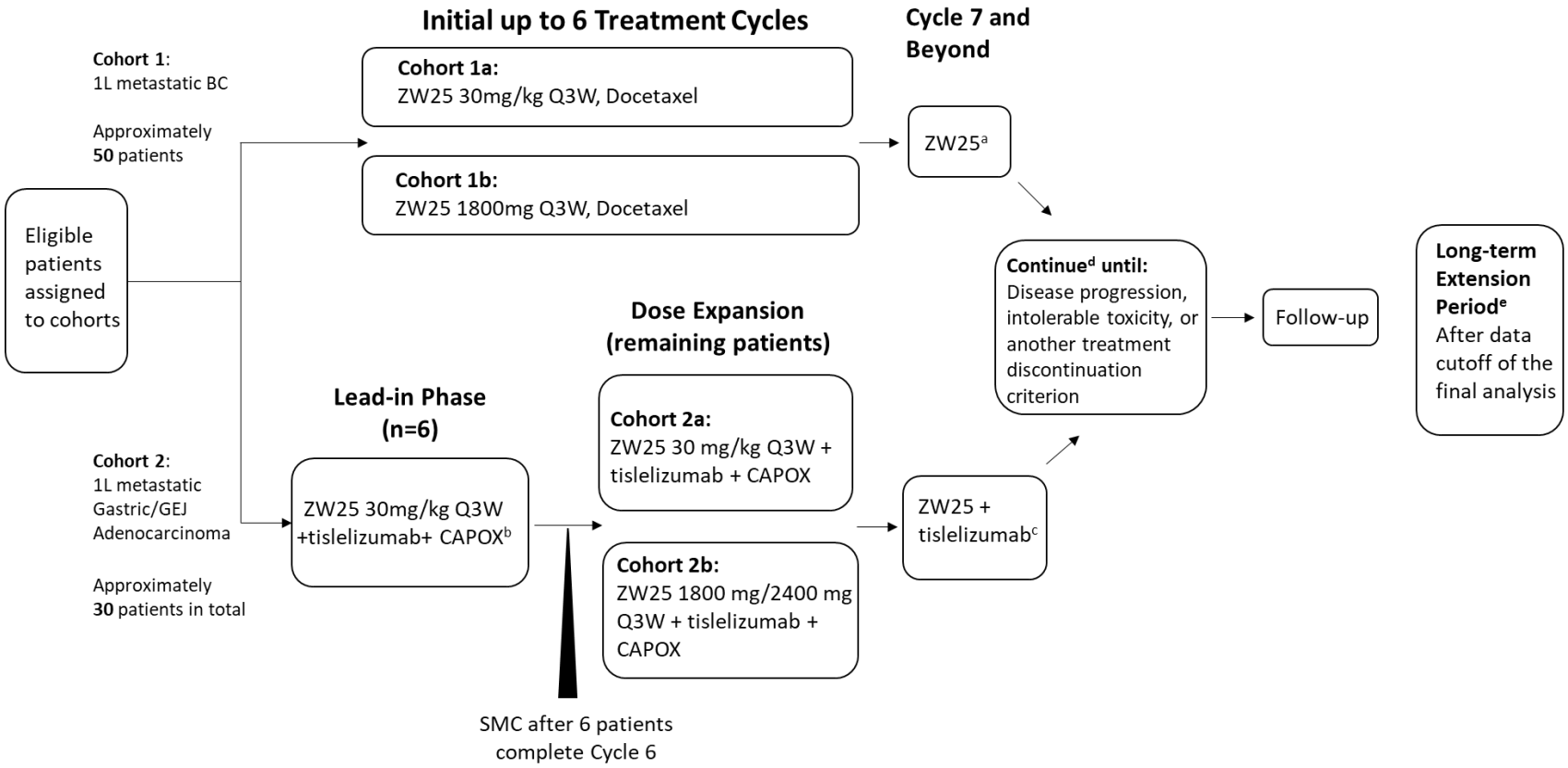
Cohort 2: patients who have unresectable, locally advanced, recurrent or metastatic HER2-positive (HER2 IHC 3+ or HER2 IHC 2+ together with in situ hybridization positive) gastric/GEJ adenocarcinoma and who have not received previous systemic therapy for locally advanced unresectable or metastatic disease are eligible, and will be treated with ZW25, tislelizumab and chemotherapy as the first-line therapy. The chemotherapy regimen will be CAPOX (1000 mg/m^2 capecitabine and 130 mg/m^2 oxaliplatin) and will be administered up to 6 cycles. On or prior to Cycle 6, capecitabine or oxaliplatin should only be discontinued for progressive disease or unacceptable toxicity, or another criterion for treatment discontinuation is met. After Cycle 6, oxaliplatin will be discontinued and continuation of capecitabine as maintenance treatment is at the discretion of the investigator. ZW25 and tislelizumab will be administered until disease progression, intolerable toxicity, or another criterion for treatment discontinuation is met. Detailed dosing schedule and administration of ZW25 and tislelizumab is described below:

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

For Cohort 2, a safety lead-in phase is designed, during which 6 patients will be enrolled. After the first 6 patients have completed at least 1 cycle (21 days) of treatment, safety data will be reviewed by SMC to ensure the tolerability before the whole cohort is fully open to enrollment. If there are no new significant or severe safety signals detected, the enrollment of dose expansion will be expanded up to approximately 30 patients in total for Cohort 2.

The study procedures will occur over a Screening Period (Section 3.2), Treatment Period (Section 3.3), End of Treatment/Safety Follow-up (Section 3.4), Survival Follow-up (Section 3.5), and Long-Term Extension Period (Section 3.6). For all study procedures, see Section 7 and Appendix 1.

Figure 1: Study Schema



Abbreviations: 1L, first-line; BC, breast cancer; GEJ, gastroesophageal junction; IV, intravenously; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SMC, Safety Monitoring Committee;
Notes: Detailed dosing schedule and administration are described below:

- **Cohort 1a:** ZW25 30 mg/kg intravenously (IV); docetaxel 75 mg/m^2 IV Q3W
- **Cohort 1b:** ZW25 1800 mg IV; docetaxel 75 mg/m^2 IV Q3W
- **Cohort 2a:** ZW25 30 mg/kg IV, tislelizumab 200 mg IV, CAPOX Q3W
- **Cohort 2b:** ZW25 1800 mg (patient's body weight< 70 kg) or 2400 mg (patient's body weight ≥ 70 kg) IV, tislelizumab 200 mg IV, CAPOX Q3W

[a] For patients in Cohort 1, continuation of docetaxel treatment is at the discretion of the investigator after Cycle 6.
[b] CAPOX is a multi-agent chemotherapy regimen consisting of capecitabine and oxaliplatin.

[c] For patients in Cohort 2, continuation of capecitabine as maintenance treatment is at the discretion of the investigator after Cycle 6.
[d] Treatment beyond initial investigator-assessed RECIST Version 1.1 defined progression is only permitted if the patient treated with tislelizumab in Cohort 2 has evidence of "pseudoprogression" and after discussion with the sponsor and re-consent of patient.
[e] After the data cutoff date of the final analysis, only patients who remain on treatment or are in the safety follow-up period will enter the long-term extension period. See Section 3.6.

Safety will be assessed throughout the study by monitoring AEs/SAEs, and laboratory results. Vital signs, physical examinations, ECOG Performance Status change, ECG results, echocardiogram/MUGA, and other examinations will also be used for safety assessment. Safety assessments are further detailed in Section 7.1.4 and the Schedule of Assessments (Appendix 1).

Preliminary anticancer activity will be evaluated by the investigator using RECIST Version 1.1 (Section 7.1.5 and Appendix 1). Radiological assessment of tumor response status will be performed every 6 weeks (± 7 days) from Cycle 1 Day 1 for the first 36 weeks and every 12 weeks (± 7 days) thereafter until disease progression, withdrawal of consent, death, or start of a new anticancer therapy, whichever occurs first.

PK and immunogenicity analysis will be performed for ZW25 and tislelizumab. Biomarker analysis will include, but is not limited to HER2 status, PD-L1 expression, presence of TILs, CNAs, gene expression profiling and/or tumor gene variations (including gene mutation, TMB, and MSI status) (in Mainland China, only the biomarkers specified above will be tested on samples collected) (Section 7.1.7).

3.2. Screening Period

Screening evaluations will be performed within 28 days prior to the first dose of study drug. Patients who agree to participate in this study will sign the informed consent form (ICF) prior to undergoing any screening procedure. Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

For patients who are suspected to have serious respiratory concurrent illness or exhibit significant respiratory symptoms unrelated to underlying cancer will also take a pulmonary function test (refer to Section 7.1.1.2 and Appendix 1 for details).

Archival tumor tissue must be provided for retrospective confirmation of HER2 status and/or other biomarker analysis. A fresh biopsy of an accessible tumor lesion is required at baseline in the absence of archival tumor tissue, unless previously discussed with sponsor's medical monitor. Refer to Section 7.1.7 for details.

3.3. Treatment Period

After completing all screening activities, eligible patients will be enrolled into the cohort accordingly. Treatment period starts with the first dose of study drug administration and ends when the patient is discontinued for study treatment when they are no longer considered to be achieving clinical benefit, due to unacceptable toxicity, death, or withdrawal of consent. Patients enrolled under Protocol Amendment 1.0 or later will be assigned to Cohort 1b or 2b.

- **Cohort 1:** ZW25 will be administered followed by docetaxel. On or prior to Cycle 6, docetaxel should only be discontinued for progressive disease or unacceptable toxicity, or another criterion for treatment discontinuation is met. After Cycle 6, continuation of docetaxel treatment is at the discretion of the investigator. ZW25 will be administered until disease progression, intolerable toxicity, or another criterion for treatment discontinuation is met. Detailed dosing schedule and administration is described below:

  - **Cohort 1a:** ZW25 30 mg/kg IV, docetaxel 75 mg/m^2 IV once every 3 weeks (Q3W)
  - **Cohort 1b:** ZW25 1800 mg IV, docetaxel 75 mg/m^2 IV Q3W
- **Cohort 2:** ZW25 will be administered followed by tislelizumab, and chemotherapy at the beginning of each 21-day cycle (once every 3 weeks). The chemotherapy regimen will be CAPOX (1000 mg/m^2 capecitabine and 130 mg/m^2 oxaliplatin) and will be administered up to 6 cycles. On or prior to Cycle 6, capecitabine or oxaliplatin should only be discontinued for progressive disease or unacceptable toxicity, or another criterion for treatment discontinuation is met. After Cycle 6, oxaliplatin will be discontinued and continuation of capecitabine as maintenance treatment is at the discretion of the investigator. ZW25 and tislelizumab will be administered until disease progression, intolerable toxicity, or another criterion for treatment discontinuation is met. Detailed dosing schedule and administration is described below:
  - **Cohort 2a:** ZW25 30 mg/kg IV, tislelizumab 200 mg IV, CAPOX (1000 mg/m^2 capecitabine and 130 mg/m^2 oxaliplatin) Q3W
  - **Cohort 2b:** ZW25 1800 mg (subject's body weight < 70 kg) or 2400 mg (subject's body weight ≥ 70 kg) IV, tislelizumab 200 mg IV, CAPOX (1000 mg/m^2 capecitabine and 130 mg/m^2 oxaliplatin) Q3W

For patients treated with tislelizumab in Cohort 2, treatment beyond initial RECIST Version 1.1 defined disease progression is permitted if the patient has evidence of "pseudoprogression" and after discussion with sponsor and re-consent of patient.

3.4. End of Treatment/Safety Follow-up

The End of Treatment visit (EOT)/Safety Follow-up is conducted when the investigator determines that study drugs will no longer be used. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT/Safety Follow-up visit, these tests need not be repeated. Tumor assessment is not required at the EOT/Safety Follow-up Visit provided that fewer than 6 weeks have passed since the last assessment.

Patients who discontinue treatment for any reason through the DCO date of the final analysis (FA) (Section 9.8) will be asked to return to the clinic for the EOT/Safety Follow-up Visit (to occur approximately 30 days [± 7 days] after the last dose of study drug(s), or before the initiation of a new anticancer treatment, whichever occurs first). In addition, safety follow-up also includes telephone contacts with patients treated with tislelizumab in Cohort 2, which should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 days (±14 days) and 90 days (±14 days) after the last dose of study drug(s), regardless of whether or not the patient starts a new anticancer therapy. If patients in Cohort 2 report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

Patients who discontinue treatment for any reason in the long-term extension period will be asked to return to the clinic for the EOT/Safety Follow-up Visit (to occur approximately 30 days [± 7 days] after the last dose of study drug[s]). In addition, safety follow-up also includes

telephone contacts with patients treated with tislelizumab in Cohort 2, which should be conducted to assess imAEs and concomitant medications, if appropriate (ie, associated with an imAE), at 60 days (±14 days) and 90 days (±14 days) after the last dose of study drug(s). If patients in Cohort 2 report a suspected imAE at a telephone follow-up contact, the investigator should arrange an unscheduled visit if further assessment is indicated.

All AEs, including SAEs, will be collected as described in Section 8.6.

Patients who discontinue study treatment prior to disease progression will have their tumors assessed as outlined in Section 7.1.5.

See Appendix 1 for assessments to be performed at the EOT/Safety Follow-up Visit.

3.5. Survival Follow-up

Patients who discontinue study drug for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments according to Section 7.1.5 and the Schedule of Assessments (Appendix 1), until the patient experiences disease progression, withdraws consent, loss to follow-up, death, or until the study completes or terminates, whichever occurs first.

Patients will be followed for survival and further anticancer therapy information after discontinuation of study treatment via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (±14 days) after the EOT/Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor through the DCO date of the FA.

3.6. Long-Term Extension Period

After the DCO date of the FA, the Protocol Amendment 3.0 will be implemented and only the patients who remain on treatment or are in the safety follow-up period will enter the long-term extension period.

The patients who remain on treatment will continue their treatments according to their previous schedule within this period. The patients in survival follow-up will end the study within this period. The patients who complete the safety follow-up within the long-term extension period will end the study.

Safety will be assessed continually by monitoring AEs, SAEs, and laboratory results. Vital signs, physical examinations, ECOG performance status changes, ECG results, echocardiograms/MUGAs, and other examinations will also be used for safety assessments.

Anticancer activity will also be evaluated by the investigator using RECIST Version 1.1. A radiological assessment of tumor response status will be performed every 12 weeks (± 7 days) according to the patient's previous schedule until disease progression, withdrawal of consent, death, or end of treatment, whichever occurs first.

The samples for the PK and immunogenicity analysis of ZW25 and tislelizumab, as well as the samples for biomarker analysis, will not be required within this period.

Within the long-term extension period, long-term survival follow-up and further anticancer therapy information will not be required.

See the study assessment and procedures within this period in Section 7.2.

See Appendix 1B for the schedule of assessments within this period.

3.7. Discontinuation From the Study Treatment or From the Study

3.7.1. Patient Discontinuation From Study Treatment

Patients have the right to discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a patient from study treatment at any time. Patients who discontinue study treatment for reasons other than progressive disease should be followed for assessments of preliminary anticancer activity (Section 7.1.5), safety (Section 7.1.4), and survival (Section 3.5), if possible.

The primary reason for discontinuation from study treatment should be documented on the appropriate electronic case report form (eCRF). Patients may discontinue study treatment for reasons, which include, but are not limited to, the following:

- Disease Progression
- AE
- Patient Decision
- Pregnancy
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she were to continue the study treatment
- Use of any concurrent anticancer systemic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other Country) herbal medicine and Chinese (or other Country) patent medicines] for the treatment of cancer)
- Patient noncompliance
  Investigative site staff should first counsel patients who are significantly noncompliant (eg, missing 2 treatment cycles) on the importance of study drug compliance and drug accountability. The investigator may, in consultation with the medical monitor, discontinue patients from treatment who are consistently noncompliant.

3.7.2. Patient Discontinuation From Study (End of Study for an Individual Patient)

Patients may discontinue from the study for reasons that include, but are not limited to, the following:

- Patient withdrawal of consent
- Death
- Lost to follow-up
- Study completion per protocol

3.8. End of Study

The end of study is defined as the timepoint when the last study patient has died, has become lost to follow-up, withdraws from the study, or completes safety follow-up, or until the sponsor decides to terminate or complete the study, whichever occurs first.

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early may include, but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory

The sponsor will notify each investigator if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT/Safety Follow-up Visit.

The investigators may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patients' interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the study.

4. STUDY POPULATION

The specific eligibility criteria for selection of patients are provided in Section 4.1 and Section 4.2. The sponsor will not grant any eligibility waivers.

4.1. Inclusion Criteria

Each patient eligible for participate in this study must meet all the following criteria:

1. Able to provide written informed consent and can understand and agree to comply with the requirements of the study and the schedule of assessments
2. Age ≥ 18 years on the day of signing the ICF (or the legal age of consent in the jurisdiction in which the study is taking place)
3. Able to provide blood and tumor tissue (for archival tumor tissue: formalin-fixed paraffin-embedded [FFPE] blocks or at least 12 unstained FFPE tumor specimen slides for retrospective confirmation of HER2 status and/or other biomarker analysis). Note: Patients may be permitted to be enrolled on a case-by-case basis after discussion with the sponsor's medical monitor if fewer than 12 unstained slides are provided.
    a. Patients who have no archival tumor tissue available must consent to provide fresh biopsy samples before receiving treatment, unless previously discussed with sponsor's medical monitor.
4. Disease diagnosis and prior treatment:
    a. Cohort 1 (the first-line breast cancer treatment cohort):
    - Female patients with histologically or cytologically confirmed unresectable, locally advanced, recurrent or metastatic adenocarcinoma of the breast and candidate for chemotherapy. Locally recurrent disease must not be amenable to resection with curative intent.
    - HER2 IHC 3+ or in situ hybridization positive on the archival tumor tissue or fresh biopsy sample. The most recently collected tissues are required if applicable. For patients who had anti-HER2 therapy in neoadjuvant or adjuvant setting, tumor tissue sample collected after completion of any prior anti-HER2 therapy is preferred. HER2 status determined (see details in Appendix 11) in the investigational site is acceptable. If HER2 status cannot be acquired in the investigational site, HER2 positivity must be confirmed in the sponsor designated central laboratory as study entry eligibility.
    - Have not received previous systemic anticancer therapy for locally advanced unresectable or metastatic disease (with the exception of one prior hormonal regimen for metastatic breast cancer which must be stopped with at least 14 days of washout period), including any approved or investigational EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy, antibody drug conjugate, checkpoint inhibitors, or more than one prior hormonal regimen for metastatic breast cancer.

If a patient receives hormonal therapy for metastatic breast cancer and is switched to a different hormonal therapy due to disease progression, this will be counted as two "regimens" and the patient is not eligible.

Note: Prior systemic treatment in neoadjuvant or adjuvant setting is permitted if the disease-free interval from completion of the systemic treatment (excluding hormonal therapy) to diagnosis of locally advanced recurrent or metastatic disease is ≥ 12 months. Prior trastuzumab with or without pertuzumab used in neoadjuvant or adjuvant setting is permitted.

b. Cohort 2 (the first-line gastric/gastroesophageal junction adenocarcinoma treatment cohort):

- Histologically or cytologically confirmed unresectable, locally advanced, recurrent or metastatic adenocarcinoma of the stomach or GEJ.
- HER2 IHC 3+ or HER2 IHC 2+ together with in situ hybridization positive on the archival tumor tissue or fresh biopsy sample. The most recently collected tissues are required if applicable. HER2 status determined (see details in Appendix 11) in the investigational site is acceptable. If HER2 status cannot be acquired in the investigational site, HER2 positivity must be confirmed in the sponsor designated central laboratory as study entry eligibility.
- Have not received previous systemic anticancer therapy for locally advanced unresectable or metastatic disease, including any approved or investigational EGFR or anti-HER2 agents or vaccines, cytotoxic chemotherapy or checkpoint inhibitors.

  Note: Prior systemic treatment in neoadjuvant or adjuvant setting will be permitted if the disease-free interval from completion of the systemic treatment to diagnosis of locally advanced recurrent or metastatic disease is longer than 6 months. Prior use of trastuzumab and/or pertuzumab is not allowed.

5. At least 1 measurable lesion as defined per RECIST Version 1.1

   Note: The target lesion(s) selected have not been previously treated with local therapy. OR The target lesion(s) selected that are within the field of prior local therapy have subsequently progressed as defined by RECIST Version 1.1.

6. ECOG Performance Status ≤ 1

7. Adequate organ function as indicated by the following laboratory values during screening:

   a. Patients must not have required blood transfusion or growth factor support ≤ 14 days before sample collection at screening for the following:

      i. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

      ii. Platelets ≥ 90 x 10^9/L

      iii. Hemoglobin ≥ 90 g/L or ≥ 5.6 mmol/L

b. Serum creatinine ≤ 1.5 x upper limit of normal (ULN), or estimated Glomerular Filtration Rate ≥ 60 mL/min/1.73 m^2 by Chronic Kidney Disease Epidemiology Collaboration Equation (Appendix 7)
c. Serum total bilirubin ≤ 1.5 x ULN (total bilirubin must be < 4 x ULN for patients with documented Gilbert's syndrome)
d. International normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 x ULN
e. Activated partial thromboplastin time ≤ 1.5 x ULN
f. AST and ALT ≤ 2.5 x ULN, or AST and ALT ≤ 5 x ULN for patients with liver metastases

8. Left ventricular ejection fraction (LVEF) ≥ 50% at baseline as determined by either echocardiogram or MUGA (echocardiogram is the preferred method) within 28 days before the first dose of study drug
9. Females of childbearing potential must have a negative urine or serum pregnancy test within 7 days of the first dose of study drug and must be willing to use a highly effective method of birth control for the duration of the study, and ≥ 7 months after the last dose of study drug(s). For Cohort 1 specifically, hormonal forms of contraception (oral, injectable, or implantable) are not allowed. See Appendix 5.
10. Non-sterile males in Cohort 2 must be willing to use a highly effective method of birth control for the duration of the study, and for ≥ 7 months after the last dose of study drug(s).

4.2. Exclusion Criteria

Patients who meet any of the following criteria are not eligible to enroll:

1. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
2. History of approved or investigative tyrosine kinase/HER inhibitors in any treatment setting
   a. except trastuzumab with or without pertuzumab used in neoadjuvant or adjuvant setting for Cohort 1
3. Active leptomeningeal disease, untreated or uncontrolled brain metastasis. Patients with equivocal findings or with confirmed brain metastases are eligible for enrollment provided that they are asymptomatic and radiologically stable without the need for corticosteroid treatment for ≥ 4 weeks before the first dose of study drug
4. Any active malignancy ≤ 2 years before the first dose of study drug, except for the specific cancer under investigation in this trial and any localized cancer that has been treated curatively (eg, resected basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix)
5. Any condition that required systemic treatment with either corticosteroids (> 10 mg daily of prednisone or equivalent) or other immunosuppressive medication ≤ 14 days before the first dose of study drug

Note: Patients who are currently or have previously been on any of the following steroid regimens are not excluded:

a. Adrenal replacement steroid (dose ≤ 10 mg daily of prednisone or equivalent)
b. Topical, ocular, intra-articular, intranasal, or inhaled corticosteroid with minimal systemic absorption
c. Short course (≤ 7 days) of corticosteroid prescribed prophylactically (eg, for contrast dye allergy) or for the treatment of a non-autoimmune condition (eg, delayed-type hypersensitivity reaction caused by contact allergen)

6. With history of interstitial lung disease, non-infectious pneumonitis or uncontrolled systemic diseases, including diabetes, hypertension, pulmonary fibrosis, acute lung diseases, etc.
7. With severe chronic or active infections requiring systemic antibacterial, antifungal or antiviral therapy.
8. A known history of HIV infection
9. Currently active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)
   Note: Patients with HBV DNA level < 500 IU/mL (or 2500 copies/mL) but with detectable hepatitis B surface antigen (HBsAg) or detectable HBV DNA are eligible for the study and should be managed per local treatment guidelines during anti-cancer treatment.
   Patients with a negative HCV antibody test at Screening or positive HCV antibody test followed by a negative HCV RNA test at Screening are eligible. The HCV RNA test will be performed only for patients testing positive for HCV antibody.
10. Any major surgical procedure ≤ 28 days before the first dose of study drug, except if the procedure is minimally invasive (for example, introduction of peripherally inserted central catheter)
11. Any of the following cardiovascular risk factors:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before the first dose of study drug
    b. Symptomatic pulmonary embolism ≤ 28 days before the first dose of study drug
    c. Any history of acute myocardial infarction ≤ 6 months before the first dose of study drug
    d. Any history of congestive heart failure meeting any New York Heart Association (NYHA) Classification II-IV (Appendix 6) ≤ 6 months before the first dose of study drug
    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before the first dose of study drug
    f. Any history of cerebrovascular accident ≤ 6 months before the first dose of study drug
    g. Inadequately controlled hypertension (ie, systolic blood pressure > 180 mmHg or diastolic blood pressure > 100 mmHg)

h. Any history of LVEF decline to below 50% during or after previous trastuzumab/pertuzumab neoadjuvant or adjuvant therapy
i. Has a QTc prolongation to > 450 millisecond (ms) in males and > 470 ms in females based on 12-lead ECG in triplicate.

12. A history of severe hypersensitivity reactions to other monoclonal antibodies
13. Has received any radiotherapy, hormonal therapy, immunotherapy (eg, interleukin, interferon, thymosin) or any investigational therapies within 28 days or 5 half-lives (whichever is shorter) of the first study drug administration. Exceptions may be considered for palliative radiotherapy to a limited field following consultation with the sponsor medical monitor.
14. Has received any herbal medicine or anti-tumor medicines used to control cancer within 14 days of the first study drug administration
15. Patients with toxicities (as a result of prior anticancer therapy) which have not recovered to baseline or stabilized. The following are exceptions: neuropathy (which must have resolved to ≤ Grade 2); congestive heart failure (which must have been ≤ Grade 1 in severity at the time of occurrence, and must have resolved completely); and specific laboratory abnormalities which are not considered a likely safety risk
16. Underlying medical conditions or alcohol or drug abuse or dependence that, in the investigator's opinion, will be unfavorable for the administration of study drug or affect the explanation of drug toxicity or AEs; or insufficient compliance during the study according to investigator's judgement
17. Concurrent participation in another therapeutic clinical trial, unless it is an observational (noninterventional) clinical study or during the follow-up period of an interventional study
18. History of exposure to the following cumulative doses of anthracyclines in adjuvant/neoadjuvant setting (for Cohort 1 only), meeting any one of the following criteria:

    a. doxorubicin or liposomal doxorubicin > 360 mg/m^2
    b. epirubicin > 720 mg/m^2
    c. mitoxantrone > 120 mg/m^2 and idarubicin > 90 mg/m^2
    d. Other anthracycline > the equivalent of 360 mg/m^2 of doxorubicin
    e. If more than 1 anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin.

19. Prior allogeneic stem cell transplantation or organ transplantation (for Cohort 2 only)
20. Active autoimmune diseases or history of autoimmune diseases that may relapse (for Cohort 2 only).

    Note: Patients with the following diseases are not excluded and may proceed to further screening:

    a. Controlled Type I diabetes
    b. Hypothyroidism (provided it is managed with hormone replacement therapy only)

c. Controlled celiac disease
d. Skin diseases not requiring systemic treatment (eg, vitiligo, psoriasis, alopecia)
e. Any other disease that is not expected to recur in the absence of external triggering factors

21. Was administered a live vaccine ≤ 4 weeks before the first dose of study drug (for Cohort 2 only)

    Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.

5. STUDY TREATMENT

5.1. Formulation, Packaging, and Handling

5.1.1. ZW25

ZW25 is supplied as either a liquid or lyophilized formulation. Both formulations are for IV administration.

Liquid ZW25 is supplied as a sterile, single-use, preservative-free, colorless to slightly yellow solution in a glass vial. Each vial of liquid ZW25 contains a nominal fill volume of 20 mL (300 mg). The final container is a 50 mL USP Type I glass vial with a gray Flurotec coated plug and yellow flip-off top seal.

Lyophilized ZW25 is supplied as a sterile, single-use, preservative-free, lyophilized powder in a glass vial. Each vial of lyophilized ZW25 contains 300 mg drug product. The final container is a 20 mL USP Type I glass vial with a gray Flurotec coated plug and yellow flip-off top seal.

Each Liquid or Lyophilized ZW25 vial will be packaged into a single carton box.

The contents of the label will be in accordance with all applicable local regulatory requirements. The study drug must be kept at the temperature condition as specified on the label.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the ZW25 Investigator's Brochure for other details regarding ZW25.

5.1.2. Tislelizumab

Tislelizumab is a monoclonal antibody formulated for IV injection in a single-use vial (20R glass, USP type I), containing a total of 100 mg of antibody in 10 mL of isotonic solution. Tislelizumab has been aseptically filled in single-use vials with a Flurotec-coated butyl rubber stopper and an aluminum cap. Each vial is packaged into a single carton box.

The contents of the label will be in accordance with all applicable local regulatory requirements. The study drug must be kept at the temperature condition as specified on the label.

Refer to the Pharmacy Manual for details regarding IV administration, accountability, and disposal. Please also refer to the Tislelizumab Investigator's Brochure for other details regarding Tislelizumab.

5.1.3. Chemotherapy Agents

Management (ie, handling, storage, administration, and disposal) of docetaxel, capecitabine and oxaliplatin will be in accordance with relevant local guidelines, prescribing information/summary of product characteristics. For further details, refer to the Pharmacy Manual for the respective chemotherapies.

5.2. Dosage, Administration, and Compliance

Dosing schedules for Cohort 1 and Cohort 2 are provided in Table 2 and Table 3, respectively. The first dose of study drug is to be administered within 2 calendar days of enrollment. All patients will be monitored continuously for AEs. Treatment modifications will be based on specific laboratory and AE criteria, as described in Section 5.5.

Table 2: Selection and Timing of Dose Administration for Each Patient in Cohort 1

Order of Administration	Study Drug	Dose (Route)	Initial 6 Treatment Cycles	Cycle 7 and Onward
First	ZW25	**Cohort 1a:** 30 mg/kg (intravenous) **Cohort 1b:** 1800 mg (intravenous)	Refer to Pharmaceutical Manual for details of ZW25 administration	Refer to Pharmaceutical Manual for details of ZW25 administration
Second	Docetaxel	75 mg/m^2 (intravenous)	Day 1 of each 21-day cycle, infusion over 1 hour	Day 1 of each 21-day cycle, infusion over 1 hour (optional[a])

[a] After Cycle 6, continuation of docetaxel treatment is at the discretion of the investigator.

Table 3: Selection and Timing of Dose Administration for Each Patient in Cohort 2

Order of Administration	Study Drug	Dose (Route)	Initial 6 Treatment Cycles	Cycle 7 and Onward
First	ZW25	**Cohort 2a:** 30 mg/kg (intravenous) **Cohort 2b:** 1800 mg (intravenous) (subject's body weight < 70 kg) or 2400 mg (intravenous) (subject's body weight ≥ 70 kg)	Refer to Pharmaceutical Manual for details of ZW25 administration	Refer to Pharmaceutical Manual for details of ZW25 administration
Second	Tislelizumab[a]	200 mg (intravenous)	Cycles 1 and 2: Day 2 of each 21-day cycle, infusion over 60 minutes (60-minute monitoring period before chemotherapy) Cycles 3 to 6: Day 1 of each 21-day cycle, infusion over 30 minutes (30-minute monitoring period before chemotherapy)	Day 1 of each 21-day cycle, infusion over 30 minutes (30-minute monitoring period before chemotherapy)

Third	Oxaliplatin	130 mg/m^2 (intravenous)	The duration of infusion follows local practice Cycles 1 and 2: Day 2 of each 21-day cycle Cycles 3 to 6: Day 1 of each 21-day cycle	Discontinue Treatment
Fourth	Capecitabine	1000 mg/m^2 (Oral)	Twice daily Cycles 1 and 2: from the evening of Day 2 to the morning of Day 16 of each 21-day cycle; Cycle 3 to 6: from the evening of Day 1 to the morning of Day 15 of each 21-day cycle	Twice daily, from the evening of Day 1 to the morning of Day 15 of each 21-day cycle (Optional[b])

[a] Reduction of tislelizumab infusion time from 60 minutes to 30 minutes is based on the 60-minute infusion time is well tolerated.
[b] After Cycle 6, continuation of capecitabine as maintenance treatment is at the discretion of the investigator.

For Cohort 1 and cycles 3 onwards in Cohort 2, study administration may expand to 2 days or longer in case any special situations (eg, when the administration is interrupted in the case of an infusion-related reaction).

5.2.1. ZW25

Prior to dosing with ZW25, all patients must receive prophylactic treatment for infusion-related reactions that includes a corticosteroid. The mandated regimen includes acetaminophen orally, diphenhydramine (or equivalent) orally or IV, and a corticosteroid (recommended dose of 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 patients who experience an infusion-related reaction despite initial premedication, additional prophylactic treatment may be added prior to subsequent doses, including an H2 blocker such as ranitidine.

ZW25 will be administered as an intravenous infusion on Day 1 of each 21-day cycle (once every 3 weeks). The dosing is based on the patient's actual body weight at baseline. Doses must be adjusted for patients who experience a ≥ 10% change in weight from baseline except for patients in Cohort 1b. Patient's weight must be measured during all relevant assessment windows as described in the schedule of assessments (Appendix 1).

Please refer to the Pharmacy Manual for infusion times. The infusion rate should not exceed 250 mL/hour. Patients who experience a Grade 1 or Grade 2 infusion reaction may resume infusion of drug at a reduced infusion rate (50% slower than initial rate). All patients should receive prophylactic treatment for infusion reactions prior to ZW25 dosing as outlined in Section 6.2.1.

5.2.2. Tislelizumab

For patients in Cohort 2, tislelizumab 200 mg will be administered on Day 2 for the first 2 cycles and on Day 1 of each 21-day cycle (once every 3 weeks) from Cycle 3 onward.

Tislelizumab will be administered by IV infusion through an IV line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter.

As a routine precaution, after infusion of tislelizumab on Day 2 of Cycle 1 and Cycle 2, patients must be monitored for at least 60 minutes afterward in an area with resuscitation equipment and emergency agents. From Cycle 3 onward, a ≥ 30-minute monitoring period is required in an area with resuscitation equipment and emergency agents.

The infusion for the first 2 cycles will be delivered over 60 minutes; if this is well tolerated, then the subsequent infusions may be administered over 30 minutes, which is the shortest time period permissible for infusion. Tislelizumab must not be concurrently administered with any other drug (refer to Section 6).

Guidelines for dose modification, treatment interruption, or discontinuation and for the management of imAEs and infusion-related reactions are provided in detail in Section 8.7 and Appendix 8. Refer to the Pharmacy Manual for detailed instructions on drug preparation, storage, and administration.

5.2.3. Chemotherapy Agents

Cohort 1

On or prior to Cycle 6, docetaxel 75 mg/m^2 will be administered as an IV infusion over 1 hour once every 3 weeks until disease progression, intolerable toxicity, or another criterion for treatment discontinuation is met. After Cycle 6, continuation of docetaxel treatment is at the discretion of the investigator. Please refer to the current docetaxel label for additional information.

Cohort 2

On or prior to Cycle 6, oxaliplatin 130 mg/m^2 will be administered intravenously once every 3 weeks and the duration of infusion follows the local practice; capecitabine 1000 mg/m^2 will be administered orally twice daily for 14 consecutive days during each 21-day cycle.

Capecitabine will be administered after the infusion of oxaliplatin. For the first 2 cycles, capecitabine will be dosed from the evening of Day 2 to the morning of Day 16 of each cycle; From Cycle 3 onward, capecitabine will be dosed from the evening of Day 1 to the morning of Day 15 of each cycle. On or prior to Cycle 6, capecitabine or oxaliplatin should only be discontinued for progressive disease or unacceptable toxicity, or another criterion for treatment discontinuation is met. After Cycle 6, oxaliplatin will be discontinued and continuation of capecitabine as maintenance treatment is at the discretion of the investigator. Please refer to the current oxaliplatin and capecitabine label for additional information.

5.3. Overdose or Incorrect Administration

Any overdose or incorrect administration of study drugs should be noted in the patient's chart and on the appropriate eCRF. AEs will be recorded on the AE eCRF, SAEs will follow process as described in Section 8.6.2. Supportive care measures should be administered as appropriate. Detailed definition is as follows:

- Tislelizumab: Overdose is defined as ≥ 600 mg of tislelizumab in a 24-hour period.

- ZW25: Incorrect administration is defined as actual dose administered ≥ 125% of the planned dose per cycle. Actual dose administered deviating ≤ ± 5% of the planned dose per cycle will be considered as dose variation, not protocol deviation.
- Chemotherapy: Incorrect administration is defined as actual dose administered ≥ 125% of the planned dose per cycle. For oxaliplatin and docetaxel, actual dose administered deviating ≤ ± 5% of the planned dose per cycle will be considered as dose variation, not protocol deviation. For capecitabine, actual daily dose administered 85% to 108% of the planned dose will be considered as dose variation, not protocol deviation.

5.4. Investigational Medicinal Product Accountability

The investigational medicinal products (IMPs) required for completion of this study (ZW25, tislelizumab) will be provided by the sponsor, as required by local or country-specific guidance. The investigational site will acknowledge receipt of IMPs. Any damaged shipments will be replaced.

Accurate records of all IMPs received, dispensed, returned, and disposed should be recorded on the site's Drug Inventory Log. Refer to the Pharmacy Manual for details of IMP management.

5.5. Dose Delay or Modification

Every effort should be made to administer the study drug(s) according to the planned dose and schedule. In the event of significant toxicities, dosing may be delayed and/or reduced based on the guidelines provided below. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

5.5.1. General Guidance Regarding Dose Delay or Modification

The severity of AEs will be graded according to the NCI-CTCAE Version 5.0. Please refer to following sections for the details of dose delay, interruption, or modification for the study drugs:

- ZW25 might be reduced or delayed as defined in Section 5.5.2;
- Tislelizumab might be delayed as defined in Section 5.5.3;
- Dose delay, interruption, or modifications for chemotherapy will be performed per local practice and per prescribing information according to the investigator's clinical judgment (see Section 5.5.4).

When several toxicities with different grades of severity occur at the same time, the dose modifications should be made according to the highest grade observed.

If, in the opinion of the investigator, a toxicity is considered to be due to one or two components (ie, ZW25, tislelizumab, or chemotherapy) of the study regimen, dose(s) of the component(s) should be delayed or modified in accordance with the guidelines below. The AE-related component(s) should be delayed until the AE was resolved to baseline or ≤ Grade 1 prior to administering the next dose of that component(s), with the exception of Grade 2 fatigue or other

AEs, which, in the opinion of the investigator, would not affect the safety evaluation of the study drug(s). Other component(s) may be administered if there is no contraindication.

- If the AE can resolve to baseline or ≤ Grade 1 within 8 days, the AE-related component(s) will be administered in the cycle. The administration of all components will be resynchronized at the subsequent cycle, which will be rescheduled according to the infusion date of last chemotherapy dose.
- If the AE cannot resolve to baseline or ≤ Grade 1 within 8 days in 1 cycle, the AE-related component(s) will be omitted and other component(s) will be administered as scheduled.
- If the AE can resolve to baseline or ≤ Grade 1 within 21 days, all the component(s) will be administered at the beginning of next planned cycle, which will be scheduled according to the infusion date of last chemotherapy dose.

If one or two drug(s) is discontinued permanently for reasons other than progressive disease, patients may continue receiving other drugs from treatment regimen per the study protocol or local practice. For Cohort 2, the exception is that oxaliplatin needs to be administered on the basis of capecitabine, while capecitabine can be continued with oxaliplatin permanently discontinued.

In case a patient is benefiting from ZW25 or tislelizumab while meeting the discontinuation criteria, resumption of ZW25 or tislelizumab may occur upon discussion and agreement with sponsor medical monitor.

5.5.2. Dose Delay or Modifications of ZW25

Dose modifications for ZW25-associated toxicity are presented in Table 4 below. The reason for dose decrease or delay must be recorded.

Up to 2 dose reductions per patient will be allowed, but the reduced dose cannot be lower than 20 mg/kg once every 3 weeks for Cohorts 1a and 2a; and cannot be lower than 50% of initial dose for Cohorts 1b and 2b. Once a dose has been reduced for a patient, all subsequent cycles should be administered at that dose, unless further dose reduction is required. Dose reescalation is not permitted.

The patients should resume ZW25 treatment after the AEs recover to baseline or ≤ Grade 1 (whichever is more severe) following the guidance in Section 5.5.1 and within 12 weeks after the last dose of ZW25. If the patient is unable to resume ZW25 within 12 weeks after the last dose of ZW25, then ZW25 should be permanently discontinued for the patient.

For patients who still cannot receive or tolerate treatment with dose reduction of ZW25 or refuse supportive treatment, study treatment should be permanently discontinued for recurrence of ≥ Grade 3 nausea, vomiting, diarrhea, or rash.

Table 4: Recommended Management and Potential Dose Modifications for ZW25-Associated Toxicity

Adverse Events Related to ZW25	Action for ZW25
Grade 1 or Grade 2 nausea and/or vomiting	• Consider initiation of an anti-emetic medication per institutional standards. • No dose modification of ZW25 is required.
Grade 3 nausea and/or vomiting	• Consider initiation of an anti-emetic medication per institutional standards. • Hold ZW25 until severity ≤ Grade 1 or pretreatment level, then resume at the same dose.
Grade 4 vomiting	• Consider initiation of an anti-emetic medication per institutional standards. • 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. • For Grade 4 vomiting lasting longer than 72 hours, permanently discontinue ZW25.
Grade 1 or Grade 2 diarrhea	• Oral hydration with fluids that contain water, salt and glucose. • Suggest oral loperamide 4 mg followed by 2 mg Q4H until no diarrhea or loose stool. • No dose modification of ZW25 is needed.
Grade 3 diarrhea	• Aggressive fluid hydration and clear liquid diet. • Loperamide 4 mg PO followed by 4 mg Q2H until resolution of diarrhea; consider octreotide 100 mcg or 150 mcg subcutaneously Q8H for patients with persistent diarrhea despite 48 hours of loperamide. If patients are refractory to loperamide, diphoxylate/atropine, and octreotide, gastroenterologist 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 reduce 1 dose level per investigator discretion. • For recurrent Grade 3 symptoms despite maximum use of loperamide, diphoxylate/atropine, and octreotide, dose reduction is mandatory. • For recurrent Grade 3 diarrhea lasting longer than 72 hours despite dose reduction of ZW25 and maximum use of loperamide, Lomotil, and octreotide, or non-compliance with maximum antidiarrheal therapy, permanently discontinue ZW25.

Adverse Events Related to ZW25	Action for ZW25
Grade 4 diarrhea	• Aggressive fluid hydration and clear liquid diet. • Loperamide 4 mg PO followed by 4 mg Q2H until resolution of diarrhea; consider diphoxylate/atropine alternating with loperamide; consider octreotide 100 or 150 mcg subcutaneously Q8H for subjects with persistent diarrhea despite 48 hours of loperamide. If subjects are refractory to loperamide, diphoxylate/atropine, 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 and reduce 1 dose level. • For Grade 4 diarrhea lasting longer than 72 hours, permanently discontinue ZW25. • For recurrent Grade 4 diarrhea, permanently discontinue ZW25.
Grade 1 or Grade 2 rash	• Consider initiation of a topical steroid as needed, per institutional standards. • No dose modification of ZW25 is needed.
Grade 3 rash	• Suggest initiation with topical steroid; if insufficient, consider oral corticosteroid. Wound care may be required for possible erosion and ulceration to prevent infection. • Consider analgesics for pain control if necessary, per institutional standards. • 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, ZW25 dosing must be reduced 1 dose level.
Grade 4 Rash	• Permanently discontinue ZW25.
Grade 1/2 Other ZW25-related AEs (other than AESIs)	• No dose modification of ZW25 is required.
Grade 3 Other ZW25-related AEs (other than AESIs)	• Hold ZW25 until severity ≤ Grade 1 or pretreatment level, then resume at the same dose.
Grade 4 Other ZW25-related AEs (other than AESIs)	• 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 (eg, Grade 4 hyponatremia) do not require ZW25 discontinuation. • For other Grade 4 AEs, permanently discontinue ZW25.

Abbreviations: Q2H, once every 2 hours; Q4H, once every 4 hours; Q8H, once every 8 hours.

[a] Up to 2 step-down dose levels of 25 and/or 20 mg/kg once every 3 weeks for patients in Cohorts 1a and 2a, dose reduction to 75% or 50% of initial dose for patients in Cohorts 1b and 2b, or an intermediate dose level of ZW25 will be allowed, but the reduced dose cannot be lower than 20 mg/kg once every 3 weeks for Cohorts 1a and 2a, and cannot be lower than 50% of initial dose for Cohorts 1b and 2b.

Dose delay or discontinuation of ZW25 for the management of left ventricular dysfunction, regardless of relationship to ZW25, is described in Table 5 below.

Table 5: Management of Left Ventricular Dysfunction

Left Ventricular Dysfunction (Regardless of Causality)	Action for ZW25
Symptomatic cardiac heart failure	• Discontinue ZW25
Absolute decrease in LVEF of ≥ 16 percentage points from pre-treatment baseline, or LVEF below 50% and absolute decrease of ≥ 10 percentage points below pretreatment baseline	• 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 ≥ 50% and the absolute decrease is ≤ 15 percentage points from baseline; otherwise, permanently discontinue

Abbreviation: LVEF, left ventricular ejection fraction.

5.5.3. Dose Delay or Modification of Tislelizumab

There will be no dose reduction for tislelizumab in this study.

Patients in Cohort 2 may temporarily suspend tislelizumab if they experience toxicity that is considered related to tislelizumab and requires a dose to be withheld. The patients should resume tislelizumab treatment as soon as possible after the AEs recover to baseline or ≤ Grade 1 (whichever is more severe) and within 12 weeks after last dose of tislelizumab. If the patient is unable to resume tislelizumab within 12 weeks after the last dose of tislelizumab, then the patient should be discontinued from treatment.

Dose modification related to imAEs and infusion-related reactions are described in Appendix 8 and Section 8.7.1, respectively.

5.5.4. Dose Delay, Interruption or Modifications of Chemotherapy Agents

Baseline body weight is used to calculate the required chemotherapy doses. Dose modifications are required if the patient's body weight changes by ≥ 10% from baseline (or the new reference body weight).

A maximum of 2 dose reductions per chemotherapeutic agent are permitted. If additional reductions are required, that chemotherapeutic agent must be discontinued. Once the dose has been decreased, it should remain reduced for all subsequent administrations or further reduced if necessary. There will be no dose re-escalations in this study.

In case of chemotherapy-related toxicity, chemotherapy will be delayed until recovery. ZW25 and/or tislelizumab should continue as scheduled. If AE is resolved within 8 days, chemotherapy will be administrated within the cycle and the administration of study drugs will be

resynchronized at the subsequent cycle according to the infusion date of last chemotherapy dose. If AE is not resolved within 8 days, chemotherapy will be omitted in this cycle and other component(s) will be administered as scheduled.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on chemotherapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the sponsor. The reason for interruption should be documented in the patient's study record. If patients are unable to resume chemotherapy within 6 weeks after the last dose of chemotherapy for unforeseen nondrug-related reasons, continued treatment may be allowed if approved by the medical monitor.

Patients may also discontinue chemotherapy following multiple cycles if, in the investigator’s judgment, cumulative toxicity is likely to increase over time and become problematic. Recommended guidance regarding dose modifications of chemotherapy for certain toxicities is presented in Appendix 10. For toxicities not listed, dose modifications are permitted per local standards.

6. CONCOMITANT MEDICATIONS AND THERAPY

6.1. Prior Therapy

The exclusion criteria (Section 4.2) specify that patients will not have received prior therapies with:

- anti-PD-1, anti-PD-L1, anti-PD-L2 or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways;
- approved or investigative tyrosine kinase/HER inhibitors (except trastuzumab with or without pertuzumab used in neoadjuvant or adjuvant setting for Cohort 1)
- History of exposure to the following cumulative doses of anthracyclines in adjuvant/neoadjuvant (for Cohort 1 only), meeting any one of the following criteria:
  a. doxorubicin or liposomal doxorubicin > 360 mg/m^2
  b. epirubicin > 720 mg/m^2
  c. mitoxantrone > 120 mg/m^2 and idarubicin > 90 mg/m^2
  d. other anthracycline > the equivalent of 360 mg/m^2 of doxorubicin
  e. if more than 1 anthracycline has been used, the cumulative dose must not exceed the equivalent of 360 mg/m^2 of doxorubicin.

6.2. Concomitant Therapy

6.2.1. Required Concomitant Medications

6.2.1.1. Prophylactic Treatment for Infusion-Related Reactions

Prior to dosing with ZW25, all patients must receive prophylactic treatment for infusion-related reactions that includes a corticosteroid. The mandated regimen includes acetaminophen orally, diphenhydramine (or equivalent) orally or IV, and a corticosteroid (recommended dose of 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 patients who experience an infusion-related reaction despite initial premedication, additional prophylactic treatment may be added prior to subsequent doses, including an H2 blocker such as ranitidine.

6.2.1.2. Prophylactic Treatment for Diarrhea (Cohort 2 Only)

Subjects receiving CAPOX chemotherapy in any combination regimen are required to receive anti-diarrheal prophylaxis with loperamide 4mg BID starting on the same day of chemotherapy treatment and continuing at least 7 days, unless subjects develop significant constipation (no bowel movement for 48 hours). Subjects with any grade of diarrhea at the end of 7 days should continue on loperamide and consult with the treating investigator for further guidance. After cycle 1, loperamide prophylaxis is at the discretion of the investigator. However, if subjects developed grade 2 or greater diarrhea during cycle 1 of therapy, prophylaxis should be continued with subsequent cycles. Detailed guidance of diarrhea management can be found in Section 5.5.2 (Table 4) and Appendix 10.

6.2.1.3. Prophylactic Granulocyte Colony-Stimulating Factor for Neutropenia/Neutrophil Count Decreased (Cohort 1 Only)

Prophylactic granulocyte colony-stimulating factor (G-CSF) could be considered for patients receiving docetaxel in Cohort 1 at the discretion of the investigator or per local/institutional guidance.

- **Filgrastim**
  - Dosage and administration: daily dosage of 5 μg/kg or follow the label, subcutaneous injection.
  - Timing: start on the next day or up to 3-4 days after completion of docetaxel and treat until post-nadir Absolute Neutrophil Count (ANC) recovery to normal or near-normal levels by laboratory standards or follow the label.
- **Pegfilgrastim**
  - Dosage and administration: 1 dose of 6 mg or follow the label, subcutaneous injection.
  - Timing: The day after (> 24 hours) completion of docetaxel or follow the label. Do not administer between 14 days before and 24 hours after administration of docetaxel.

6.2.2. Permitted Concomitant Medications/Procedures

Most concomitant medications and therapies deemed necessary and in keeping with local standards of medical care at the discretion of the investigator for supportive care (eg, anti-emetics, antidiarrheals) and in a patient's interest are allowed.

All concomitant medications received within 30 days before the first dose of study drug and 30 days after the last dose of study drug should be recorded.

According to NCCN 2019 guidelines (https://www.nccn.org/), erythropoiesis-stimulating agents (ESAs) may be considered for the treatment of cancer-related anemia in patients undergoing palliative treatment. Erythropoietic therapy may be considered for treatment of chemotherapy-induced anemia in cases where hemoglobin is < 11 g/dL or a decrease of ≥ 2 g/dL from baseline, but only after the patient has been counseled about the risks and benefits of ESA use.

The use of prophylactic medication such as magnesium/calcium infusions or others for prevention of oxaliplatin-induced neuropathy is at the discretion of the investigator; however, these treatments are not recommended for use in this study, as their benefits have not been clearly established.

As a precautionary measure, it is recommended, but not strictly required, that if patients require placement of a central venous access device (CVAD), that procedure should be done 7 days prior to first study treatment start. The date of CVAD placement should be noted in the medical record and recorded in the eCRF. Episodes of CVAD replacement should be recorded, as should CVAD-related thrombosis, infection, or dysfunction.

For patients treated with tislelizumab in Cohort 2, systemic corticosteroids given for the control of imAEs must be tapered gradually (see Appendix 8) and be at non-immunosuppressive doses

(≤ 10 mg/day of prednisone or equivalent) before the next tislelizumab administration. The short-term use of steroids as prophylactic treatments (eg, patients with contrast allergies to diagnostic imaging contrast dyes) is permitted.

Palliative (limited-field) radiation therapy is permitted, but only for pain control or prophylaxis of bone fracture to sites of bone disease present at baseline provided the following criteria are met:

- Repeat imaging demonstrates no new sites of bone metastases
- The lesion being considered for palliative radiation is not a target lesion for RECIST Version 1.1
- The case is discussed with the medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met

Additionally, palliative radiation or other focally ablative therapy for other non-target sites of the disease is permitted if clinically indicated per investigators' discretion and after consultation with the medical monitor. Whenever possible, these patients should have a tumor assessment of the lesion(s) before receiving the radiotherapy in order to rule out progression of disease. It is not required to withhold study treatment during palliative radiotherapy.

6.2.3. Prohibited Concomitant Medications/Procedures

The following medications are prohibited during the study:

- Any concurrent antineoplastic systemic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including Chinese (or other Country) herbal medicine] for the treatment of cancer) is not allowed.
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or that are known to potentially interfere with liver or other major organ functions (eg, hypericin). Patients must notify the investigator of all herbal remedies used during the study.
- Any oral, injected or implanted hormonal methods of contraception (for Cohort 1 only).
- Live vaccines within 28 days before first dose of tislelizumab and 60 days following the last dose of tislelizumab (for Cohort 2 only).

6.2.4. Restricted Concomitant Medications/Procedures

The following medications are restricted during the study:

- Immunosuppressive agents (except to treat a drug-related AE).
- Systemic corticosteroids > 10 mg daily (prednisone or equivalent), except the protocol required premedication as prophylactic treatment for infusion-related reactions (Section 6.2.1), to treat or control a drug-related AE (per protocol) or for other short-term use as prophylactic treatment.
- Patients should not abuse alcohol or other drugs during the study.

- Use of potentially hepatotoxic drugs in patients with impaired hepatic function should be carefully monitored.
- Radiation therapy is not allowed, except for palliative radiation therapy described in Section 6.2.2.

Opiates and other medication required for palliative management of patients are allowed. Patients must notify the investigator of all concurrent medications used during the study.

For patients who receive docetaxel in Cohort 1, any medications that have significant interactions with docetaxel (eg, substrates or inhibitors of the cytochrome P450 isoenzymes CYP3A4) should be avoided. Refer to the manufacturer's prescribing information for complete information regarding drug-drug interactions.

Phenytoin has been observed to have toxicity associated with elevated phenytoin concentrations in patients concomitantly taking capecitabine. Concentrations of phenytoin should be carefully monitored in patients taking capecitabine in Cohort 2 and phenytoin.

Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. Caution should be exercised with use of coumarin-derivative anticoagulants in the patients participating in Cohort 2 of this study.

6.3. Potential Interactions Between the Study Drug and Concomitant Medications

The potential for drug-drug interaction between the investigational drugs (ZW25 and tislelizumab) and standard chemotherapy is low. Because ZW25 and tislelizumab are therapeutic monoclonal antibodies, which are expected to be degraded into amino acids and recycled into other proteins, it is unlikely to have an effect on drug metabolizing enzymes or transporters.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Study Period Through the Data Cutoff Date of the Final Analysis

A table of scheduled study assessments is provided in Appendix 1A for this period. Patients will be closely monitored for safety and tolerability within this period. All assessments must be performed and documented in the medical record for each patient.

Dosing will occur only if the clinical assessment and local laboratory test values (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

7.1.1. Screening

Screening evaluations will be performed within 28 days prior to the first dose of study drug. Patients who agree to participate will sign the ICF prior to undergoing any screening procedure. The screening period begins on the first day that a screening procedure is conducted. Screening evaluations may be repeated as needed within the screening period; the investigator is to assess preliminary patient eligibility according to the latest screening assessment results.

Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first dose of study drug may be used for the purposes of screening rather than repeating the standard-of-care tests unless otherwise indicated.

Procedures conducted during the Screening Visit only are described in this section. For the description of other assessments that are conducted during screening as well as throughout the study, refer to Safety Assessments (Section 7.1.4), Tumor and Response Evaluations (Section 7.1.5), PK and antidrug antibody (ADA) Assessments (Section 7.1.6) and Biomarkers (Section 7.1.7) sections.

Rescreening under limited conditions may be allowed after consultation with BeiGene, eg, when a patient's laboratory result narrowly miss laboratory criterion and it is correctable and not due to rapidly deteriorating condition or disease progression. Rescreening is allowed only once.

7.1.1.1. Informed Consent and Screening Log

Voluntary, written informed consent for participation in the study must be obtained before performing any study-specific procedures. Informed consent forms for enrolled patients and for patients who are screened but not enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the first dose of study drug. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

7.1.1.2. Pulmonary Function Tests

Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will undergo pulmonary function testing which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the Screening period to assist the determination of suitability on the study.

7.1.2. Confirmation of Eligibility

The investigator is responsible for ensuring that each patient meets the eligibility criteria for this study. The investigator will assess and confirm the eligibility of each patient. All results from the screening procedures and relevant medical history must be available before eligibility can be determined. All inclusion criteria must be met and none of the exclusion criteria may be met. No eligibility waivers will be granted.

After a patient is screened and the investigator determines that the patient is eligible, study site personnel will complete the Treatment Eligibility Form (TEF) by transcribing information on inclusion/exclusion criteria, significant medical history, concomitant medications, disease history, pathology diagnosis, information from relevant imaging reports (as applicable), prior anticancer therapies, and screening safety laboratory results requested in the TEF.

To confirm eligibility, the TEF will be sent by the site to the medical monitor or designee, via secure transmission, for review during the screening period. Per the patient privacy/confidentiality provisions in this protocol, the TEF should be coded with the patient's screening ID number to protect the patient's personal data in accordance with local laws and regulations and BeiGene requirements (eg, direct identifiers such as names, initials, and full date of birth should never be shared, and personal data not specifically required by the protocol should never be included or otherwise provided).

The medical monitor will review the TEF and confirm the investigator has accurately assessed that all inclusion criteria have been met and none of the exclusion criteria apply and communicate their conclusion to the site. If the medical monitor raises concerns about the eligibility of a potential patient or the contents of the TEF, the investigator is responsible for reviewing and responding to the medical monitor's concerns and/or correcting the contents of the TEF, as appropriate. A patient cannot be started on study drug until confirmation of eligibility from the medical monitor or designee is received by the site. The site is responsible for filing the confirmation according to each site's policy.

7.1.3. Drug Dispensation

ZW25, tislelizumab, and chemotherapy will be dispensed and administered as described in Section 5.2.

7.1.4. Safety Assessments

7.1.4.1. Vital Signs

Vital signs will include measurements of temperature (˚C), pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes.

Height (baseline only) and weight should be measured and recorded in the eCRF.

For Cohort 1, in the first 2 cycles, vital signs should be collected within 60 minutes before the infusion of the ZW25, during and within 30 minutes after the infusion of the ZW25. In the subsequent cycles, vital signs should be collected within 60 minutes before infusion of ZW25, and as clinically indicated during or after the infusion of ZW25.

For Cohort 2, in the first 2 cycles, vital signs should be collected within 60 minutes before the infusion of the ZW25, during and within 30 minutes after the infusion of the ZW25 on Day 1, and before the infusion of the tislelizumab, during and within 30 minutes after the infusion of the tislelizumab on Day 2. In the subsequent cycles, vital signs should be collected within 60 minutes before infusion of ZW25, within 60 minutes before infusion of tislelizumab and as clinically indicated during or after the infusion of both agents.

7.1.4.2. Physical Examinations

During the Screening Visit, a complete physical examination will be conducted, including evaluations of 1) head, eyes, ears, nose, and throat; 2) cardiovascular; 3) dermatological; 4) musculoskeletal; 5) respiratory; 6) gastrointestinal; and 7) neurological systems. Any abnormality identified during screening will be graded according to NCI-CTCAE Version 5.0 and recorded on the eCRF with appropriate disease/condition terms.

At subsequent visits (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities are to be recorded as AEs on the eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.1.4.3. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (Appendix 3) will be assessed within this period.

7.1.4.4. Laboratory Safety Tests

Local laboratory assessments of serum chemistry, hematology, coagulation, urinalysis, and thyroid function (only for patients in Cohort 2) will be conducted, of which certain elements will be collected as specified in Appendix 2.

If laboratory tests at screening are not performed within 7 days prior to the administration of study drug(s) on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug(s) administration. Hematology and serum chemistry (including liver function tests) as specified in Appendix 2 should be performed weekly for the first 2 cycles and at the beginning of subsequent cycles. After Cycle 1, laboratory tests should be performed and results are to be reviewed within 72 hours before study drug(s) administration. Coagulation and urinalysis are to be conducted if clinically warranted during the treatment period and at the EOT/Safety Follow-up Visit. Thyroid function tests (analysis of free triiodothyronine, free thyroxine, and thyroid stimulating hormone) for patients in Cohort 2 will be performed at screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc.), and at the EOT/Safety Follow-up Visit.

Details about sample collection and shipment will be provided in a separate instruction manual. Investigators may use results from local laboratories for assessing eligibility, safety monitoring and dosing decision.

7.1.4.5. Electrocardiograms

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the patient's permanent study file at the site.

Patient should rest in semi-recumbent supine position for at least 10 minutes prior to ECG collection.

7.1.4.6. Echocardiogram/Multiple Gated Acquisition Scan

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 5.5.2. If deterioration of LVEF is observed, then echocardiogram/MUGA should be performed at a higher frequency as clinically indicated.

7.1.4.7. Adverse Events

AEs will be graded and recorded throughout the study according to NCI-CTCAE Version 5.0. Characterization of toxicities will include severity, duration, and time to onset.

All AEs, including SAEs, will be collected as described in Section 8.6.

7.1.4.8. Hepatitis B and C Testing

Testing will be performed by a local laboratory at screening (and as clinically indicated) and will include HBV/HCV serology (HBsAg, hepatitis B surface antibody [HBsAb], hepatitis B core antibody [HBcAb], and HCV antibody).

7.1.4.9. Cardiac Enzyme Monitoring

Serum creatinine kinase (CK) and creatine kinase-muscle/brain (CK-MB) will be performed for all patients in both cohorts (see Appendix 1 for the blood collection schedule). Serum troponins may be used substituted per local guidelines if used consistently throughout the study.

7.1.5. Tumor and Response Evaluations

Tumor imaging will be performed ≤ 28 days before the first dose of study drug. Results of standard-of-care tests or examinations performed prior to obtaining written informed consent and ≤ 28 days before the first dose of study drug may be used for the purposes of screening rather than repeating the standard-of-care tests. During the study, tumor imaging will be performed every 6 weeks (± 7 days) from Cycle 1 Day 1 for the first 36 weeks, then every 12 weeks (± 7 days) thereafter until disease progression, withdrawal of consent, death, or start of a new anticancer therapy, whichever occurs first.

Screening assessments and each subsequent assessment of the tumor must include the computed tomography (CT) scans (with oral/intravenous contrast, unless contraindicated) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc).

All measurable and evaluable lesions should be assessed and documented at the Screening Visit and reassessed at each subsequent tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

- Imaging of the brain (preferably MRI or CT) at baseline is required for all screened patients. Screening evaluations will be performed ≤ 28 days before the first dose of study drug.
- If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the study, a non-contrast CT of the chest plus a contrast-enhanced MRI (if possible) of abdomen and pelvis should be performed.
- If a CT scan for tumor assessment is performed on a positron-emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards of a diagnostic CT scan.
- Bone scans (Technetium-99m [TC-99m]) or PET should be performed at screening if clinically indicated. If bone metastases are present at screening and cannot be seen on CT or MRI scans, TC-99m or PET bone scans should be repeated when a CR is suspected in target lesion or when progression in bone is suspected.
- CT scans of the neck or extremities should be performed at screening, only if clinically indicated, and followed throughout the study, if there is evidence of metastatic disease in these regions at screening.
- At the investigator's discretion, other methods of assessment of target lesion and non-target lesions per RECIST Version 1.1 may be used.

Response will be assessed by the investigator using RECIST Version 1.1 (Appendix 9). The same evaluator should perform assessments, if possible, to ensure internal consistency across visits.

After first documentation of response (CR or PR), confirmation of tumor response should occur at 4 weeks or later after the first response or at the next scheduled assessment timepoint.

For immune therapies such as patients treated with tislelizumab in Cohort 2, pseudoprogression may occur due to immune-cell infiltration and other mechanisms leading to apparent increase of existing tumor masses or appearance of new tumor lesions. Also, some patients may benefit from additional immune therapies despite evidence of disease progression. Thus, if radiographic progressive disease is suspected by the investigator to reflect pseudoprogression, patients in Cohort 2 may continue treatment with study drug(s) until progressive disease is confirmed by repeated imaging ≥ 4 weeks later (but not exceeding 6 to 8 weeks from the date of initial documentation of progressive disease). The following criteria must be met to treat patients with suspected pseudoprogression or confirmed evidence of disease progression:

- Absence of clinical symptoms and signs of disease progression (including clinically significantly worsening of laboratory values)
- Stable ECOG Performance Status ≤ 1
- Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (eg, cord compression) that requires urgent alternative medical intervention
- Investigators must obtain written informed consent for treatment beyond radiologic disease progression and inform patients that this practice is not considered standard in the treatment of cancer.

- The decision to continue study drug(s) beyond initial investigator-assessed progression must be agreed with the sponsor medical monitor and documented in the study records. If patients receive study drugs beyond initial progressive disease per RECIST 1.1, tumor assessment should continue as planned schedule until study treatment discontinuation.

Patients who discontinue study treatment early for reasons other than disease progression (eg, toxicity) will continue to undergo tumor assessments following the original plan until the patient begins a subsequent anticancer therapy, experiences disease progression, withdraws consent, is lost to follow-up, dies, or until the study terminates or completes, whichever occurs first.

Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held.

7.1.6. Pharmacokinetic Assessment and Antidrug Antibody Testing

Blood will be collected to characterize the PK and ADA of ZW25 (and tislelizumab, if applicable). Blood sampling for PK assessment and ADA testing will be collected at the timepoints specified in the Schedule of Assessments (Appendix 1). The actual collection date and time of each blood sample will be recorded. The timing of PK and ADA samples may be altered and/or PK and ADA samples may be obtained at additional timepoints upon sponsor approval to ensure thorough PK and ADA monitoring.

For ZW25 PK characterization, serial blood samples will be collected during treatment cycle 1/2 for up to 10 patients enrolled in Cohort 1a, up to 6 patients from Cohort 1b, up to the first 6 patients enrolled in the safety lead-in period of Cohort 2a, and up to 6 patients from Cohort 2b (see the full details in Appendix 1C. For the remaining patients in both cohorts, please see the full details in Appendix 1D for ZW25 PK characterization.

As therapeutic monoclonal antibodies, both ZW25 and tislelizumab may elicit endogenous immune response. To evaluate the incidences of immunogenicity, sparse blood samples will be collected at specified cycles for all patients in order to evaluate anti-ZW25-antibody and paired ZW25 PK (and also anti-tislelizumab-antibody and its paired PK, applicable for patients in Cohort 2, details please see Appendix 1E).

Shipping, storage, and handling of samples will be managed through a central laboratory. The serum concentrations of ZW25 (or tislelizumab) and the presence of anti-ZW25 antibodies (or anti-tislelizumab antibodies) will be tested using validated immunoassays. Full details on sample collection, processing, storage, and shipment will be provided in the laboratory manual.

7.1.7. Biomarkers

Shipping, storage, and handling of blood as well as archival tumor and/or fresh tumor tissue for the assessment of biomarkers will be managed through a central laboratory. Refer to the laboratory manual for details of sample handling.

Patients must have documented HER2-positive disease by overexpression and/or gene amplification as determined by investigators or central laboratory, using the archival tumor tissue or fresh biopsy sample. The most recently collected tissues are required if applicable. For patients in Cohort 1 who had anti-HER2 therapy in neoadjuvant or adjuvant setting, tumor tissue

sample collected after completion of any prior anti-HER2 therapy is preferred. For patients whose HER2 status cannot be acquired in an investigational site, HER2 positivity must be confirmed in the sponsor designated central laboratory as study entry eligibility. If a patient's tumor is tested locally for HER2 status and other biomarkers of interest, these historical testing results may be collected.

Archival tumor tissue (FFPE blocks or at least 12 unstained FFPE tumor specimen slides) must be provided for retrospective confirmation of HER2 status and/or other biomarker analyses. Other biomarker analyses include, but not limited to, PD-L1 expression, presence of TILs, gene expression profiling and/or tumor gene alterations (including gene mutation, TMB, and MSI status) (in Mainland China, only the biomarkers specified above will be tested on FFPE samples collected).

A fresh biopsy of an accessible tumor lesion is required at screening (within 28 days prior to the first dose of study drug) in the absence of archival tumor tissue, unless previously discussed with sponsor's medical monitor. Optional tumor biopsies will also be obtained at the time of disease progression in consenting patients to evaluate the resistance mechanisms.

Tumor tissue should be of good quality based on total and viable tumor content. Fine-needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Acceptable fresh biopsy samples include core needle biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written informed consent is required prior to fresh tumor biopsies. The code and unique identifier (block ID) of tissue sample will be collected to make sure the tissue sample submitted can be traced back.

Peripheral blood samples will also be collected from all patients at baseline (predose at Day 1 of Cycle 1), Day 1 of Cycle 3 (predose) and at EOT/Safety Follow-up Visit to explore the association of blood-based biomarkers with response, prognosis and resistance to ZW25 in combination with docetaxel or ZW25 in combination of tislelizumab and chemotherapy. Such assessments will include, but are not limited to, germline mutations, CNAs and serum HER2 levels (in Mainland China, only the biomarkers specified above will be tested on blood samples collected). Blood samples will be individually processed and stored as described in the Laboratory Manual.

Archived samples with coding may be used for additional medical and/or scientific research projects that are outside of the current study purpose and objectives (but always in compliance with applicable law). These research projects may relate to the diseases that are the subject of this study, validation of new techniques/assays and/or associated potential medicines. This may include research to help develop ways to detect, monitor or treat the disease that is the subject of this study.

7.1.8. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see Appendix 1). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment

administration (Day 1) of each cycle should be performed before study treatment infusion/dose unless otherwise noted. Laboratory results must be reviewed prior to dosing.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled for the nearest feasible date (the visit window is provided in Appendix 1), with subsequent visits conducted according to the planned schedule every 3 weeks from infusion date of last chemotherapy dose.

7.1.9. Unscheduled Visits

Unscheduled visits may be performed at any time at the patient's or the investigator's request and may include vital signs/physical examination; ECOG Performance Status; AE review; concomitant medications and procedures review; radiographic assessments; physical examination of liver, spleen, and lymph nodes; disease-related constitutional symptoms; hematology and clinical chemistry laboratory assessments; ECG, and echocardiogram/MUGA. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on the investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

7.2. Long-Term Extension Period

After the DCO date of the FA, the patients who remain on treatment will continue their treatments and will be monitored for safety, tolerability, and antitumor activity according to their previous schedule within this period.

A table of scheduled study assessments is provided in Appendix 1B. Patients will be continually monitored for safety and tolerability within this period. All assessments must be performed and documented in the medical record for each patient. Dosing will occur only if the clinical assessment and local laboratory test values (that must be available before any dosing) have been reviewed and found to be acceptable per protocol guidelines.

7.2.1. Drug Dispensation

ZW25, tislelizumab, and chemotherapy will be dispensed and administered as described in Section 5.2.

7.2.2. Safety Assessments

7.2.2.1. Vital Signs

Vital signs will include measurements of temperature (˚C), pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position, after resting for 10 minutes. Weight should be measured and recorded in the eCRF. For Cohort 1, vital signs should be collected within 60 minutes before infusion of ZW25, and as clinically indicated during or after the infusion of ZW25.

For Cohort 2, vital signs should be collected within 60 minutes before infusion of ZW25, within 60 minutes before infusion of tislelizumab and as clinically indicated during or after the infusion of both agents.

7.2.2.2. Physical Examinations

At every visit (and as clinically indicated), limited, symptom-directed physical examinations will be performed. New or worsened clinically significant abnormalities are to be recorded as AEs on the eCRF. Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

7.2.2.3. Eastern Cooperative Oncology Group Performance Status

ECOG Performance Status (Appendix 3) will be assessed within this period.

7.2.2.4. Laboratory Safety Tests

Local laboratory assessments of serum chemistry, hematology, coagulation, urinalysis, and thyroid function (only for patients in Cohort 2) will be conducted, of which, certain elements will be collected as specified in Appendix 2.

Laboratory tests should be performed and results are to be reviewed within 72 hours before study drug(s) administration. Coagulation and urinalysis are to be conducted if clinically warranted during the treatment period and at the EOT/Safety Follow-up Visit. Thyroid function tests (analysis of free triiodothyronine, free thyroxine, and thyroid stimulating hormone) for patients in Cohort 2 will be performed every 12 weeks, and at the EOT/Safety Follow-up Visit. Details about sample collection and shipment will be provided in a separate instruction manual. Investigators may use results from local laboratories for assessing eligibility, safety monitoring, and dosing decision.

7.2.2.5. Electrocardiogram and Echocardiogram/Multiple Gated Acquisition Scan

Refer to Section 7.1.4.5 and Section 7.1.4.6.

7.2.2.6. Adverse Events

Refer to Section 7.1.4.7.

7.2.2.7. Hepatitis B and C Testing

Testing will be performed by a local laboratory as clinically indicated.

7.2.2.8. Cardiac Enzyme Monitoring

Serum creatinine kinase (CK) and creatine kinase-muscle/brain (CK-MB) will be performed for all patients in both cohorts (see Appendix 1B for the blood collection schedule). Serum troponins may be used substituted per local guidelines if used consistently throughout the study.

7.2.3. Tumor and Response Evaluations

Within this period, tumor imaging will be performed every 12 weeks (± 7 days) according to the patient's previous schedule, until disease progression, withdrawal of consent, death, or end of treatment, whichever occurs first. Each subsequent assessment of the tumor must include the CT scans (with oral/intravenous contrast, unless contraindicated) or MRI of the chest, abdomen, and pelvis. Other known or suspected sites of disease must be included in the imaging assessments (neck, brain, etc). All measurable and evaluable lesions should be assessed and documented at

each tumor evaluation. The same radiographic procedure used to assess disease sites at screening must be used throughout the study (eg, the same contrast protocol for CT scans).

Tumor assessments are required to be performed on schedule regardless of whether study treatment has been administered or held.

See the details in Section 7.1.5.

7.2.4. Pharmacokinetic Assessment and Antidrug Antibody Testing

Samples for the PK and immunogenicity analysis of ZW25 and tislelizumab will not be required within this period.

7.2.5. Biomarkers

Samples for biomarker analysis will not be required within this period.

7.2.6. Visit Windows

All visits must occur within ± 3 days from the scheduled date, unless otherwise noted (see Appendix 1B). All assessments will be performed on the day of the specified visit unless an acceptable time window is specified. Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed before study treatment infusion/dose, unless otherwise noted. Laboratory results must be reviewed prior to dosing. If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the visit should be scheduled for the nearest feasible date, with subsequent visits conducted according to the planned schedule every 3 weeks from the infusion date of the last chemotherapy dose.

7.2.7. Unscheduled Visits

Refer to Section 7.1.9.

8. SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

8.1. Risks Associated With Study Drug

8.1.1. Risks Associated With ZW25

ZW25 is an investigational agent that is currently in clinical development. Limited safety data in patients are available, and the full safety profile has not been characterized. Diarrhea and infusion-related reactions are identified risks based on the results from nonclinical and preliminary clinical data from clinical studies with ZW25.

The following potential risks are suggested based on the results from nonclinical and preliminary clinical data from clinical studies with ZW25 and published data on other drugs of similar mechanisms of action.

- Left ventricular ejection fraction decrease
- Embryo-fetal toxicity
- Pulmonary toxicity
- Exacerbation of antineoplastic therapy-induced neutropenia

8.1.2. Risks Associated With Tislelizumab

Tislelizumab is an investigational agent that is currently in clinical development. The following recommendation is based on results from nonclinical and clinical studies with tislelizumab and published data on other molecules within the same biologic class.

The programmed cell death protein ligand-1 (PD-L1)/PD-1 pathway is involved in peripheral immune tolerance; therefore, such therapy may increase the risk of imAEs, specifically the induction or enhancement of autoimmune conditions. Immune-mediated AEs observed with anti-PD-1 therapy are presented in Section 8.7.3.

Although most imAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Suggested evaluation and management guidelines for suspected imAEs are provided in Appendix 8.

8.1.3. Risks Associated With Chemotherapy Agents

Refer to the most recent, locally approved prescribing information for information on the risk associated with docetaxel, capecitabine, and oxaliplatin, respectively.

8.2. General Plan to Manage Safety Concerns

8.2.1. Eligibility Criteria

Eligibility criteria were selected to guard the safety of patients in this study. Results from the nonclinical toxicology studies and clinical data with ZW25 and tislelizumab, as well as the

nonclinical/clinical data from other HER2 inhibitors and PD-L1/PD-1 inhibitors, were considered. Specifically, patients with cardiovascular risk factors are exclude from both cohorts of the study, and patients at risk for study-emergent active autoimmune diseases or with a history of autoimmune diseases that may relapse, patients who have undergone allogeneic stem cell or organ transplantation, and patients who have received a live viral vaccine ≤ 28 days before the first dose of study drug are excluded from Cohort 2 in this study. Patients with contraindications for chemotherapy treatment are also excluded from the study (see Section 4.2 for the full list of exclusion criteria).

8.2.2. Safety Monitoring Plan

Safety will be evaluated in this study through the monitoring of all AEs, defined and graded according to NCI-CTCAE Version 5.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Appendix 1. Clinical laboratory results must be reviewed before the study drug(s) administration.

In this study, all enrolled patients will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of AEs, physical examinations, laboratory measurements (hematology, clinical chemistry, etc), and other assessments. In addition, patients will be closely monitored for the development of any signs or symptoms of autoimmune conditions and infection.

Serum samples will be drawn for determination of ADAs to ZW25 and tislelizumab (if applicable) in patients. Administration of study drug(s) will be performed in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available (for additional information, see Section 5.2).

All AEs will be recorded during the study (AE from the time of the first dose of study drug and SAEs from the time of signing of informed consent) and for up to 30 days after the last dose of study drug(s) or until the initiation of a different anticancer therapy, whichever occurs first. At the end of treatment, ongoing AEs considered related to study drug(s) will be followed until the event has resolved to baseline or ≤ Grade 1, the event is assessed by the investigator as stable, the patient is lost to follow-up, the patient withdraws consent, or it has been determined that study drug(s) or participation is not the cause of the AE.

Immune-mediated AEs for patients treated with tislelizumab in Cohort 2 will be recorded until up to 90 days after the last dose of tislelizumab, regardless of whether or not the patient starts a subsequent anticancer therapy. All drug-related SAEs will be recorded by investigator after study drug(s) discontinuation until patient death, withdrawal of consent, or loss to follow-up, whichever occurs first.

Investigators are instructed to report all AEs (includes pregnancy-related AEs).

The potential safety issues anticipated in this study, as well as measures intended to avoid or minimize such toxicities, are outlined in the following sections.

8.3. Adverse Events

8.3.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug(s), whether considered related to study drug(s) or not.

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug(s) administration even though the condition might have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected incorrect dose of either study drug(s) or a concurrent medication (incorrect dose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records before submission to the sponsor.

8.3.2. Assessment of Severity

The investigator will assess the severity of each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon NCI-CTCAE Version 5.0.

Toxicities that are not specified in NCI-CTCAE will be defined as follows:

- 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
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care, activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms “severe” and “serious” are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]); whereas seriousness is classified by the criteria based on the

regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.6.2.

8.3.3. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug(s) and the occurrence of each AE or SAE using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, and other risk factors, and the temporal relationship of the AE or SAE to the study drug(s) should be considered and investigated. The investigator should consult the ZW25 and Tislelizumab Investigator's Brochures in the determination of his/her assessment.

There may be situations when an SAE has occurred and the investigator has only limited information to include in the initial report to the sponsor. However, it is very important that the investigator always assesses causality for every SAE before transmission of the SAE report to the sponsor because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may subsequently change his/her opinion of causality considering follow-up information and may amend the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related" based on all information available at the time of reporting. An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug(s) (ie, there are facts, evidence, or arguments to suggest possible causation). In generally, a number of factors should be considered in making this assessment including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug(s)
- Biological plausibility

An AE should be considered "related" to study drug(s) if any of the following are met; otherwise, the event should be assessed as "not related":

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug[s]). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.3.4. Following Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, if available, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 8.6.2.

8.3.5. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, echocardiogram/MUGA, x-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and that worsen significantly during the study. The definition of clinically significant is based on the judgment of the investigator. In general, these are the laboratory test abnormalities or other abnormal assessments that:

- are associated with clinical signs or symptoms, or
- require active medical intervention, or
- lead to dose interruption or discontinuation, or
- require close observation, more frequent follow-up assessments, or
- further diagnostic investigation.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the AE eCRF.

If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the AE eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

8.4. Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it was more severe.

- Requires hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.

- Results in disability/incapacity

  Note: The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is a medically significant event that does not meet the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above.

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

8.5. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the study drug's reference safety information) and meets the definition of an SAE/serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the ZW25 and Tislelizumab Investigator's Brochures.

8.6. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

8.6.1. Adverse Event Reporting Period

After the ICF has been signed, but before the administration of the study drug(s), protocol mandated procedures meeting SAE reporting criteria should be reported to the sponsor.

After initiation of study drug(s), all AEs and SAEs, regardless of relationship to study drug(s), will be reported until either 30 days after last dose of study drug(s) or initiation of subsequent anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or nonserious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether or not the patient in Cohort 2 starts a subsequent anticancer therapy. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment.

8.6.2. Reporting Serious Adverse Events

8.6.2.1. Prompt Reporting of Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 6.

Table 6: Time Frames and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Time frame for making initial report	Documentation method	Time frame for making follow-up report	Documentation method	Reporting method
All SAEs	Within 24 hours after first knowledge of the SAE	SAE report	As expeditiously as possible	SAE report	Email or fax SAE form

Abbreviation: SAE, serious adverse event.

8.6.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours, as outlined above in Section 8.6.2.1. The SAE report will always be completed as thoroughly as possible, including all available details of the event, and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality for each SAE as described in Section 8.3.3.

The sponsor will provide contact information for SAE receipt.

8.6.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.6.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a drug under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All suspected unexpected serious adverse reactions (as defined in Section 8.5) will be submitted to all applicable regulatory authorities and investigators for ZW25 and tislelizumab studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised Investigator's Brochure) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of safety reports from the sponsor in the investigator site file.

8.6.3. Eliciting Adverse Events

The investigator or designee will ask patients about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

8.6.4. Disease Progression

Disease progression, which is expected in this study population and measured as an efficacy endpoint, should not be reported as an AE term. Similarly, AEs (excluding SAEs) which are clearly consistent with the pattern of progression of the underlying disease and which are considered unequivocally due to disease progression, should not be reported as an AE (excluding SAEs). However, if there is any uncertainty as to whether an AE is due to disease progression, it should be recorded as an AE.

8.6.5. Deaths

Death is an outcome and is not usually considered an AE. If the only information available is death and the cause of death is unknown, then the death is reported as an event (eg, "death," "death of unknown cause," or "death unexplained").

8.6.6. Pregnancies

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 7 months after the last dose of ZW25 or tislelizumab, a pregnancy report form must be completed and expeditiously submitted (within 24 hours after first knowledge of pregnancy) to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug(s) should be recorded and reported as an SAE.

8.6.7. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference safety information documents:

- ZW25 Investigator's Brochure
- Tislelizumab Investigator's Brochure

8.6.8. Assessing and Recording Immune-Mediated Adverse Events

Since treatment with anti-PD-1 therapy can cause autoimmune disorders, AEs considered by the investigator to be immune-mediated (see Section 8.7.3) should be classified as imAEs and identified as such on the eCRF AE page until Day 90 after the discontinuation of tislelizumab in Cohort 2.

Investigators should consult the guidance on diagnostic evaluation and management of imAEs, which are commonly seen with immune checkpoint inhibitors, in Appendix 8.

An extensive list of potential imAEs appears in Section 8.7.3, Table 8. All conditions like those listed should be evaluated to determine whether they are imAEs based on a similar diagnostic process to those reactions that are presented in more detail in Appendix 8.

8.7. Management of Adverse Events of Special Interest

As a routine precaution, following completion of study drug(s) administration, patients must be monitored for a period afterward in a setting where emergency medical equipment and staff who are trained to respond to medical emergencies are available.

The management for infusion-related reactions, severe hypersensitivity reactions, cardiac events, imAEs (only for patients treated with tislelizumab in Cohort 2), and non-infectious pulmonary toxicities according to the NCI-CTCAE criteria are outlined in the following subsections.

8.7.1. Infusion-Related Reactions

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. Patients 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.

Treatment modification for symptoms of infusion-related reactions due to study drug(s) is provided in Table 7.

Table 7: Treatment Modification for Symptoms of Infusion-Related Reactions Due to Study Drug(s)

NCI-CTCAE grade	Treatment modification for tislelizumab or ZW25
Grade 1 - mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease infusion rate by 50%. Any worsening is closely monitored. Medical management as needed. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 2 - moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, intravenous fluids); prophylactic medications indicated for ≤ 24 hours.	Stop infusion. Infusion may be resumed at 50% of previous rate once infusion-related reactions has resolved or decreased to Grade 1 in severity. Any worsening is closely monitored. Proper medical management should be instituted as described in the text following this table. Subsequent infusions should be given after premedication and at the reduced infusion rate.
Grade 3 – severe Prolonged (eg, 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. Proper medical management should be instituted as described in the text following this table. The patient should be withdrawn from study drug(s) treatment.
Grade 4 – life-threatening Life-threatening consequences; urgent intervention indicated.	Immediately stop the infusion. Proper medical management should be instituted as described in the text following this table. The patient should be withdrawn from study drug(s) treatment. Hospitalization is recommended.

Abbreviation: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Once the tislelizumab or ZW25 infusion rate has been decreased by 50% or suspended due to an infusion-related reaction, it must remain decreased for all subsequent infusions and premedication must be administered. Premedication for infusion-related reactions is described in Section 6.2.1.1. If the patient has a second infusion-related reaction (≥ Grade 2) on the slower infusion rate, the infusion should be discontinued and the patient should be withdrawn from tislelizumab or ZW25 treatment.

NCI-CTCAE Grade 1 or 2 infusion-related reaction: Proper medical management should be instituted, as indicated per the type of reaction. This includes but is not limited to an antihistamine (eg, diphenhydramine or equivalent), antipyretic (eg, paracetamol or equivalent), and, if considered indicated, oral or intravenous glucocorticoids, epinephrine, bronchodilators, and oxygen. Patient should be closely monitored for clinical signs and symptoms of an infusion-related reaction as described in Section 6.2.1.1.

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

8.7.2. Decreased LVEF

Cardiac events are of absolute decreases in LVEF ≥ 10 % points from pretreatment baseline and absolute value < 50%, and/or Grade ≥ 2 heart failure.

Management of left ventricular dysfunction is described in Section 5.5.2.

Permanently discontinue ZW25 for a persistent (> 8 weeks) decrease in LVEF or if dosing has been suspended on more than 3 occasions for cardiomyopathy.

8.7.3. Immune-Mediated Adverse Events

Immune-mediated AEs are of special interest for patients treated with tislelizumab in Cohort 2 of this study. If the events listed below or similar events occur, the investigator should exclude alternative explanations (eg, combination drugs, infectious disease, metabolic, toxin, PD, or other neoplastic causes) with appropriate diagnostic tests that may include but are not limited to serologic, immunologic, and histologic (biopsy) data. If alternative causes have been ruled out, the AE required the use of systemic steroids, other immunosuppressants, or endocrine therapy and is consistent with an immune-mediated mechanism of action, the imAE indicator on the eCRF AE page should be checked.

A list of potential imAEs is shown below in Table 8. All conditions similar to those listed should be evaluated in patients receiving tislelizumab in Cohort 2 to determine whether they are immune-mediated.

Recommendation for diagnostic evaluation and management of imAEs is based on European Society for Medical Oncology and American Society of Clinical Oncology guidelines (Haanen et al 2017; Brahmer et al 2018) and common immune-mediated toxicities are detailed in Appendix 8. For any AEs not included in Appendix 8, please refer to the American Society of Clinical Oncology Clinical Practice Guideline (Brahmer et al 2018) for further guidance on diagnostic evaluation and management of immune-mediated toxicities.

Table 8: Examples of Immune-Mediated Adverse Events

Body system affected	Events
Skin (mild-common)	pruritus or maculopapular rash; vitiligo
Skin (moderate)	follicular or urticarial dermatitis; erythematous/lichenoid rash; Sweet syndrome
Skin (severe-rare)	full-thickness necrolysis/Stevens-Johnson syndrome
Gastrointestinal	colitis (includes diarrhea with abdominal pain or endoscopic/radiographic evidence of inflammation); pancreatitis; hepatitis; aminotransferase (ALT/AST) elevation; bowel perforation
Endocrine	thyroiditis, hypothyroidism, hyperthyroidism; hypophysitis with features of hypopituitarism (eg, fatigue, weakness, weight gain); insulin-dependent diabetes mellitus; diabetic ketoacidosis; adrenal insufficiency
Respiratory	pneumonitis/diffuse alveolitis
Eye	episcleritis; conjunctivitis; iritis/uveitis
Neuromuscular	arthritis; arthralgia; myalgia; neuropathy; Guillain-Barre syndrome; aseptic meningitis; myasthenic syndrome/myasthenia gravis; meningoencephalitis; myositis
Blood	anemia; leukopenia; thrombocytopenia
Renal	interstitial nephritis; glomerulonephritis; acute renal failure
Cardiac	pericarditis; myocarditis; heart failure

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Recommendations for managing imAEs are detailed in Appendix 8.

If a toxicity does not resolve to ≤ Grade 1 within 12 weeks, study drug(s) should be discontinued after consultation with the sponsor. Patients who experience a recurrence of any event at the same or higher severity grade with rechallenge should permanently discontinue treatment.

8.7.4. Non-infectious Pulmonary Toxicities

Subjects with symptoms or findings consistent with ≥ Grade 2 interstitial lung disease (ILD) should hold treatment with ZW25 pending evaluation per institutional standards. ZW25 will be permanently discontinued for ZW25-associated ≥ Grade 2 ILD that is confirmed.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

The statistical analyses will be performed by the sponsor or designee after the data collection is completed and the database is locked and released. Details of the statistical analyses will be included in a separate Statistical Analysis Plan.

9.1. Statistical Analysis

9.1.1. Analysis Sets

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

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

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

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

9.1.2. Patient Disposition

The number of patients treated, discontinued from study drug(s) and/or the study, and those with important protocol deviations will be counted. The primary reason for study drug(s) and/or study discontinuation will be summarized according to the categories in the eCRF. The end-of-study status at the DCO date will be summarized using the data from the eCRF.

Important protocol deviations will be summarized and listed by category.

9.1.3. Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized using the Safety Analysis Set and descriptive statistics. Continuous variables include age, height, weight, time since initial cancer diagnosis, and time since advanced/metastatic disease diagnosis, etc. Categorical variables include sex, ECOG Performance Status, country, race, Tumor Node Metastasis (TNM) staging, metastatic site, site of primary tumor, Estrogen-receptor and Progesterone-receptor status, female reproductive status (for Cohort 1), smoking status, etc.

9.1.4. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary drug codes. Prior and concomitant medications will be further coded to the appropriate Anatomical Therapeutic Chemical code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class. Prior

medications will be defined as medications that stopped before the day of first dose of study drug. Concomitant medications will be defined as medications that 1) were started before the first dose of study drug and were continuing at the time of the first dose of study drug, or 2) were started on or after the date of the first dose of study drug up to 30 days after the patient's last dose (as of the EOT/Safety Follow-up Visit). A listing of prior and concomitant medications will be provided. In addition, safety follow-up also includes telephone contacts with patients treated with tislelizumab in Cohort 2, which should be conducted to assess imAEs and concomitant medications (if appropriate, ie, associated with an imAE or is a new anticancer therapy) at 60 (± 14 days) and 90 days (± 14 days) after the last dose of study drugs regardless of whether or not the patient starts a new anticancer therapy.

9.2. Efficacy Analyses

Primary and secondary efficacy endpoints will be based upon investigators' tumor assessments per RECIST Version 1.1 and will be summarized as follows to evaluate the preliminary anticancer activities of ZW25. No formal hypotheses testing is planned for efficacy.

9.2.1. Primary Efficacy Analysis

The ORR is the proportion of patients who had a BOR of confirmed CR or PR assessed by investigator per RECIST Version 1.1. The 2-sided Clopper-Pearson 95% CIs for ORR will be calculated for each cohort. ORR will be estimated on the Efficacy Evaluable Analysis Set.

9.2.2. Secondary Efficacy Analysis

Progression-free survival will be estimated using the Kaplan-Meier method. Progression-free survival will be estimated on the Efficacy Evaluable Analysis Set. The median PFS and the cumulative probability of PFS at every 3 months will be calculated and presented with 2-sided 95% CIs.

Duration of response will be estimated using the Kaplan-Meier method and will be estimated on the Efficacy Evaluable Analysis Set.

Time to response (TTR) will be estimated descriptively on the Efficacy Evaluable Analysis Set; the mean, standard deviation, median, and range of TTR will be provided. Only the subset of patients who achieved a CR or PR will be included in the TTR analysis.

Disease control rate will be analyzed similarly to ORR, and DCR will be estimated on the Efficacy Evaluable Analysis Set.

Overall survival will be estimated using the Kaplan-Meier method and will be estimated on the Safety Analysis Set.

Graphical methods will be applied as appropriate in addition to summary tables and listings.

9.3. Safety Analyses

Safety data will be summarized using the Safety Analysis Set. Safety will be assessed by the spontaneous reporting of AEs and by laboratory values (hematology, clinical chemistry, coagulation, and urinalysis). Vital signs, physical examinations, ECG findings, and echocardiogram or MUGA will also be used in determining the safety profile. The severity of

AEs will be graded according to NCI-CTCAE Version 5.0. The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) and changes from baseline will be determined for laboratory parameters and vital signs.

9.3.1. Extent of Exposure

Extent of exposure to each study drug will be summarized descriptively as the number of cycles received (number and percentage of patients), duration of exposure (days), cumulative total dose received per patient (mg), dose intensity, and relative dose intensity.

The number (percentage) of patients requiring dose interruption, dose delay, and drug discontinuation will be summarized for each study drug. Reasons for dose modifications will be summarized as well.

Patient data listings will be provided for all dosing records.

9.3.2. Adverse Events

The AE verbatim descriptions (investigator's description from the eCRF) will be coded using MedDRA. AEs will be coded to MedDRA lowest level term, preferred term, and primary system organ class.

A TEAE is defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) on or after the first dose of study drug up to 30 days following study drug discontinuation or initiation of subsequent anticancer therapy, whichever occurs first. For patients in Cohort 2, the TEAE classification also applies to imAEs that are recorded up to 90 days after discontinuation from tislelizumab, regardless of whether or not the patient starts a subsequent anticancer therapy. Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in patient data listings.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by system organ class and preferred term. A patient will be counted only once by the highest severity grade per NCI-CTCAE Version 5.0 within a system organ class and preferred term, even if the patient experienced ≥ 1 TEAE within a specific system organ class and preferred term. The number (percentage) of patients with TEAEs will also be summarized by relationship to the study drug(s).

Treatment-related TEAEs include those events considered by the investigator to be related to study treatment or with missing assessment of the causal relationship.

SAEs, deaths, ≥ Grade 3 TEAEs, imAEs, treatment-related TEAEs, and TEAEs that led to treatment discontinuation, dose interruption, or dose delay will be summarized.

9.3.3. Laboratory Analyses

Clinical laboratory (eg, hematology, clinical chemistry, coagulation, and urinalysis) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be

flagged and identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the clinical study report for this protocol. Descriptive summary statistics (eg, n, mean, standard deviation, median, minimum, and maximum for continuous variables; n [%] for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by visit and by worst postbaseline visit.

Laboratory parameters that are graded in NCI-CTCAE Version 5.0 or higher will be summarized by NCI-CTCAE grade. In the summary of laboratory parameters by NCI-CTCAE grade, parameters with NCI-CTCAE grading in both high and low directions (eg, calcium, glucose, magnesium, potassium, and sodium) will be summarized separately.

9.3.4. Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure, pulse rate, temperature, and weight) and changes from baseline will be presented by visit for all visits. Vital signs will be listed by patient and visit.

9.3.5. Physical Examinations, ECOG Performance Status, ECGs and Other Tests

Physical examinations, ECOG Performance Status, ECGs, and other tests and monitoring such as pulmonary function test, hepatitis B and C testing, cardiac enzyme monitoring, echocardiogram/MUGA will be descriptively summarized based upon data availability. Data listing will be provided.

9.4. Pharmacokinetic Analyses

Serial PK samples from up to 28 patients are planned to characterize the PK profiles of ZW25 in targeted patient population. Serum concentration-time data of each patient will be tabulated and graphically presented on linear semi-logarithmic scales. Pharmacokinetic parameters will be determined using a standard noncompartmental method. A listing of patients excluded from the analysis set and individual data points excluded from the analysis will be provided. The parameters will be summarized with descriptive statistics (N, arithmetic mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation (CV) % associated to the geometric mean).

- PK parameters will include, but are not limited to, the following as allowed by data:
- C_{max} (ng/mL): Observed maximum plasma concentration during a sample interval.
- t_{max} (hour): Observed time to maximum plasma concentration during a sampling interval.
- $t_{½}$ (hour): Terminal elimination half-life, determined from the quotient 0.693/λz.
- $AUC_{(0-t)}$ (ng·h/mL): Area under the plasma concentration-time curve from time zero to the last measurable timepoint calculated by log-linear trapezoidal summation.
- CL (L/hr): Apparent clearance

The ZW25 and tislelizumab PK concentration data collected sparsely at predose and postdose (end of infusion) will be tabulated and summarized by visit/cycle. Descriptive statistics will include means, standard deviations, medians, and ranges as appropriate.

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

9.5. Immunogenicity Analyses

Samples to assess anti-ZW25 antibodies and anti-tislelizumab antibodies will be collected only in patients who receive study drug(s) and at sites that are able to adequately perform sampling, handling, and processing as outlined in the laboratory manual.

The ADA results will be summarized using descriptive statistics by the number and percentage of patients who develop detectable ADAs. The incidence of positive ADAs and neutralizing ADAs will be reported for evaluable patients. The effect of immunogenicity on PK, efficacy, and safety may be evaluated if data allow.

9.7. Sample Size Consideration

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

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

9.8. Planned Analyses

There are 3 planned analyses for this study. The first planned analysis is planned after all patients in Cohort 2 have been followed for at least 4 months. The second planned analysis is planned after all patients in Cohort 1 have been followed for at least 4 months. The third planned analysis (the FA) will take place at least 12 months after the first dose of the last patient (whichever cohort is later), or until study termination or study completion decided by the sponsor, whichever occurs first. The sponsor will notify each investigator when a decision is made on the DCO date of the FA.

10. STUDY COMMITTEES

10.1. Safety Monitoring Committee

A SMC will be established and include both the sponsor and investigators. After the first 6 patients in safety lead-in phase have completed at least 1 cycle (21 days), the SMC will review all available safety data, including AEs and laboratory assessments, and make recommendations if the Cohort 2 could be fully open to enrollment. The SMC may also be called upon by the sponsor when deemed necessary or where applicable to the conduct of the study. For more details on SMC, please refer to SMC charter.

11. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

The investigator must maintain adequate and accurate records to ensure that the conduct of the study may be fully documented. Such records include but are not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approvals. In addition, at the end of the study, the investigator will receive patient data, which will include an audit trail containing a complete record of all changes to such data.

11.1. Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

11.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to the appropriate regulatory agency before the study is initiated at a study center in that country.

12.2. Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

12.3. Study Site Inspections

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits may be performed periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

Site visits will be conducted by the sponsor or an authorized representative to inspect study data, patients' medical records, and eCRFs. The investigator is to permit national and local health authorities; sponsor study monitors, representatives, and collaborators; and IRB/IEC members to inspect all facilities and records relevant to this study.

12.4. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug(s). This includes acknowledgment of receipt of each shipment of study drug(s) (quantity and condition), patient drug dispensation records, and returned or destroyed study drug(s). Dispensation records will document quantities received from BeiGene and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the site's standard operating procedure for study drug disposal/destruction to ensure that it complies with BeiGene requirements. At appropriate times during the conduct of the study or at the end of the study following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet BeiGene's requirements for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

13. ETHICS/PROTECTION OF HUMAN PATIENTS

13.1. Ethical Standard

This study will be conducted by the principal investigator and the study center in full conformance with the ICH E6 guidelines for GCP and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will also comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

13.2. Institutional Review Board/Independent Ethics Committee

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/IEC by the principal investigator (or designated personnel) and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/IEC. Copies of the IRB/IEC correspondence and approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

The principal investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments. In addition to the requirements for reporting all AEs to the sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/IEC. Investigators may receive written Investigational New Drug Safety Reports or other safety-related communications from the sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/IEC and archived in the site's study file.

13.2.1. Protocol Amendments

Any protocol amendments will be prepared by the sponsor. All protocol modifications must be submitted to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained by the sponsor before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (eg, change in medical monitor or contact information).

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign each revised ICF confirming their willingness to remain in the study.

13.3. Informed Consent

The sponsor's sample ICF will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The final IRB/IEC-approved ICFs must be provided to the sponsor for health authority submission purposes according to local requirements.

The ICFs must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained before participation in the study.

The ICFs will be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/IEC-approved consent forms must be provided to the sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the ICFs (or to a significant new information/findings addendum in accordance with applicable laws and IRB/IEC policy) during their participation in the study. For any updated or revised ICFs, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

13.4. Patient and Data Confidentiality

The principal investigator and sponsor will maintain confidentiality and privacy standards by following applicable data privacy laws covering the collection, storage, transmission, and processing of patients' personal and medical information.

The principal investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' names are not included in any data set transmitted to any sponsor location.

Patient medical information obtained during this study is confidential and may be disclosed only to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In the event of a breach of the confidentiality of a patient's personal and medical information, the principal investigator and sponsor, as appropriate, shall fulfil all mediation steps and reporting obligations under applicable data privacy laws.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated during this study must be available for inspection upon request by representatives of the US Food and Drug Administration, the NMPA, and all other national and local health authorities; by sponsor monitors, representatives, and collaborators; and by the IRBs/IECs for each study site, as appropriate.

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator agrees that all information received from the sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the IND, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study is executed, and that contract includes confidentiality provisions inconsistent with this section, that contract's provisions shall apply to the extent they are inconsistent with this section.

13.5. Financial Disclosure

Investigators are required to provide the sponsor with sufficient accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of clinical investigators and/or disclose those financial interests, as required, to the appropriate health authorities. This is intended to ensure financial interests and arrangements of clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators are responsible for providing information about their financial interests before participation in the study and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

14.1.1. Data Collection

Data required by the protocol will be entered into an electronic data capture (EDC) system. All study-related data collected or received by the investigator or study team shall be promptly entered into the eCRFs. In no event should the entry of the study data into the eCRF be later than what is stipulated in the site contract after the data is collected or received by the investigator or study team without prior communication with and approval by sponsor.

Data collection in the eCRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator must provide e-signature in the EDC system to attest to their accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

14.1.2. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored by BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries and maintenance of an audit file that includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies and completeness.

During the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

The eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out with due consideration given to data protection and medical confidentiality.

AEs will be coded using the MedDRA. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Concomitant diseases/medical history will be coded using MedDRA.

14.2. Study Records Retention

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least 1 of the following 2 categories: 1) investigator's study file and 2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include documents such as (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, x-ray, pathology and special assessment reports, consultant letters, and screening and enrollment log, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable backup of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements including but not limited to the following: archival at an off-site facility or transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the CRO managing the biological samples, for the shorter of the following: a period of up to 10 years or as allowed by your IRB/IEC.

14.3. Protocol Deviations

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and to the IRB/IEC, in accordance with established IRB/IEC policies and procedures, and shall report all protocol deviations to the sponsor.

14.4. Publication and Data Sharing Policy

A clinical study report will be prepared and provided to the regulatory agency(ies). BeiGene will ensure that the report meets the standards set out in the International Council for Harmonisation Guideline for Structure and Content of Clinical Study Reports (ICH E3). An abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication, or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors or stricter local criteria (International Committee of Medical Journal Editors 2016).

After conclusion of the study and without prior written approval from BeiGene, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media *only after the following conditions have been met:*

- The results of the study in their entirety have been publicly disclosed by or with the consent of BeiGene in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 2 years.
- No such communication, presentation, or publication will include BeiGene's confidential information.
- Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the sponsor prior to submission. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement.

14.5. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return/provide of all study data to the sponsor
- Resolve and close all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

In addition, the sponsor reserves the right to suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance with this protocol, GCP, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

14.6. Information Disclosure and Inventions

All rights, title, and interests in any inventions, expertise, or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor and are hereby assigned to the sponsor.

If a written contract for the conduct of the study, which includes ownership provisions inconsistent with this statement, is executed between the sponsor and the study center that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) will be kept by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 14.4.

If a written contract for the conduct of the study, which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

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16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS

APPENDIX 1A. STUDY SCHEDULE OF ASSESSMENTS THROUGH THE DATA CUTOFF DATE OF THE FINAL ANALYSIS

Assessment	Screening [a]	Treatment Cycles				End-of-Treatment/Safety Follow-up Visit [b]	Survival Follow-up [c]
		Cycles 1 to 2 (Every 21 days)			Cycle 3 and Subsequent Cycles (Every 21 Days)		
Days (Window)	**-28 to -1**	**1 (± 3 days for Cycle 2)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 ± 7 Days After Last Dose**	**Every 3 Months**
Informed consent	x						
Inclusion/exclusion criteria	x						
Demographics/medical history/prior medications [d]	x						
Vital signs/ height and weight [e]	x	x			x	x	
Physical examination [f]	x	x			x	x	
ECOG Performance Status	x	x			x	x	
12-lead ECG [g]	x	x			x	x	
Echocardiogram/MUGA [h]	x	First postbaseline scan at 6 weeks (± 7 days) from Cycle 1 Day 1, then every 12 weeks (± 7 days) thereafter				x	
Adverse events [i]	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	
Hematology [j]	x [a]	x	x	x	x	x	
Serum chemistry [j]	x [a]	x	x	x	x	x	
Coagulation parameters [j]	x	As clinically indicated					
Urinalysis [j]	x	As clinically indicated					
Thyroid function [k] (Cohort 2)	x	every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc.)				x	

Assessment	Screening [a]	Treatment Cycles				End-of-Treatment/Safety Follow-up Visit [b]	Survival Follow-up [c]
		Cycles 1 to 2 (Every 21 days)			Cycle 3 and Subsequent Cycles (Every 21 Days)		
Days (Window)	**-28 to -1**	**1 (± 3 days for Cycle 2)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 ± 7 Days After Last Dose**	**Every 3 Months**
CK-MB or Troponin [j, l]	x	x	x	x	x	x	
Pregnancy test [m]	x	x			x	x	
HBV/HCV tests [n]	x	As clinically indicated					
Pulmonary function tests [o]	x						
ZW25 PK		See Appendix 1C and Appendix 1D					
ZW25 ADA							
Tislelizumab PK		See Appendix 1E					
Tislelizumab ADA							
Tumor assessment [p]	x	every 6 weeks (± 7 days) from Cycle 1 Day 1 for the first 36 weeks, then every 12 weeks (± 7 days) thereafter					
Archival tumor tissue [q]	x						
Fresh tumor tissue [q]	x					x	
Peripheral blood samples [r]		x			x (Cycle 3 only)	x	
ZW25 administration [s]		x			x		
Docetaxel administration [t] (Cohort 1)		x			x		
Tislelizumab administration [u] (Cohort 2)		x			x		
Capecitabine administration [v] (Cohort 2)		x			x		
Oxaliplatin administration [v] (Cohort 2)		x			x		

Assessment	Screening [a]	Treatment Cycles				End-of-Treatment/Safety Follow-up Visit [b]	Survival Follow-up [c]
		Cycles 1 to 2 (Every 21 days)			Cycle 3 and Subsequent Cycles (Every 21 Days)		
Days (Window)	**-28 to -1**	**1 (± 3 days for Cycle 2)**	**8 (± 2)**	**15 (± 2)**	**1 (± 3)**	**30 ± 7 Days After Last Dose**	**Every 3 Months**
Survival status							x

Abbreviations: ADA, antidrug antibody; AE, adverse event; CK-MB, creatine kinase-muscle/brain; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; FFPE, formalin-fixed paraffin-embedded; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAb, hepatitis B surface antibody; HER2, human epidermal growth factor receptor 2; IEC, Independent Ethics Committee; imAE, immune-mediated adverse event; IRB, Institutional Review Board; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MUGA, multiple gated acquisition scan; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PK, pharmacokinetic; SAE, serious adverse event; TSH, thyroid stimulating hormone; ZW25, zanidatamab.

[a] Written informed consent is required prior to performing any study-specific tests or procedures. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and ≤ 28 days prior to the first dose of study drug may be used for Screening assessments rather than repeating such tests unless otherwise indicated.

[b] The EOT/Safety Follow-up Visit is required to be conducted at approximately 30 days (± 7 days) after the last dose of study drug(s), or before the initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT/Safety Follow-up Visit, tests need not be repeated. Tumor assessment is not required at the EOT/Safety Follow-up Visit provided that fewer than 6 weeks have passed since the last assessment. In addition, safety follow-up also includes telephone contacts with patients treated with tislelizumab in Cohort 2, which should be conducted to assess immune-mediated AEs and concomitant medications (if appropriate, ie, associated with an immune-mediated AE or is a new anticancer therapy) at 60 (±14 days) and 90 days (±14 days) after the last dose of study drug(s) regardless of whether or not the patient starts a new anticancer therapy.

[c] Survival Follow-up information will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (±14 days) after the EOT/Safety Follow-up Visit or as directed by the sponsor until death, loss to follow-up, withdrawal of consent, or study completion by the sponsor. All patients will be followed for survival and subsequent anticancer therapy information unless a patient requests to be withdrawn from follow-up.

[d] Includes age, year of birth, sex, and self-reported race/ethnicity; history of treatment for the primary diagnosis, including prior medication, loco-regional treatment(s), and surgical treatment(s). Information on radiographic studies performed prior to study entry may be collected for review by the Investigator.

[e] Vital signs collected on study include temperature, pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. Regarding the timepoints for collecting vital signs during treatment period, please see the details in Section 7.1.4.1. The height is only measured at screening.

[f] A complete physical examination is required at screening while subsequent visits entail limited, symptom-directed physical examinations (as detailed in Section 7.1.4.2).

[g] The ECG recordings will be obtained during screening, prior to the study drug administration in each cycle, and the EOT/Safety Follow-up Visit. Triplicate ECG recordings are needed for screening. Patient should rest in semi-recumbent supine position for at least 10 minutes prior to ECG collection.

[h] After screening, an echocardiogram/MUGA should be done at 6 weeks 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/Safety Follow-up Visit if ≤ 3 months since the previous scan. If deterioration of LVEF is observed, then echocardiogram/MUGA should be performed at a higher frequency as clinically indicated.

[i] The AEs and laboratory abnormalities will be graded per NCI-CTCAE Version 5.0. All AEs will also be evaluated for seriousness. After the informed consent form has been signed, but prior to the administration of study drug, only SAEs should be reported. After initiation of study drug(s), all AEs and SAEs, regardless of relationship to study drug(s), will be reported until either 30 days after last dose of study drug(s) or initiation of subsequent anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether or not the patient in Cohort 2 starts a subsequent anticancer therapy.

[j] Local laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. If laboratory tests at screening are not performed within 7 days prior to the administration of study drug(s) on Day 1 of Cycle 1, these tests should be repeated and reviewed before study drug(s) administration. Hematology and serum chemistry (including liver function tests) will be performed weekly for the first 2 cycles and then at the beginning of subsequent cycles. After Cycle 1, laboratory tests should be performed and results are to be reviewed within 72 hours before study drug(s) administration. Coagulation and urinalysis are to be conducted if clinically warranted during the treatment period and at the EOT/Safety Follow-up Visit. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[k] Analysis of free triiodothyronine, free thyroxine, and TSH for patients in Cohort 2 will be performed by a local study site laboratory. Thyroid function tests will be performed at screening and every 3 cycles (ie, Day 1 of Cycles 4, 7, 10, etc.), and at the EOT/Safety Follow-up Visit.

[l] In the event that CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Investigators should make every effort to perform either CK-MB, troponin I and/or troponin T consistently at screening and in follow up visits.

[m] Urine or serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 7 days prior to the first dose of study drug. Urine pregnancy tests will be performed at each visit prior to dosing. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[n] Testing will be performed by a local laboratory at screening and will include HBV/HCV serology (HBsAg, HBsAb, HBcAb, and HCV antibody).

[o] Patients who are suspected or known to have serious/severe respiratory conditions or exhibit significant respiratory symptoms unrelated to the underlying cancer will have pulmonary function testing which may include, but is not limited to, spirometry and assessment of diffusion capacity done during the Screening period to assist the determination of suitability on the study.

[p] Radiological images captured as standard-of-care tests prior to obtaining written informed consent and ≤ 28 days before the first dose of study drug may be used rather than repeating tests. All measurable and evaluable lesions are required to be assessed and documented at the Screening Visit. An MRI (or CT scan if MRI is contraindicated or not readily available) of the brain is required at screening; bone scan or PET is required at screening if clinically indicated. The same radiographic procedure must be used throughout the study for each patient. Tumor imaging will be performed every 6 weeks (± 7 days) from Cycle 1 Day 1 for the first 36 weeks, then every 12 weeks (± 7 days) thereafter until disease progression, withdrawal of consent, death, or start of a new anticancer therapy, whichever occurs first.

[q] Patients are required to provide archival tumor tissues (FFPE blocks or at least 12 unstained slides) for biomarker analysis. In the absence of archival tumor tissues, a fresh biopsy of a tumor lesion at screening (within 28 days before the first dose of study drug) is mandatory unless previously discussed with sponsor's medical monitor. Optional tumor biopsies will also be obtained at the time of disease progression in consenting patients to evaluate the resistance mechanisms. If feasible, any follow up biopsy should be ideally taken from the same tumor lesion as the baseline biopsy. Written informed consent is required prior to fresh tumor biopsies. See Section 7.1.7 for more information.

[r] Peripheral blood samples will be collected at screening (predose at Day 1 of Cycle 1), Day 1 of Cycle 3 (predose) and EOT/Safety Follow-up Visit for all patients to explore the association of blood-based biomarkers with response, prognosis and resistance. At screening, a blood sample of approximately 4 mL will be taken for germline mutation testing, 10 mL will be taken for circulating nucleic acids analysis and another 5 mL will be taken for serum HER2 testing. On Day 1 of Cycle 3 (predose) and at the EOT/Safety Follow-up Visit, a 10 mL of blood sample will be taken for circulating nucleic acids analysis and another 5 mL blood sample will be taken for serum HER2 testing. Blood samples will be prepared as indicated in the Laboratory Manual.

[s] ZW25 will be administered as an IV infusion on Day 1 of each 21-day cycle (once every 3 weeks). The dosing is based on the patient's actual body weight at baseline for Cohort 1a and Cohort 2a. Doses must be adjusted for patients who experience a ≥ 10% change in weight from baseline except for patients in Cohort 1b.

[t] Docetaxel will be administered after the infusion of ZW25 on Day 1 of each 21-day cycle. On or prior to Cycle 6, docetaxel 75 mg/m^2 will be administered as an IV infusion over 1 hour once every 3 weeks until disease progression, intolerable toxicity, or another criterion for treatment discontinuation is met. After Cycle 6, continuation of docetaxel treatment is at the discretion of the investigator.

[u] Tislelizumab will be given IV once every 3 weeks after the infusion of ZW25. Tislelizumab 200 mg will be administered on Day 2 for the first 2 cycles and on Day 1 of each 21-day cycle (once every 3 weeks) from Cycle 3 onward. The infusion for the first 2 cycles will be delivered over 60 minutes, and then can be administered over 30 minutes for subsequent infusions if well tolerated.

[v] Oxaliplatin will be administered after the infusion of tislelizumab. On or prior to Cycle 6, oxaliplatin 130 mg/m^2 will be administered intravenously once every 3 weeks and the duration of infusion follows the local practice; capecitabine 1000 mg/m^2 will be administered orally twice daily for 14 consecutive days during each 21-day cycle. Capecitabine will be administered after the infusion of oxaliplatin. For the first 2 cycles, capecitabine will be dosed from the evening of Day 2 to the morning of Day 16 of each cycle; From Cycle 3 onward, capecitabine will be dosed from the evening of Day 1 to the morning of Day 15 of each cycle. After Cycle 6, oxaliplatin will be discontinued and continuation of capecitabine as maintenance treatment is at the discretion of the investigator.

APPENDIX 1B. STUDY SCHEDULE OF ASSESSMENTS AFTER THE DATA CUTOFF DATE OF THE FINAL ANALYSIS

Assessments	**Treatment Cycles**	**End-of-Treatment/Safety Follow-up Visit [a]**
Days (Window)	**Every 21± 3 days**	**30 ± 7 Days After Last Dose**
Vital signs/Weight/Physical examination/ECOG Performance Status [b]	X	X
Adverse events/Concomitant medications [c]	X	X
Pregnancy test [d]	X	X
Hematology/Serum chemistry [e]	X	X
Thyroid function (Cohort 2) [f]	Every 12 weeks (± 7 days)	X
Coagulation parameters, Urinalysis, HBV/HCV tests [g]	As clinically indicated	
Tumor assessment [h]	Every 12 weeks (± 7 days)	X
12-lead ECG/CK-MB or Troponin [i]	X	X
Echo/MUGA [j]	Every 12 weeks (± 7 days)	X
ZW25 administration [k]	X (if applicable)	
Docetaxel administration (Cohort 1) [l]	X (if applicable)	

Assessments	Treatment Cycles	End-of-Treatment/Safety Follow-up Visit [a]
Days (Window)	**Every 21± 3 days**	**30 ± 7 Days After Last Dose**
Tislelizumab administration (Cohort 2) [m]	X (if applicable)	
Capecitabine administration (Cohort 2) [n]	X (if applicable)	

Abbreviations: AE, adverse event; CK-MB, creatine kinase-muscle/brain; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; HBV, hepatitis B virus; HCV, hepatitis C virus; IV, intravenous(ly); LVEF, left ventricular ejection fraction; MUGA, multiple gated acquisition scan; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SAE, serious adverse event; TSH, thyroid stimulating hormone; ZW25, zanidatamab.

[a] The EOT/Safety Follow-up Visit is required to be conducted at approximately 30 days (± 7 days) after the last dose of study drug(s), or before the initiation of a new anticancer treatment, whichever occurs first. If routine laboratory tests (eg, hematology, serum chemistry) are completed within 7 days before the EOT/Safety Follow-up Visit, tests need not be repeated. Tumor assessment is not required at the EOT/Safety Follow-up Visit provided that fewer than 6 weeks have passed since the last assessment. In addition, safety follow-up also includes telephone contacts with patients treated with tislelizumab in Cohort 2, which should be conducted to assess immune-mediated AEs and concomitant medications (if appropriate, ie, associated with an immune-mediated AE or is a new anticancer therapy) at 60 (±14 days) and 90 days (±14 days) after the last dose of study drug(s) regardless of whether or not the patient starts a new anticancer therapy.

[b] Vital signs collected on study include temperature, pulse rate, and blood pressure (systolic and diastolic) while the patient is in a seated position after resting for 10 minutes. Regarding the timepoints for collecting vital signs during treatment period, please see the details in Section 7.2.2.1. A limited physical examination is required, symptom-directed physical examinations (as detailed in Section 7.2.2.2).

[c] The AEs and laboratory abnormalities will be graded per NCI-CTCAE Version 5.0. All AEs will also be evaluated for seriousness. After initiation of study drug(s), all AEs and SAEs, regardless of relationship to study drug(s), will be reported until either 30 days after last dose of study drug(s) or initiation of subsequent anticancer therapy, whichever occurs first. Immune-mediated AEs (serious or non-serious) should be reported until 90 days after the last dose of tislelizumab, regardless of whether or not the patient in Cohort 2 starts a subsequent anticancer therapy.

[d] Urine pregnancy tests will be performed at each visit prior to dosing. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.

[e] Local laboratory assessments on serum chemistry, hematology, coagulation, and urinalysis will be conducted, of which certain elements will be collected as specified in Appendix 2. Hematology and serum chemistry (including liver function tests) will be performed at the beginning of every cycle. Laboratory tests should be performed and results are to be reviewed within 72 hours before study drug(s) administration. Coagulation and urinalysis are to be conducted if clinically warranted during the treatment period and at the EOT/Safety Follow-up Visit. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[f] Analysis of free triiodothyronine, free thyroxine, and TSH for patients in Cohort 2 will be performed by a local study site laboratory. Thyroid function tests will be performed every 12 weeks and at the EOT/Safety Follow-up Visit.

[g] Coagulation and urinalysis are to be conducted if clinically warranted during the treatment period and at the EOT/Safety Follow-up Visit. Refer to Section 8.3.5 for additional information regarding clinical assessment and management of clinical laboratory abnormalities.

[h] The same radiographic procedure must be used throughout the study for each patient. Tumor imaging will be performed every 12 weeks (± 7 days) according to their previous schedule until disease progression, withdrawal of consent, death, or end of treatment, whichever occurs first.

[i] The ECG recordings will be obtained prior to the study drug administration in each cycle, and the EOT/Safety Follow-up Visit. Patient should rest in semi-recumbent supine position for at least 10 minutes prior to ECG collection. In the event that CK-MB fractionation is not available, assess troponin I and/or troponin T instead. Investigators should make every effort to perform either CK-MB, troponin I and/or troponin T consistently at screening and in follow up visits.

[j] An echocardiogram/MUGA should be done every 12 weeks thereafter within a ± 7 day time window. An echocardiogram/MUGA is not required at EOT/Safety Follow-up Visit if ≤ 3 months since the previous scan. If deterioration of LVEF is observed, then echocardiogram/MUGA should be performed at a higher frequency as clinically indicated.

[k] ZW25 will be administered as an IV infusion on Day 1 of each 21-day cycle (once every 3 weeks). The dosing is based on the patient's actual body weight at baseline for Cohort 1a and Cohort 2a. Doses must be adjusted for patients who experience a ≥ 10% change in weight from baseline except for patients in Cohort 1b.

[l] Docetaxel will be administered after the infusion of ZW25 on Day 1 of each 21-day cycle. On or prior to Cycle 6, docetaxel 75 mg/m2 will be administered as an IV infusion over 1 hour once every 3 weeks until disease progression, intolerable toxicity, or another criterion for treatment discontinuation is met. After Cycle 6, continuation of docetaxel treatment is at the discretion of the investigator.

[m] Tislelizumab will be given IV once every 3 weeks after the infusion of ZW25. Tislelizumab 200 mg will be administered on Day 1 of each 21-day cycle (once every 3 weeks) and the infusion can be administered over 30 minutes.

[n] Capecitabine will be administered after the infusion of study drugs and will be dosed from the evening of Day 1 to the morning of Day 15 of each cycle. After Cycle 6, oxaliplatin will be discontinued and continuation of capecitabine as maintenance treatment is at the discretion of the investigator.

APPENDIX 1C. ZW25 PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING SCHEDULE – SERIAL FOR UP TO 10 PATIENTS IN COHORT 1A, UP TO 6 FROM COHORT 1B, UP TO 6 FROM COHORT 2A, AND UP TO 6 FROM COHORT 2B

Time	**Cycle 1**								**Cycle 2**				**Cycle 5, 9,17, 26, 35, and Every 17 Cycles Thereafter[a]**		**EOT/Safety Follow-up Visit[a]**
	Day 1				**Day 2**	**Day 5[b]**	**Day 8**	**Day 15**	**Day 1**		**Day 8**	**Day 15**	**Day 1**		
	Pre-dose	**0 h post dose**	**2 h**	**4 h**	**24 h**	**96 h**	**168 h**	**336 h**	**Pre-dose**	**0 h post dose**	**168 h**	**336 h**	**Pre-dose**	**0 h post dose**	
Window Allowed	**-1 h**	**+15 min**	**±30 min**	**±30 min**	**±1 h**	**±1 h**	**±1 h**	**±1 h**	**-1 h**	**+15 min**	**±1 h**	**±1 h**	**-1 h**	**+15 min**	
PK Serum Sample	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[c]
ADA Serum Sample	X							X	X				X		X[d]

Abbreviations: ADA, antidrug antibody; EOT, end of treatment; h, hour; min, minutes; PK, pharmacokinetic; ZW25, zanidatamab.

[a] The samples for the PK and immunogenicity analysis of ZW25 will not be required after the data cutoff date of the final analysis.

[b] Sampling on Cycle 1 Day 5 is optional.

[c] Only required if the patient has completed less than 6 months of treatment.

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

APPENDIX 1D. ZW25 PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING SCHEDULE – SPARSE FOR REMAINING PATIENTS IN COHORTS 1A/B AND COHORTS 2A/B

Time	Cycle 1 Day 1		Cycle 2 Day 1		Day 1 of Cycle 5, 9, 17, 26, 35, and Every 17 Cycles Thereafter[a]		EOT/Safety Follow-up Visit[a]
	Predose	0 h postdose	Predose	0 h postdose	Predose	0 h postdose	
Window Allowed	**-1 h**	**+15 min**	**-1 h**	**+15 min**	**-1 h**	**+15 min**	
PK Serum Sample	X	X	X	X	X	X	X [b]
ADA Serum Sample	X		X		X		X [c]

Abbreviations: ADA, antidrug antibody; EOT, end of treatment; h, hour; min, minutes; PK, pharmacokinetic; ZW25, zanidatamab.

[a] The samples for the PK and immunogenicity analysis of ZW25 will not be required after the data cutoff date of the final analysis.

[b] Only required if the patient has completed less than 6 months of treatment.

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

APPENDIX 1E. TISLELIZUMAB PHARMACOKINETIC AND IMMUNOGENICITY SAMPLING SCHEDULE – FOR PATIENTS IN COHORT 2

Time[a]	Cycle 1 Day 2		Cycle 2 Day 2	Cycle 5 Day 1		Cycle 9 Day 1	Cycle 17 Day 1[b]	EOT/Safety Follow-up Visit[b]
	Predose	0 h postdose	Predose	Predose	0 h postdose	Predose	Predose	
Window Allowed	**-1 h**	**+15 min**	**-1 h**	**-1 h**	**+15 min**	**-1 h**	**-1 h**	
PK Serum Sample[c]	X	X	X	X	X	X	X	X
ADA Serum Sample[d]	X		X	X		X	X	X

Abbreviations: ADA, antidrug antibody; EOT, end of treatment; h, hour; IEC, Independent Ethics Committee; IRB, Institutional Review Board; min, minutes; PK, pharmacokinetic; ZW25, zanidatamab.

[a] On each cycle, ZW25 will be dosed on Day 1, and for the first 2 cycles, tislelizumab and chemotherapy will be dosed on Day 2; please refer to Section 5.2 for the details of dosing arrangement.

[b] The samples for the PK and immunogenicity analysis of tislelizumab will not be required after the data cutoff date of the final analysis.

[c] Should a patient taken tislelizumab present with any Grade 3 or above immune-mediated adverse event, an additional blood PK samples may be taken to determine the serum concentration of tislelizumab. These tests are required when it is allowed by local regulations/IRBs/IECs.

[d] All samples should be drawn at the same time as blood collection for pre-dose PK samples. These tests are required when it is allowed by local regulations/IRBs/IECs.

APPENDIX 2. CLINICAL LABORATORY ASSESSMENTS

Clinical chemistry	Hematology	Coagulation	Urinalysis (screening and as clinically indicated)	Thyroid Function (for Cohort 2)
Alkaline phosphatase	Red blood cell count	Prothrombin time	pH	Free T3[a]
Alanine aminotransferase	Hematocrit	Partial thromboplastin time or activated partial thromboplastin time	Specific gravity	Free T4
Aspartate aminotransferase	Hemoglobin	International normalized ratio	Glucose	TSH
Albumin	Monocyte count		Protein	
Total bilirubin	Basophil count		Ketones	
Blood urea nitrogen	Eosinophil count		Blood	
Potassium	Platelet counts		24-hour protein[b]	
Sodium	Neutrophil count			
Calcium	Lymphocyte count			
Phosphorus	White blood cell count			
Creatinine				
Glucose				
Lactate dehydrogenase				
Total protein				
Lipase				
Amylase				
Creatine kinase/ CK-MB[c]				

Abbreviations: CK-MB, creatine kinase-muscle/brain; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

[a] For local sites where free T3 testing is not available, total T3 will be tested as an alternative option.

[b] On routine urinalysis, if urine protein is ≥ 2+ by dipstick then obtain a 24-hour urine sample for total protein directly.

[c] Cardiac isoenzyme testing will be performed for all patients in both cohorts. In the event that CK-MB fractionation is not available, please assess troponin I and/or troponin T instead. Investigators should make every effort to perform either CK-MB, troponin I and/or troponin T consistently at screening and at follow-up visits.

APPENDIX 3. ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published by Oken et al 1982. Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

APPENDIX 4. PRE-EXISTING IMMUNE DEFICIENCIES OR AUTOIMMUNE DISEASES

Prospective patients in Cohort 2 should be carefully questioned to determine whether they have any history of an acquired or congenital immune deficiency or autoimmune disease. Please contact the medical monitor regarding any uncertainty about immune deficiency/autoimmune disease exclusions.

Acute disseminated encephalomyelitis	Addison disease
Ankylosing spondylitis	Antiphospholipid antibody syndrome
Aplastic anemia	Autoimmune hemolytic anemia
Autoimmune hepatitis	Autoimmune hypoparathyroidism
Autoimmune hypophysitis	Autoimmune myocarditis
Autoimmune oophoritis	Autoimmune orchitis
Autoimmune thrombocytopenic purpura	Behcet disease
Bullous pemphigoid	Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome	Crohn disease
Dermatomyositis	Dysautonomia
Epidermolysis bullosa acquisita	Gestational pemphigoid
Giant cell arteritis	Goodpasture syndrome
Granulomatosis with polyangiitis	Graves disease
Guillain-Barré syndrome	Hashimoto disease
Immunoglobulin A (IgA) neuropathy	Inflammatory bowel disease
Interstitial cystitis	Kawasaki disease
Lambert-Eaton myasthenia syndrome	Lupus erythematosus
Lyme disease (chronic)	Mooren ulcer
Morphea	Multiple sclerosis
Myasthenia gravis	Neuromyotonia
Opsoclonus myoclonus syndrome	Optic neuritis
Ord thyroiditis	Pemphigus
Pernicious anemia	Polyarteritis nodosa
Polyarthritis	Polyglandular autoimmune syndrome
Primary biliary cirrhosis	Psoriasis
Reiter syndrome	Rheumatoid arthritis
Sarcoidosis	Sjögren syndrome
Stiff person syndrome	Takayasu arteritis
Ulcerative colitis	Vogt-Koyanagi-Harada disease

APPENDIX 5. CONTRACEPTION GUIDELINES AND DEFINITIONS OF "WOMEN OF CHILDBEARING POTENTIAL," "NO CHILDBEARING POTENTIAL"

Contraception Guidelines

All male patients with partners of childbearing potential who take part in this study must use condoms during sexual intercourse in addition to 1 of the highly effective methods of contraception listed below, for the duration of the study and for at least 7 months after taking the last dose of study drug(s). If a female partner of a male patient is already pregnant, the male patient must use condoms during sexual intercourse for the duration of the study and for at least 7 months after the last dose of study drug(s).

Female patients of childbearing potential must use one of the highly effective forms of birth control listed below (preferably those with low user dependency) for the duration of the study and for at least 7 months after the last dose of study drug(s). Specifically, for females of childbearing potential in Cohort 1, hormonal forms of contraception (oral, injectable, or implantable) are not allowed.

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control (Clinical Trials Facilitation Group 2020). These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
  - oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation:
  - Oral, injectable, implantable
  - Note: Oral birth control pills are not considered a highly effective form of birth control, and if they are selected, they must be used with a second, barrier method of contraception such as condoms with or without spermicide
- An intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized male partner,
  - Note: This is only considered a highly effective form of birth control when the vasectomized partner is the sole partner of the study participant and there has been a medical assessment confirming surgical success
  - A sterile male is one for whom azoospermia, in a semen sample, has been demonstrated as definitive evidence of infertility

- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment). NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence for the duration of exposure to study drug(s), and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception and if used, this method must be combined with another acceptable method listed above.

Definitions of "Women of Childbearing Potential," "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as female patients meeting any of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

Adapted from: Clinical Trials Facilitation Group. Recommendations related to contraception and pregnancy testing in clinical trials. September 21, 2020. https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf.

APPENDIX 6. NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity (eg, no shortness of breath when walking, climbing stairs, et cetera).
II	Mild symptoms (eg, mild shortness of breath and/or angina). Slight limitations during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, (eg, walking short distances [20-100 meters]). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

APPENDIX 7. CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI) EQUATION

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[a] equation and the Modification of Diet in Renal Disease Study equation. National Kidney Disease Education Program calculators rely on creatinine determinations which are isotope dilution mass spectrometry traceable. All laboratories should be using creatinine methods calibrated to be isotope dilution mass spectrometry traceable.

The CKD-EPI equation calculator should be used when serum creatinine (S_{cr}) reported in mg/dL. This equation is recommended when estimated GFR values above 60 mL/min/1.73 m^2 are desired.

$$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{cr}/κ or 1, and

max indicates the maximum of S_{cr}/κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area.

The online calculator for CKD-EPI can be found here: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators

[a] Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

APPENDIX 8. IMMUNE-MEDIATED ADVERSE EVENT EVALUATION AND MANAGEMENT

The recommendations below for the diagnosis and management of any immune-mediated adverse event (imAE) are intended as guidance. This document should be used in conjunction with expert clinical judgement (by specialist physicians experienced in the treatment of cancer using immunological agents) and individual institutional guidelines or policies.

Criteria used to diagnose imAEs include blood tests, diagnostic imaging, histopathology, and microbiology assessments to exclude alternative causes such as infection, progressive disease, and adverse effects of concomitant drugs. In addition to the results of these tests, the following factors should be considered when making an imAE diagnosis:

- What was the temporal relationship between initiation of study drug(s) and the AE?
- How did the patient respond to withdrawal of study drug(s)?
- Did the event recur when study drug(s) was/were reintroduced?
- Was there a clinical response to corticosteroids?
- Is the event an autoimmune endocrinopathy?
- Is progressive disease or an alternative diagnosis a more likely explanation?

When alternative explanations to autoimmune toxicity have been excluded, the imAE field associated with the AE in the electronic case report form should be checked.

Recommended diagnostic tests in the management of possible immune-mediated adverse events	
Immune-mediated toxicity	**Diagnostic evaluation guideline**
Thyroid disorders	Scheduled and repeat thyroid function tests (TSH and T4).
Hypophysitis	Check visual fields and consider pituitary endocrine axis blood profile. Perform pituitary and whole brain MRI in patients with headache, visual disturbance, unexplained fatigue, asthenia, weight loss, and unexplained constitutional symptoms. Consider consultation with an endocrinologist if an abnormality is detected.
Pneumonitis	All patients presenting with new or worsened pulmonary symptoms or signs, such as an upper respiratory infection, new cough, shortness of breath or hypoxia should be assessed by high-resolution CT. Consider pulmonary function test including *D*LCO. Radiographic appearance is often nonspecific. Depending on the location of the abnormality, bronchoscopy and bronchoalveolar lavage or lung biopsy may be considered. Consult with a respiratory medicine physician for cases of uncertain cause.
Neurological toxicity	Perform a comprehensive neurological examination and brain MRI for all CNS symptoms; review alcohol history and other medications. Conduct a diabetic screen, and assess blood B12/folate, HIV status, TFTs, and consider autoimmune serology. Consider the need for brain/spine MRI/MRA and nerve conduction study for peripheral neuropathy. Consult with a neurologist if there are abnormal findings.

Recommended diagnostic tests in the management of possible immune-mediated adverse events	
Immune-mediated toxicity	**Diagnostic evaluation guideline**
Colitis	Review dietary intake and exclude steatorrhea. Consider comprehensive testing, including the following: FBC, UEC, LFTs, CRP, TFTs, stool microscopy and culture, viral PCR, *Clostridium difficile* toxin, and cryptosporidia (drug-resistant organism). In case of abdominal discomfort, consider imaging, eg, X-ray, CT scan. If a patient experiences bleeding, pain or distension, consider colonoscopy with biopsy and surgical intervention, as appropriate.
Eye disorders	If a patient experiences acute, new onset, or worsening of eye inflammation, blurred vision, or other visual disturbances, refer the patient urgently to an ophthalmologist for evaluation and management.
Hepatitis	Check ALT/AST/total bilirubin, INR/albumin; the frequency will depend on severity of the AE (eg, daily if ≥ 3-4; every 2-3 days if Grade 2, until recovering). Review medications (eg, statins, antibiotics) and alcohol history. Perform liver screen including hepatitis A/B/C serology, hepatitis E PCR and assess anti-ANA/SMA/LKM/SLA/LP/LCI, iron studies. Consider imaging (eg, ultrasound scan for metastases or thromboembolism). Consult with a hepatologist and consider liver biopsy.
Renal toxicity	Review hydration status and medication history. Test and culture urine. Consider renal ultrasound scan, protein assessment (dipstick/24-hour urine collection), or phase-contrast microscopy. Refer to nephrology for further management assistance.
Dermatology	Consider other causes by conducting a physical examination; consider dermatology referral for skin biopsy.
Joint or muscle inflammation	Conduct musculoskeletal history and perform complete musculoskeletal examination. Consider joint X-ray and other imaging as required to exclude metastatic disease. Perform autoimmune serology and refer to rheumatology for further management assistance. For suspected myositis/rhabdomyolysis/myasthenia include: CK, ESR, CRP, troponin I and consider a muscle biopsy.
Myocarditis	Perform ECG, echocardiogram, troponin I, and refer to a cardiologist.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CK, creatine kinase; CNS, central nervous system; CRP, C-reactive protein; CT, computed tomography; *D*LCO, diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; FBC, full blood count; INR, international normalized ratio; LCI, liver cytosolic antigen; LFT, liver function test; LKM, liver kidney microsomal antibody; LP, liver pancreas antigen; MRA, magnetic resonance angiogram; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; SLA, soluble liver antigen; SMA, smooth muscle antibody; T4, thyroxine; TFT, thyroid function tests; TSH, thyroid-stimulating hormone; UEC, urea electrolytes and creatinine.

Treatment of Immune-mediated Adverse Events

- Immune-mediated AEs can escalate quickly; study treatment interruption, close monitoring, timely diagnostic work-up, and treatment intervention, as appropriate, with patients is required
- Immune-mediated AEs should improve promptly after introduction of immunosuppressive therapy. If this does not occur, review the diagnosis, seek further specialist advice, and contact the medical monitor
- For some Grade 3 toxicities that resolve quickly, rechallenge with study drug(s) may be considered if there is evidence of a clinical response to study treatment after consultation with the medical monitor
- Steroid dosages in the table below are for oral or intravenous (methyl)prednisolone. Equivalent dosages of other corticosteroids can be substituted. For steroid-refractory imAEs, consider use of steroid-sparing agents (eg, mycophenolate mofetil [MMF])
- Consider prophylactic antibiotics for opportunistic infections if the patient is receiving long-term immunosuppressive therapy

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Thyroid disorders	**1-2** Asymptomatic TFT abnormality or mild symptoms	Replace thyroxine if hypothyroid, until TSH/T4 levels return to normal range. Thyrotoxic patients should be referred to an endocrinologist. In cases with systemic symptoms: withhold study treatment, treat with a beta blocker and consider oral prednisolone 0.5 mg/kg/day for thyroid pain. Taper corticosteroids over 2-4 weeks. Monitor thyroid function regarding the need for hormone replacement.	Continue study treatment or withhold treatment in cases with systemic symptoms.
	3-4 Severe symptoms, hospitalization required	Refer patient to an endocrinologist. If hypothyroid, replace with thyroxine 0.5-1.6 µg/kg/day (for the elderly or those with co-morbidities, the suggested starting dose is 0.5 µg/kg/day). Add oral prednisolone 0.5 mg/kg/day for thyroid pain. Thyrotoxic patients require treatment with a beta blocker and may require carbimazole until thyroiditis resolves.	Hold study treatment; resume when resolved/improved to Grade 0-1.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Hypophysitis	**1-2** Mild symptoms	Refer patient to an endocrinologist for hormone replacement. Add oral prednisolone 0.5-1 mg/kg/day for patients with pituitary inflammation. Taper corticosteroids over at least 1 month. If there is no improvement in 48 hours, treat as Grade 3-4. Taper corticosteroids over at least 1 month.	Continue study treatment.
	3-4 Moderate-severe symptoms	Refer patient to an endocrinologist for assessment and treatment. Initiate pulse IV methylprednisolone 1 mg/kg for patients with headache/visual disturbance due to pituitary inflammation. Convert to oral prednisolone and taper over at least 1 month. Maintain hormone replacement according to endocrinology advice. Maintain hormone replacement according to endocrinology advice.	Hold study treatment for patients with headache/visual disturbance due to pituitary inflammation until resolved/improved to Grade 2 or less. Discontinuation is usually not necessary.
Pneumonitis	**1** Radiographic changes only	Monitor symptoms every 2-3 days. If appearance worsens, treat as Grade 2.	Consider holding study treatment until appearance improves and cause is determined.
	2 Symptomatic: exertional breathlessness	Commence antibiotics if infection suspected. Add oral prednisolone 1 mg/kg/day if symptoms/appearance persist for 48 hours or worsen. Consider *Pneumocystis* infection prophylaxis. Taper corticosteroids over at least 6 weeks. Consider prophylaxis for adverse steroid effects: eg, blood glucose monitoring, vitamin D/calcium supplement.	Hold study treatment. Retreatment is acceptable if symptoms resolve completely or are controlled on prednisolone ≤ 10 mg/day. Discontinue study treatment if symptoms persist with corticosteroid treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	3-4 Severe or life-threatening symptoms Breathless at rest	Admit to a hospital and initiate treatment with IV methylprednisolone 2-4 mg/kg/day. If there is no improvement, or worsening after 48 hours, add infliximab 5 mg/kg (if no hepatic involvement). Convert to oral prednisolone and taper over at least 2 months. Cover with empiric antibiotics and consider prophylaxis for *Pneumocystis* infection and other adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement.	Discontinue study treatment.
Neurological toxicity	**1** Mild symptoms	–	Continue study treatment.
	2 Moderate symptoms	Treat with oral prednisolone 0.5-1 mg/kg/day. Taper over at least 4 weeks. Obtain neurology consultation.	Hold study treatment; resume when resolved/improved to Grade 0-1.
	3-4 Severe/life-threatening	Initiate treatment with oral prednisolone or IV methylprednisolone 1-2 mg/kg/day, depending on symptoms. Taper corticosteroids over at least 4 weeks. Consider azathioprine, MMF, cyclosporine if no response within 72-96 hours.	Discontinue study treatment.
Colitis/diarrhea	**1** Mild symptoms: < 3 liquid stools per day over baseline and feeling well	Symptomatic management: fluids, loperamide, avoid high fiber/lactose diet. If Grade 1 persists for > 14 days manage as a Grade 2 event.	Continue study treatment.
	2 Moderate symptoms: 4-6 liquid stools per day over baseline, or abdominal pain, or blood in stool, or nausea, or nocturnal episodes	Oral prednisolone 0.5 mg/kg/day (non-enteric coated). Do not wait for any diagnostic tests to start treatment. Taper steroids over 2-4 weeks, consider endoscopy if symptoms are recurring.	Hold study treatment; resume when resolved/improved to baseline grade.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	3 Severe symptoms: > 6 liquid stools per day over baseline, or if episodic within 1 hour of eating	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Consider prophylaxis for adverse steroid effects, eg, blood glucose monitoring, vitamin D/calcium supplement. If no improvement in 72 hours or symptoms worsen, consider infliximab 5 mg/kg if no perforation, sepsis, TB, hepatitis, NYHA Grade III/IV CHF or other immunosuppressive treatment: MMF or tacrolimus. Consult gastroenterologist to conduct colonoscopy/sigmoidoscopy.	Hold study treatment; retreatment may be considered when resolved/improved to baseline grade and after discussion with the study medical monitor.
	4 Life-threatening symptoms		Discontinue study treatment.
Skin reactions	**1** Skin rash, with or without symptoms, < 10% BSA	Avoid skin irritants and sun exposure; topical emollients recommended.	Continue study treatment.
	2 Rash covers 10%-30% of BSA	Avoid skin irritants and sun exposure; topical emollients recommended. Topical steroids (moderate strength cream once a day or potent cream twice a day) ± oral or topical antihistamines for itch. Consider a short course of oral steroids.	Continue study treatment.
	3 Rash covers > 30% BSA or Grade 2 with substantial symptoms	Avoid skin irritants and sun exposure; topical emollients recommended. Initiate steroids as follows based on clinical judgement: For moderate symptoms: oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For severe symptoms: IV methylprednisolone 0.5-1 mg/kg/day; convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment. Re-treat when AE is resolved or improved to mild rash (Grade 1-2) after discussion with the study medical monitor.
	4 Skin sloughing > 30% BSA with associated symptoms (eg, erythema, purpura, epidermal detachment)	Initiate IV methylprednisolone 1-2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks. Admit to a hospital and seek urgent dermatology consultation.	Discontinue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Hepatitis	**1** ALT or AST > ULN to 3X ULN	Check LFTs within 1 week and before the next dose check LFTs to verify that there has been no worsening. If LFTs are worsening, recheck every 48-72 hours until improvement is seen.	Continue study treatment if LFTs are unchanged or improving. Hold study treatment if LFTs are worsening until improvement is seen.
	2 ALT or AST 3-5X ULN	Recheck LFTs every 48-72 hours: For persistent ALT/AST elevation: consider oral prednisolone 0.5-1 mg/kg/day for 3 days then taper over 2-4 weeks. For rising ALT/AST: start oral prednisolone 1 mg/kg/day and taper over 2-4 weeks; re-escalate dose if LFTs worsen, depending on clinical judgement.	Hold study treatment; treatment may be resumed when resolved/improved to baseline grade and prednisolone tapered to ≤ 10 mg.
	3 ALT or AST 5-20X ULN	ALT/AST < 400 IU/L and normal bilirubin/INR/albumin: Initiate oral prednisolone 1 mg/kg and taper over at least 4 weeks. ALT/AST > 400 IU/L or raised bilirubin/INR/low albumin: Initiate IV (methyl)prednisolone 2 mg/kg/day. When LFTs improve to Grade 2 or lower, convert to oral prednisolone and taper over at least 4 weeks.	Hold study treatment until improved to baseline grade; reintroduce only after discussion with the study medical monitor.
	4 ALT or AST > 20X ULN	Initiate IV methylprednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 6 weeks.	Discontinue study treatment.
	Worsening LFTs despite steroids: If on oral prednisolone, change to pulsed IV methylprednisolone If on IV, add MMF 500-1000 mg twice a day If worsens on MMF, consider addition of tacrolimus Duration and dose of steroid required will depend on severity of event		
Nephritis	**1** Creatinine 1.5X baseline or > ULN to 1.5X ULN	Repeat creatinine weekly. If symptoms worsen, manage as per criteria below.	Continue study treatment.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	2 Creatinine > 1.5X-3X baseline or > 1.5X-3X ULN	Ensure hydration and review creatinine in 48-72 hours; if not improving, consider creatinine clearance measurement by 24-hour urine collection. Discuss with nephrologist the need for kidney biopsy. If attributed to study drug, initiate oral prednisolone 0.5-1 mg/kg and taper over at least 2 weeks. Repeat creatinine/U&E every 48-72 hours.	Hold study treatment. If not attributed to drug toxicity, restart treatment. If attributed to study drug and resolved/improved to baseline grade: Restart study drug if tapered to < 10 mg prednisolone.
	3 Creatinine > 3X baseline or > 3X-6X ULN	Hospitalize patient for monitoring and fluid balance; repeat creatinine every 24 hours; refer to a nephrologist and discuss need for biopsy. If worsening, initiate IV (methyl)prednisolone 1-2 mg/kg. Taper corticosteroids over at least 4 weeks.	Hold study treatment until the cause is investigated. If study drug suspected: Discontinue study treatment.
	4 Creatinine > 6X ULN	As per Grade 3, patient should be managed in a hospital where renal replacement therapy is available.	Discontinue study treatment.
Diabetes/ hyperglycemia	**1** Fasting glucose value ULN to 160 mg/dL; ULN to 8.9 mmol/L	Monitor closely and treat according to local guideline. Check for C-peptide and antibodies against glutamic acid decarboxylase and islet cells are recommended.	Continue study treatment.
	2 Fasting glucose value 160-250 mg/dL; 8.9-13.9 mmol/L	Obtain a repeat blood glucose level at least every week. Manage according to local guideline.	Continue study treatment or hold treatment if hyperglycemia is worsening. Resume treatment when blood glucose is stabilized at baseline or Grade 0-1.
	3 Fasting glucose value 250-500 mg/dL; 13.9-27.8 mmol/L	Admit patient to hospital and refer to a diabetologist for hyperglycemia management. Corticosteroids may exacerbate hyperglycemia and should be avoided.	Hold study treatment until patient is hyperglycemia symptom-free, and blood glucose has been stabilized at baseline or Grade 0-1.
	4 Fasting glucose value > 500 mg/dL; > 27.8 mmol/L	Admit patient to hospital and institute local emergency diabetes management. Refer the patient to a diabetologist for insulin maintenance and monitoring.	

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Ocular toxicity	**1** Asymptomatic eye exam/test abnormality	Consider alternative causes and prescribe topical treatment as required.	Continue study treatment.
	2 Anterior uveitis or mild symptoms	Refer patient to an ophthalmologist for assessment and topical corticosteroid treatment. Consider a course of oral steroids.	Continue study treatment or hold treatment if symptoms worsen or if there are symptoms of visual disturbance.
	3 Posterior uveitis/panuveitis or significant symptoms	Refer patient urgently to an ophthalmologist. Initiate oral prednisolone 1-2 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
	4 Blindness (at least 20/200) in the affected eyes	Initiate IV (methyl)prednisolone 2 mg/kg/day. Convert to oral prednisolone and taper over at least 4 weeks.	Discontinue study treatment.
Pancreatitis	**2** Asymptomatic, blood test abnormalities	Monitor pancreatic enzymes.	Continue study treatment.
	3 Abdominal pain, nausea and vomiting	Admit to hospital for urgent management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when amylase/lipase improved to Grade 2, and taper over at least 4 weeks.	Hold study treatment; reintroduce only after discussion with the study medical monitor.
	4 Acute abdominal pain, surgical emergency	Admit to hospital for emergency management and appropriate referral.	Discontinue study treatment.
Arthritis	**1** Mild pain with inflammation, swelling	Management per local guideline.	Continue study treatment.
	2 Moderate pain with inflammation, swelling, limited instrumental (fine motor) activities	Management as per local guideline. Consider referring patient to a rheumatologist. If symptoms worsen on treatment manage as a Grade 3 event.	Continue treatment or, if symptoms continue worsens, hold study treatment until symptoms improve to baseline or Grade 0-1.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
	3 Severe pain with inflammation or permanent joint damage, daily living activity limited	Refer patient urgently to a rheumatologist for assessment and management. Initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment unless improved to Grade 0-1; reintroduce only after discussion with the study medical monitor.
Mucositis/ stomatitis	**1** Test findings only or minimal symptoms	Consider topical treatment or analgesia as per local guideline.	Continue study treatment.
	2 Moderate pain, reduced oral intake, limited instrumental activities	As per local guidelines, treat with analgesics, topical treatments, and oral hygiene care. Ensure adequate hydration. If symptoms worsen or there is sepsis or bleeding, manage as a Grade 3 event.	Continue study treatment.
	3 Severe pain, limited food and fluid intake, daily living activity limited	Admit to hospital for appropriate management. Initiate IV (methyl)prednisolone 1-2 mg/kg/day. Convert to oral prednisolone when symptoms improved to Grade 2 and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	4 Life-threatening complications or dehydration	Admit to hospital for emergency care. Consider IV corticosteroids if not contraindicated by infection.	Discontinue study treatment.
Myositis/ rhabdomyolysis	**1** Mild weakness with/without pain	Prescribe analgesics. If CK is significantly elevated and patient has symptoms, consider oral steroids and treat as Grade 2.	Continue study treatment.
	2 Moderate weakness with/without pain	If CK is 3 X ULN or worse initiate oral prednisolone 0.5-1 mg/kg and taper over at least 4 weeks.	Hold study treatment until improved to Grade 0-1.
	3-4 Severe weakness, limiting self-care	Admit to hospital and initiate oral prednisolone 1 mg/kg. Consider bolus IV (methyl)prednisolone and 1-2 mg/kg/day maintenance for severe activity restriction or dysphagia. If symptoms do not improve add immunosuppressant therapy. Taper oral steroids over at least 4 weeks.	Hold study treatment until improved to Grade 0-1. Discontinue if any evidence of myocardial involvement.

Autoimmune toxicity	Grade	Treatment guidelines (subject to clinical judgement)	Study drug management
Myocarditis	**1** Asymptomatic but abnormal CK-MB, cardiac troponin I or intraventricular conduction delay	Admit to hospital and refer to a cardiologist. Transfer all patients with moderate/severe cardiac symptoms or any increase in cardiac serum markers to the coronary care unit. Initiate oral prednisolone or IV (methyl)prednisolone at 1-2 mg/kg/day. Manage symptoms of cardiac failure according to local guidelines. If no immediate response change to pulsed doses of (methyl)prednisolone 1 g/day and add MMF, infliximab or anti-thymocyte globulin.	Hold study treatment until completely resolved or myocarditis has been ruled out.
	2 Symptoms on mild-moderate exertion		Discontinue study treatment unless cardiac involvement has been excluded and symptoms have completely resolved.
	3 Severe symptoms with mild exertion		
	4 Life-threatening		

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BSA, body surface area; CK, creatine kinase; CK-MB, creatine kinase-muscle/brain; CHF, congestive heart failure; INR, international normalized ratio; IV, intravenous; LFT, liver function test; MMF, mycophenolate mofetil; NYHA, New York Heart Association; T4, thyroxine; TB, tuberculosis; TFT, thyroid function test; TSH, thyroid-stimulating hormone; U&E, urea and electrolytes; ULN, upper limit of normal.

APPENDIX 9. THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) GUIDELINES, VERSION 1.1

The text below was obtained from the following reference:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-7.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical examination (when superficial).
- 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT or MRI scan (CT/MRI scan slice thickness recommended to be no > 5 mm). At baseline and in 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 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT

or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- 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 patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, 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 organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT or MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

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 as noted above, 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 pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph node" or "multiple liver metastases").

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start 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 should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are accessible by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

- Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, because CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete

pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.
- Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

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 diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of 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 1 or more new lesions is also considered progression).
- Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, stable

disease, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

- Target lesions that become "too small to measure." While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure."
- When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
- Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the protocol.

- 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).
- PD: Unequivocal progression (as detailed below) of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression.)
- Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable

disease or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of stable disease or PR of target disease will therefore be extremely rare.

- When the patient has only non-measurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general concept applies here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion).
- Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy." If "unequivocal progression" is seen, the patient should be considered to have had overall progressive disease at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes PD; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the patient who has visceral disease at baseline and while on trial has a CT or MRI brain scan ordered that reveals metastases. The patient's brain metastases are considered to be evidence of progressive disease even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While fluorine-18 [F-18] fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up, is a sign of progressive disease based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of progressive disease will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all timepoints (for example, a patient who has stable disease at first assessment, PR at second assessment, and progressive disease on last assessment has a best overall response of PR). When stable disease is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when stable disease is otherwise the best timepoint response, the patient's best response depends on the subsequent assessments. For example, a patient who has stable disease at first assessment, progressive disease at second and does not meet minimum duration for stable disease, will have a best response of PD. The same patient lost to follow-up after the first stable disease assessment would be considered inevaluable.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
Stable disease	Non-PD or not all evaluated	No	Stable disease
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response.

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

In trials where confirmation of response is required, repeated 'NE' timepoint assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with timepoint responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of progressive disease at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

Conditions that define "early progression, early death, and inevaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of stable disease, measurements must have met the stable disease criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/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 on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent 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 sum on study (if the baseline sum is the smallest, this is the reference for calculation of progressive disease).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between 2 measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX 10. DOSE MODIFICATION OF CHEMOTHERAPY

Cohort 1 – Docetaxel

Guidelines for docetaxel dose modifications to manage general toxicities are shown in Table 1 below.

Table 1. Guidelines for Docetaxel Dose Modifications

Adverse Event (Worst Grade in Previous Cycle)	Action to Be Taken
Febrile neutropenia/Grade 4 AGC ≥ 7 days	Withhold docetaxel until symptoms resolve[a] Reduce docetaxel to 75% of previous dose (e.g., from 75 mg/m^2 to 55 mg/m^2).
Grade 3 skin/neuropathy/major organ/non-hematologic toxicity	Withhold docetaxel until symptoms resolve. Reduce docetaxel to 75% of previous dose.
Grade 4 skin/neuropathy/major organ/non-hematologic toxicity OR Recurrence of Grade 3 toxicity after prior dose reduction	Discontinue docetaxel treatment.

Abbreviation: AGC, absolute granulocyte count.
[a] Do not re-treat until AGC ≥ 1.5 × 10^9, platelets ≥ 100 × 10^9, and toxicity ≤ Grade 2.

Patients who are dosed initially at 75 mg/m^2 and who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 (Grade 4) for more than 1 week, severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity and treatment then resumed at 55 mg/m^2. Patients who develop Grade > 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

Guidelines for the management of hepatotoxicity for docetaxel-treated patients are shown in Table 2.

Table 2. Guidelines for Management of Hepatotoxicity in Patients Receiving Docetaxel

	AST/ALT		Alkaline Phosphatase		Bilirubin	Docetaxel Dose
Mild to moderate	> 1.5 × ULN	and	> 2.5 × ULN			75%
Severe	> 3.5 × ULN[a]	and	> 6 × ULN	OR	> 1.5 x ULN[b]	Do not treat. Discontinue treatment if it is already started.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.
[a.] > 5 x ULN if liver metastasis exists; [b.] > 3 x ULN if Gilbert Syndrome or indirect bilirubin approved to be extrahepatic

Cohort 2 – Capecitabine and Oxaliplatin

Recommended Dose Modifications for Hematologic Toxicity

Dose adjustments are based on nadir blood counts since the preceding chemotherapy administration. Dose level adjustments are relative to that of the preceding administration. Recommended dose modifications for hematologic and non-hematologic toxicity are provided in Table 4 and Table 5 as below. Toxicities related to chemotherapy must be resolved to baseline or ≤ Grade 1 prior to administering the next dose of chemotherapy, with the exceptions of alopecia, Grade 2 fatigue, or other AEs, which, in the opinion of the investigator, would not affect the safety evaluation of the study drugs.

Table 3: Dose Reduction Level

Drug	Standard Level (Every 3 weeks as a cycle)	1st Level	2nd Level
Capecitabine	1000 mg/m^2, BID (total 14 days)	Reduce dose to 75%	Reduce dose to 50%
Oxaliplatin	130 mg/m^2 (Day 1)	Reduce dose to 100 mg/m^2	Reduce dose to 80 mg/m^2

Table 4: Dose Modifications for Hematologic Toxicities

AE	Grade	Dose Modifications
Febrile Neutropenia	3	1st occurrence: 1st reduced dose level 2nd occurrence: Stop treatment permanently unless it is in the best interest of the patient to treat with 2nd reduced dose level
	4	1st occurrence: Stop treatment permanently unless it is in the best interest of the patient to treat with 2nd reduced dose level 2nd occurrence: Stop treatment permanently
Neutrophil count decreased	1/2	Maintain dose level
	3/4	1st occurrence: 1st reduced dose level 2nd occurrence: 2nd reduced dose level 3rd occurrence: Stop treatment permanently
Platelet count decreased	1	Maintain dose level
	≥ 2	1st occurrence: 1st reduced dose level 2nd occurrence: 2nd reduced dose level 3rd occurrence: Stop treatment permanently

NOTE: If considered in the best interest of the patient and consistent with local practice, investigators may decide to use supportive measures / treatment and/or secondary prophylaxis instead of dose reductions for the next cycle. The provided triggers for dose modifications are recommendations only.

Table 5: Dose Modifications for Non-hematologic Toxicities

AE	Grade	Dose Modifications
Capecitabine		
Nausea/Vomiting	2	Immediately interrupted, 1st reduced dose level
	3 or 4	Immediately interrupted, 2nd reduced dose level
Hand/foot syndrome	2 or 3	Immediately interrupted, 1st reduced dose level
Stomatitis	2 or 3	Immediately interrupted, 1st reduced dose level
	4	Immediately interrupted, 2nd reduced dose level
Cardiac toxicity	≥ 2	Stop capecitabine permanently
Oxaliplatin		
Respiratory symptoms indicative of pulmonary fibrosis	any	Interrupt treatment and investigate cause of symptoms
Nausea and/or vomiting	3 or 4	1st reduced dose level
Diarrhea	3 or 4	1st reduced dose level
Peripheral neuropathy (Paresthesia)	2	Last < 21 days: Maintain dose level Last ≥ 21 days: Delay then 1st reduced dose level
	3	Last < 7 days: Maintain dose level Last ≥ 7 days: 1st reduced dose level Last ≥ 21 days: Stop Oxaliplatin permanently
	4	Stop Oxaliplatin permanently

Recommended Dose Modifications and Management for Diarrhea

Careful consideration of which agent is most likely to be contributing is important for evaluation, treatment, and management, including appropriate dose modification(s) Persistent diarrhea despite standard antidiarrheal medications (eg, loperamide, octreotide, and diphenoxylate-atropine) or diarrhea that is associated with significant abdominal pain, bloody stools, or signs of systemic inflammation should be further investigated to rule out infectious etiologies as well as immunotherapy-associated colitis. Gastroenterology consultation and sigmoidoscopy with biopsy should be strongly considered in such cases. Refer to Appendix 8 for recommendations on evaluation of suspected immune-mediated colitis.

Subjects receiving CAPOX in any combination regimen require mandatory diarrhea prophylaxis during the first cycle of treatment (Section 6.2.1.2). If subjects develop diarrhea despite mandatory prophylaxis or after completion of mandatory prophylaxis, loperamide should be increased or restarted. Dose modification of ZW25 is listed in Section 5.5.2, Table 4.

For 1st occurrence of Grade 2 diarrhea, capecitabine should be interrupted immediately and should not be restarted until the diarrhea has resolved to Grade 0 or 1. When resuming capecitabine, either in the same cycle or at subsequent cycles, consider dose reduction by one dose level. Symptomatic treatment with loperamide is recommended, and prevention or reversal of fluid and electrolyte depletion should be taken into consideration. Diarrhea of > 2 days duration requires medical evaluation including relevant diagnostic procedures and alternative or additional anti-diarrheal treatments.

If subjects develop Grade 3 diarrhea, or recurs Grade 2 diarrhea despite prophylaxis, the dose of capecitabine should be mandatorily modified down by one dose level. In addition, subjects with severe diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated. Oxaliplatin dose reduction, by one dose level, should also be considered.

For 1st occurrence of Grade 4 diarrhea or recurring Grade 3 diarrhea, discontinuation of capecitabine should be strongly considered. Alternatively, re-challenge with capecitabine with dose reduction by two dose levels, could be considered based on Investigator's risk-benefit assessment and discussion with Sponsor's Medical Monitor. Dose of oxaliplatin also should be modified. If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.

APPENDIX 11. PRINCIPLES OF PATHOLOGIC REVIEW AND HER2 TESTING

Table 1: Optimal Algorithm for HER2 Testing in Breast Cancer by ASCO-CAP Recommendations[a]

2013 Recommendations	2018 Focused Update Recommendations
Must report HER2 test result as positive for HER2 if: IHC 3+ based on circumferential membrane staining that is complete, intense ISH positive based on: • Single-probe average HER2 copy number ≥ 6.0 signals/cell • Dual-probe HER2/CEP17 ratio of ≥ 2.0; with an average HER2 copy number ≥ 4.0 signals/cell • Dual-probe HER2/CEP17 ratio of ≥ 2.0; with an average HER2 copy number < 4.0; • Dual-probe HER2/CEP17 ratio of < 2.0 with an average HER2 copy number ≥ 6.0 signals/cell Must report HER2 test result as equivocal and order reflex test (same specimen using the alternative test) or new test (new specimen, if available, using same or alternative test) if: IHC 2+ based on circumferential membrane staining that is incomplete and/or weak to moderate and within > 10% of the invasive tumor cells or complete and circumferential membrane staining that is intense and within ≤ 10% of the invasive tumor cells ISH equivocal based on: • Single-probe ISH average HER2 copy number ≥ 4.0 and ≤ 6.0 signals/cell • Dual-probe HER2/CEP17 ratio of < 2.0 with an average HER2 copy number ≥ 4.0 and ≤ 6.0 signals/cell Must report HER2 test result as negative if a single test (or both tests) performed show: • IHC 1+ as defined by incomplete membrane staining that is faint or barely perceptible and within > 10% of the invasive tumor cells	1.The revised definition of IHC 2+ (equivocal) is invasive breast cancer with "weak to moderate complete membrane staining observed in > 10% of tumor cells." 2. It is now stated that, on the basis of some criteria (including a tumor grade 3), "If the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may be ordered on the excision specimen" 3. If a case has a HER2/CEP17 ratio of ≥ 2.0 but the average HER2 signals/cell is < 4.0, a definitive diagnosis will be rendered based on additional work-up. If not already assessed by the institution or laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH, and the slides from both ISH and IHC should be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant assessment): a. If the IHC result is 3+, diagnosis is HER2-positive b. If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that include the area of invasive cancer with IHC 2+ staining: • If reviewing the count by the additional observer changes the result into another ISH category, the result should be adjudicated per internal procedures to define the final category. • If the count remains an average of < 4.0 HER2 signals/cell and the HER2/CEP17 ratio is ≥ 2.0, diagnosis is HER2-negative with a comment c. If the IHC result is 0 or 1+, diagnosis is HER2-negative with a comment. 4. If a case has an average of ≥ 6.0 HER2 signals/cell with a HER2/CEP17 ratio of < 2.0, formerly diagnosed as ISH positive for HER2, a

2013 Recommendations	2018 Focused Update Recommendations
• IHC 0 as defined by no staining observed or membrane staining that is incomplete and is faint or barely perceptible and within ≤ 10% of the invasive tumor cells ISH negative based on: • Single-probe average HER2 copy number < 4.0 signals/cell • Dual-probe HER2/CEP17 ratio of < 2.0 with an average HER2 copy number of 4.0 signals/cell Must report HER2 test result as indeterminate if technical issues prevent one or both tests (IHC and ISH) from being reported as positive, negative, or equivocal. Conditions may include: • Inadequate specimen handling • Artifacts (crush or edge artifacts) that make interpretation difficult • Analytic testing failure • Another specimen should be requested for testing to determine HER2 status • Reason for indeterminate testing should be noted in a comment in the report.	definitive diagnosis will be rendered based on additional work-up. If not already assessed by the institution or laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH, and the slides from both ISH and IHC should be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant review): a. If the IHC result is 3+, diagnosis is HER2-positive b. If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that include the area of invasion with IHC 2+ staining: • If reviewing the count by the additional observer changes the result into another ISH category, the result should be adjudicated per internal procedures to define the final category • If the HER2/CEP17 ratio remains < 2.0 with ≥ 6.0 HER2 signals/cell, diagnosis is HER2-positive c. If the IHC result is 0 or 1+, diagnosis is HER2-negative with a comment 5. If the case has an average HER2 signals/tumor cell of ≥ 4.0 and < 6.0 and the HER2/CEP17 ratio is < 2.0, formerly diagnosed as ISH equivocal for HER2, a definitive diagnosis will be rendered based on additional work-up. If not already assessed by the institution or laboratory performing the ISH test, IHC testing for HER2 should be performed using sections from the same tissue sample used for ISH, and the slides from both ISH and IHC should be reviewed together to guide the selection of areas to score by ISH (local practice considerations will dictate the best procedure to accomplish this concomitant review): a. If the IHC result is 3+, diagnosis is HER2-positive b. If the IHC result is 2+, recount ISH by having an additional observer, blinded to previous ISH results, count at least 20 cells that include the area of invasion with IHC 2+ staining:

2013 Recommendations	2018 Focused Update Recommendations
	• If reviewing the count by the additional observer changes the result into another ISH category, the result should be adjudicated per internal procedures to define the final category • If the count remains an average of ≥ 4.0 and < 6.0 HER2 signals/cell with a HER2/CEP17 ratio of < 2.0, diagnosis is HER2-negative with a comment c. If the IHC result is 0 or 1+, diagnosis is HER2-negative with a comment

Abbreviations: CEP17, chromosome enumeration probe 17; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.

[a] Wolff AC, Hammond MEH, Allison KH, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J. Clin. Oncol. 2018; 36(20):2105-22.

Table 2: Immunohistochemical Criteria for Scoring HER2 Expression in Gastric Cancer[a]

	Surgical specimen expression pattern, immunohistochemistry	Biopsy specimen expression pattern, immunohistochemistry	HER2 overexpression assessment
0	No reactivity or membranous reactivity in < 10% of cancer cells	No reactivity or no membranous reactivity in any cancer cell	Negative
1+	Faint or barely perceptible membranous reactivity in ≥ 10% of cancer cells; cells are reactive only in part of their membrane	Cancer cell cluster with a faint or barely perceptible membranous reactivity irrespective of percentage of cancer cells positive	Negative
2+	Weak to moderate complete, basolateral, or lateral membranous reactivity in ≥ 10% of cancer cells	Cancer cell cluster with a weak to moderate complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Equivocal
3+	Strong complete, basolateral, or lateral membranous reactivity in ≥ 10% of cancer cells	Cluster of five or more cancer cells with a strong complete, basolateral, or lateral membranous reactivity irrespective of percentage of cancer cells positive	Positive

Abbreviation: HER2, human epidermal growth factor receptor 2.

Notes: The NCCN Guidelines panel recommends that HER2 immunohistochemistry (IHC) be ordered/performed first, followed by in situ hybridization methods in cases showing 2+ (equivocal) expression by IHC. Positive (3+) or

negative (0 or 1+) HER2 IHC results do not require further ISH testing. Cases with HER2:CEP17 ratio ≥2 or an average HER2 copy number ≥6.0 signals/cell are considered positive by ISH/FISH.

[a] NCCN Guidelines Gastric Cancer, Version 2. 2019.

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Approved Date 2023年05月26日

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