

Protocol Number: ADCT-502-101

Official Title: A Phase 1, Open-Label, Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of ADCT-502 in Patients With Advanced Solid Tumors With HER2 Expression

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A Phase 1, Open-Label, Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of ADCT-502 in Patients with Advanced Solid Tumors with HER2 Expression

PROTOCOL NO.: ADCT-502-101**Sponsor:****ADC Therapeutics SA**
**Sponsor Contact:****Medical Monitor:**

Date of Original Protocol: 18 January 2017
Date of Protocol Amendment 1: 20 March 2017
Date of Protocol Amendment 2: 17 August 2017

Confidentiality Statement

All financial and nonfinancial support for this study will be provided by ADC Therapeutics SA. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of ADC Therapeutics SA. The study will be conducted according to the current version of the International Council for Harmonisation harmonised tripartite guideline E6, Good Clinical Practice.

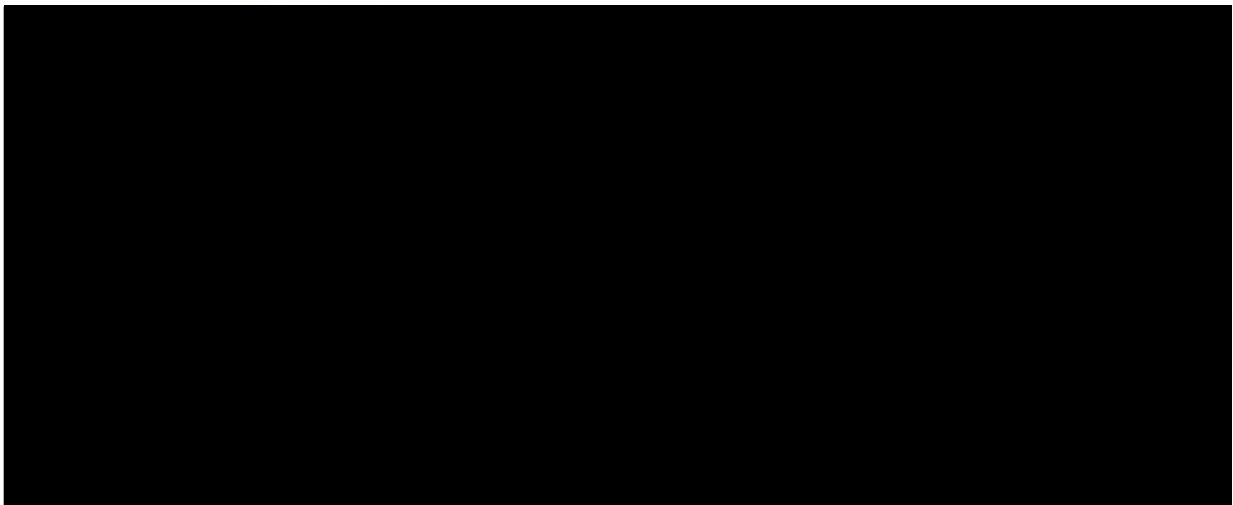
Protocol Approval – Sponsor Signatory

Study Title A Phase 1, Open-Label, Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of ADCT-502 in Patients with Advanced Solid Tumors with HER2 Expression

Protocol Number ADCT-502-101

Date of Protocol Amendment 2: 17 August 2017

Protocol accepted and approved by:



Declaration of Investigator

I have read and understood all sections of the protocol entitled: “A Phase 1, Open-Label, Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of ADCT-502 in Patients with Advanced Solid Tumors with HER2 Expression “ and the accompanying Investigator Brochure (IB).

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Amendment 2, dated 17 August 2017, the current version of the International Council for Harmonisation (ICH) harmonised tripartite guideline E6: Good Clinical Practice and all applicable governmental regulations. I will not make changes to the protocol before consulting with ADC Therapeutics or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a sub-Investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ADC Therapeutics SA.

Signature of Principal Investigator

Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number:	ADCT-502-101
Title:	A Phase 1, Open-Label, Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of ADCT-502 in Patients with Advanced Solid Tumors with HER2 Expression
Sponsor:	ADC Therapeutics SA
Study Phase:	Phase 1
Indication:	<p>Five (5) types of patients, based on HER2 expression levels and mutations, are selected in this FIH study of ADCT-502:</p> <ol style="list-style-type: none">1. Patients with indications and HER2 expression levels that qualified them for (prior) treatment with trastuzumab and/or ado-trastuzumab emtansine, e.g., HER2 positive BC and HER2 positive G/GE cancer.2. Patients with BC or G/GE cancer with HER2 expression that is present, but at a level that is below the threshold qualifying them for Item Number 1.3. Patients with HER2 expression levels equivalent to Item Number 1, but who have a tumor type other than BC or G/GE cancer (NSCLC, small cell lung cancer (SCLC), CRC, bladder, pancreatic, biliary tract, prostate, ovarian, endometrial, and salivary gland cancer).4. Patients from the same indication list as in Item Number 3, except with HER2 expression levels present but lower than that, i.e. equivalent to expression levels in Item Number 2.5. Patients with 1 of the 12 indications mentioned in Items 1–4 who have been shown to possess a <i>HER2</i> hotspot mutation; they are either classified as HER2-high if a concomitant amplification was demonstrated, otherwise they are classified as HER2-low. Patients with such <i>HER2</i> genetic alteration pre-defined prior to study enrollment and not belonging to 1 of the 12 indications may be included in the dose escalation part after sponsor agreement.
Rationale:	<p>The mechanism of action and preclinical data of ADCT-502 supports its use in patients with relapsed or refractory metastatic breast and gastric cancer who have been previously treated with trastuzumab/T-DM1. Given the substantial prevalence of HER2 expression in a range of other advanced cancers, including NSCLC, bladder, biliary tract, and ovarian cancer, for which HER2 targeted therapies are not licensed, ADCT-502 will also be evaluated as an anticancer treatment in patients with such tumor types for which there is published clinical evidence of HER2 expression. Also, there is high unmet medical need in breast and gastric/GE junction cancers in which HER2 expression is observed but below the defined thresholds for HER2 targeted therapy.</p> <p>Results of preclinical studies in PDX suggest that ADCT-502 may have potent clinical activity in both groups of patients, those with HER2-positive/high tumors as well as those [REDACTED]</p>

Objectives:

Primary Objectives

- Evaluate safety, tolerability, and determine the MTD and/or RDE of single agent ADCT-502 in patients with advanced solid tumors with known HER2 status (IHC $\geq 1+$ or HER2 amplified/mutated) (Part 1).
- Further evaluate safety and tolerability at the dose level determined in Part 1 in patients with advanced solid tumors including breast cancer, lung, gastroesophageal, and bladder cancer or a basket of other solid tumors known to express HER2 (HER2-high or HER2-low status confirmed prospectively for study entry) (Part 2).

Secondary Objectives

- Evaluate the preliminary antitumor activity of ADCT-502.
- Characterize the PK profile of ADCT-502.
- Determine the immunogenicity of ADCT-502.

Patient Selection:

Inclusion Criteria

1. Male or female age 18 years or older.
2. Refractory to or intolerant of existing therapy(ies) known to provide clinical benefit for their condition.
3. Eastern Cooperative Oncology Group (ECOG) performance status:
 - a. Part 1: 0-2
 - b. Part 2: 0-1
4. Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block (or unstained slides (minimum 7; 10 preferred) if block is not available) to demonstrate HER2 expression.

Note: any biopsy since initial diagnosis is acceptable, but if several are available, the most recent sample is preferred.
5. Pathologic diagnosis of solid tumor malignancy that is locally advanced or metastatic at time of Screening:

Part 1 (Dose Escalation):

Advanced solid tumors with documented HER2 status of IHC $\geq 1+$ or HER2 amplified/mutated by FISH or NGS.

Note: Clinical pathology report of HER2 status must be available for review to confirm eligibility in Part 1.

Part 2 (Dose Expansion):

HER2-high* or HER2-low** advanced solid tumor belonging to one of the pre-specified indications for groups A – E (breast cancer, gastric & gastroesophageal cancer, bladder cancer, non-small cell lung cancer) or one of the eight pre-specified indications for the basket group

(SCLC, CRC, pancreatic, biliary tract, prostate, ovarian, endometrial, or salivary gland) according to assigned treatment group for which HER2 status has been confirmed prospectively (HER2-high or HER2-low) for study entry.

* A HER2-high patient is defined as IHC 3+, or IHC 2+ with FISH amplification.

** A HER2-low patient is defined as IHC 1+, or IHC 2+ without FISH amplification.

Note: A patient with IHC 0 / IHC 1+ with amplification is HER2-high for study purposes; a patient with IHC 3+ with negative amplification results is HER2-low for study purposes.

6. Part 2/Dose Expansion Only: Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Note: 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 per RECIST.

7. Screening laboratory values within the following parameters:

- a. Absolute neutrophil count (ANC) $\geq 1500/\text{mm}^3$ ($\geq 1.5 \times 10^9/\text{L}$).
- b. Platelet count $\geq 100,000/\text{mm}^3$ ($\geq 100 \times 10^9/\text{L}$).
- c. Hemoglobin $\geq 9 \text{ g/L}$ ($\geq 5.6 \text{ mmol/L}$).
- d. Aspartate transaminase (AST) and alanine aminotransferase (ALT) $\leq 2.5\text{x}$ upper limit of normal (ULN); or $\leq 5.0\text{x}$ ULN if liver metastases are present.
- e. Total bilirubin $\leq 1.5\text{x}$ ULN (or $\leq 3\text{x}$ ULN, with direct bilirubin $\leq 1.5\text{x}$ ULN, in patients with known Gilbert syndrome).
- f. Serum/plasma creatinine $\leq 1.5\text{x}$ ULN; or, if creatinine $> 1.5\text{x}$ ULN, a measured creatinine clearance must be $> 60\text{mL/min}$ as calculated by the Cockcroft and Gault equation for patient to be eligible.
8. Women of childbearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of ADCT-502. Men with female partners who are of childbearing potential must agree that they or their partners will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of ADCT-502.

*Defined as: Sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal (i.e., who have not menstruated at all) for at least 1 year.

**Defined as: Hormonal contraceptives (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient.

Note: The double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only are not acceptable as highly effective methods of contraception.

Exclusion Criteria

1. Known history of \geq Grade 3 hypersensitivity to a therapeutic antibody.
2. Known history of positive serum human ADA to trastuzumab.
3. History of Stevens-Johnson syndrome or toxic epidermal necrolysis syndrome.
4. Major surgical procedure or significant traumatic injury, radiotherapy, chemotherapy, targeted therapy, hormone therapy (except for luteinizing hormone-releasing hormone (LHRH) agonists or denosumab) or other anticancer therapy within 21 days OR within 5 half-lives of the product, whichever is shorter, prior to the Cycle 1, Day 1 visit.

Note: cumulative dose of anthracycline >450 mg/m² is prohibited.

5. Failure to recover to Grade 0 or Grade 1 from acute non-hematologic toxicity due to previous therapy, prior to screening (with the exception of alopecia).
6. Central Nervous System (CNS) disease only.
7. Symptomatic CNS metastases or evidence of leptomeningeal disease (brain MRI or previously documented cerebrospinal fluid (CSF) cytology).

Previously treated asymptomatic CNS metastases are permitted provided that the last treatment (systemic anticancer therapy and/or local radiotherapy) was completed \geq 8 weeks prior to Day 1 except usage of low dose of steroids on a taper (i.e. up to 10 mg on Day 1 and consecutive days is permissible if being tapered down). Patients with discrete dural metastases are eligible.

8. Active cardiac disease including any of the following:
 - Angina pectoris that requires the use of anti-anginal medication.
 - Ventricular arrhythmias except for benign premature ventricular contractions.
 - Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication.
 - Clinically significant valvular disease with documented compromise in cardiac function.
 - Symptomatic pericarditis.
 - Congenital long QT syndrome or a corrected QTc [QTcF] interval \geq 450 ms at Screening.
 - LVEF $<$ 50% at Screening or a history of decrease in LVEF to $<$ 40% during previous treatment with HER2 targeted therapy.
9. History of clinically significant cardiovascular dysfunction including any one of the following:
 - History of myocardial infarction (MI) or recent MI documented by elevated cardiac enzymes or persistent regional wall abnormalities on

assessment of left ventricular function within 6 months prior to Day 1.

- History of documented congestive heart failure (New York Heart Association functional classification III-IV).
- Documented cardiomyopathy.
- Uncontrolled hypertension (systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg).

10. Active ulceration of the upper gastrointestinal tract or gastrointestinal bleeding.

11. Active autoimmune disease, motor neuropathy considered of autoimmune origin, and other CNS autoimmune disease.

12. Patients receiving concomitant immunosuppressive agents or chronic corticosteroids use, at study entry except in cases outlined below:

- Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular), or as physiologic replacement, are permitted.

13. Known human immunodeficiency virus (HIV) infection; known seropositive for hepatitis B surface antigen (HBsAg), or antibody to hepatitis C virus (anti-HCV) with confirmatory testing and requiring anti-viral therapy.

Note: Testing is not mandatory to be eligible. Testing for HCV should be considered if the patient is at risk for having undiagnosed HCV (e.g., history of injection drug use).

14. Any other malignancy within 3 years prior to Day 1, with the exception of adequately treated in-situ carcinoma of the cervix uteri, basal or squamous cell carcinoma or other non-melanomatous skin cancer.

15. Active bleeding diathesis or significant anticoagulation (such as with an oral anti-vitamin K medication. Low-dose warfarin, aspirin, or equivalent, are permitted as long as the INR ≤ 2.0).

16. History of thromboembolic or cerebrovascular events within the last 6 months, including transient ischemic attack, cerebrovascular accident, deep vein thrombosis or pulmonary embolism.

17. Clinically significant third space fluid accumulation (i.e., ascites requiring tap or pleural effusion that is either requiring tap or associated with shortness of breath).

18. Breastfeeding or pregnant.

19. Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes mellitus, active untreated or uncontrolled infection including viral and systemic fungal infections, chronic obstructive or chronic restrictive pulmonary disease including dyspnea at rest from any cause) that could cause unacceptable safety risks or compromise compliance with the protocol.

Study Design:

This is a first-in-human (FIH) Phase 1, multicenter, open-label study to evaluate the safety, tolerability, PK, pharmacodynamics (PD), immunogenicity, and preliminary antitumor activity of ADCT-502 used as a single agent in patients with advanced solid tumors with documented HER2 expression. The study consists of two parts.

During Part 1 (Dose Escalation), patients will receive escalating doses of

**Estimated Duration
of Patient
Participation and
Study Duration:**

ADCT-502 according to a modified continual reassessment method (mCRM) to determine the MTD and/or RDE.

Patients participating in Part 2 (Dose Expansion) will have their HER2 status prospectively measured to be classified as either HER2-high or HER2-low as defined for the study and assigned to 1 of 9 groups as follows:

- Group A: HER2-high breast cancer
- Group B: HER2-low breast cancer
- Group C: HER2-high gastric/GE cancer (and staggered HER2-low)
- Group D: HER2-high bladder cancer (and staggered HER2-low)
- Group E: HER2-high NSCLC (and staggered HER2-low)
- Group F: Basket of 8 HER2-high solid tumor indications (SCLC, CRC, pancreatic, biliary tract, prostate, ovarian, endometrial, or salivary gland)

The proposed indication for Group C (HER2-high gastric/GE cancer) may be exchanged with the indication of Group D or E (HER2-high bladder cancer or NSCLC), or one of the indications from the basket group, depending on emerging data from Part 1.

Simon's 2-Stage design will be used during Part 2. Enrollment will be paused and a futility analysis performed after Stage 1. If futility is not triggered, enrollment for that group will continue to Stage 2.

Groups A, B, and C will be opened for enrollment simultaneously. If for one or more of Groups A, B, or C futility is not triggered, Groups D, E, and F will be opened.

If futility for the HER2-high patients enrolled in Stage 1 of Groups C, D, or E is not triggered, enrollment of HER2-low expressing patients in the respective group will be opened.

This recruitment of HER2-low patients in indications of Groups C, D and E is also subject to a Simon 2-stage design.

The duration of each patient's participation will be dependent on individual response to treatment and will include a Screening Period (of up to 28 days), Treatment Period, and Follow-up Period. Patients may continue treatment until disease progression or unacceptable toxicity.

All patients will have an end of treatment (EOT) visit as soon as possible after decision to discontinue ADCT-502 and prior to initiation of new anticancer treatment. If possible, patients will have an additional follow-up visit 12 weeks after the last dose of ADCT-502 for collection of PK, soluble HER2, and ADA samples, unless a new anticancer treatment has been initiated.

All patients will be followed approximately every 12 weeks after the last dose of study drug to collect survival information. Follow-up for survival may continue for up to 2 years after treatment discontinuation.

Any patients who discontinue treatment for any reason other than disease progression will continue to be followed by radiographic examination every 12 weeks until disease progression or initiation of new anticancer treatment.

The duration of the study participation for each patient is defined as the time from the date of signed written informed consent through the completion of the follow-up period, or withdrawal of consent.

**Efficacy
Assessments:**

Study duration will be dependent on overall patient tolerability and response to treatment. It is anticipated that the entire study (Part 1 and Part 2) could be approximately 3 years from first patient treated to last patient completed.

Computerized tomography (CT) or magnetic resonance imaging (MRI) scans with contrast of the chest, abdominal and pelvic area or brain scans (CT or MRI with contrast), and bone scans or X-ray exam if clinically indicated, will be performed. For image acquisition specifications, including instruction in the event of allergy to contrast dye, refer to Appendix II of RECIST version 1.1 (Specifications for Standard Anatomical Radiological Imaging).

The same methods used at Baseline which identify sites of disease should be used uniformly for all subsequent assessments. Response to treatment will be determined by the Investigator as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to RECIST version 1.1.

**Pharmacokinetic,
Pharmacodynamic,
and Other
Exploratory
Assessments:**

Pharmacokinetics

The PK profile of ADCT-502 (total antibody), pyrrolobenzodiazepine (PBD)-conjugated antibody, and free warhead SG3199 will be assessed centrally. The PK profile will include determination of standard PK parameters (e.g., maximum concentration [C_{max}], time to C_{max} [T_{max}], area under the curve [AUC]).

Safety Assessments:

The safety objective will be evaluated by summarization of AEs, SAEs, and changes in laboratory parameters, vital signs, ECGs, and MUGA/echocardiograms. Dose interruptions, reductions, and relative dose intensity will also be summarized. Adverse events will be graded according to CTCAE version 4.0.

Definition of DLT

A DLT is defined as any of the following events that occur during the 21-day DLT evaluation period, except those that are clearly due to underlying disease or extraneous causes.

A **hematologic** DLT is defined as:

Event	Severity
Febrile neutropenia or neutropenic infection	Grade 3 or 4
Neutropenia lasting > 7 days	Grade 4
Thrombocytopenia	Grade 4
Thrombocytopenia with clinically significant bleeding	Grade 3
Thrombocytopenia requiring a platelet transfusion	Grade 3

Anemia	Grade 4
Anemia requiring transfusion	Grade 3

A **non-hematologic** DLT is defined as:

Event	Severity
Hy's law case	AST and/or ALT > 3x ULN and bilirubin > 2x ULN, and without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity < 2x ULN) and no other reason that could explain the combination of increased transaminases and serum total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.
Hypersensitivity/infusion-related reaction (regardless of premedication)	Grade 3 or higher. A Grade 3 hypersensitivity / infusion-related reaction that resolves within 24 hours after onset with appropriate clinical management does not qualify as a DLT.
All other non-hematologic toxicity	Grade 3 & 4.

The following conditions **are not** considered non-hematologic DLTs:

Event	Severity
Fatigue	Grade 3 for ≤ 7 days.
Diarrhea, nausea, or vomiting	Grade 3 in the absence of premedication that responds to therapy and improves by at least 1 grade within 3 days for Grade 3 events or to ≤ Grade 1 within 7 days.
Serum lipase or serum amylase	Grade 3 for ≤ 7 days if without clinical signs or symptoms of pancreatitis.
Electrolyte abnormalities	≤ Grade 3 which normalize within 48 hrs (with or without medical intervention) and which do not manifest themselves clinically; in such instance, a follow-up sample MUST be taken within 48 hrs to check whether such normalization has occurred.

Investigational

ADCT-502 is a sterile formulation containing PBD-conjugated humanized

**Product, Dosage,
and Mode of
Administration:**

monoclonal IgG1 antibody (DAR 1.8 \pm 0.3) and engineered trastuzumab (DAR = 0). ADCT-502 is formulated as a sterile liquid at 5 mg/mL in a 10 mL glass vial (2.0 mL nominal fill). The drug product is designed to deliver 10 mg ADCT-502 per vial and is intended for intravenous infusion following dilution in 0.9% sodium chloride

Patients will receive a 1-hour IV infusion of ADCT-502 on Day 1 of each 3-week (21-day) cycle. If ADCT-502 is well tolerated after the first cycle, the infusion duration may be shortened to 30 minutes for subsequent cycles for that patient at the discretion of the Investigator.

**Part 1
(Dose-Escalation
Design):**

Each cohort will consist of 2 patients. There will be a 24-hour observation before enrolling the second patient at Dose Level 1. The DLT observation period at each dose level is 1 cycle (3 weeks), after which it will be determined whether to escalate to the next dose level, stay at the current dose level, or de-escalate to the previous dose level for the next cohort.

There will be no de-escalation from Dose Level 1. Inpatient dose escalation is not permitted.

Dose escalation is not permitted unless two or more patients have complete DLT information through the first cycle in any given dose level.

Dose escalation will be determined by using a mCRM with a target DLT rate of 30% and an equivalence interval of 20% to 35%, and with dose escalation-with-overdose-control (EWOC) and no dose skipping.

The mCRM will be implemented in Part 1 under the oversight of a Dose Escalation Steering Committee (DESC). The DESC will confirm each escalating dose level after reviewing all available safety data. The PK data from patients in that dose level and prior dose levels may also inform DESC decision making. The DESC may halt dose escalation prior to determining the MTD based on emerging PK, PD, toxicity, or response data.

Additional patients may be included at any dose level to further assess the safety and tolerability if at least 1 patient in the study has achieved a partial response or better, or if further evaluation of PK or PD data is deemed necessary by the DESC to determine the RDE.

Furthermore, to better understand the potential efficacy of ADCT-502 in an indication approved for treatment with HER2 targeted antibodies, up to 3 additional breast cancer patients who have previously been treated with an approved HER2 targeted therapy may be enrolled per cohort at given dose levels \geq 60 μ g/kg determined by the mCRM model to be safe.

Dose escalation will be stopped after the mCRM has assigned 3 cohorts consecutively to the same dose level.

If the MTD is not reached, the recommended dose for expansion (RDE) will be determined.

Sample Size:

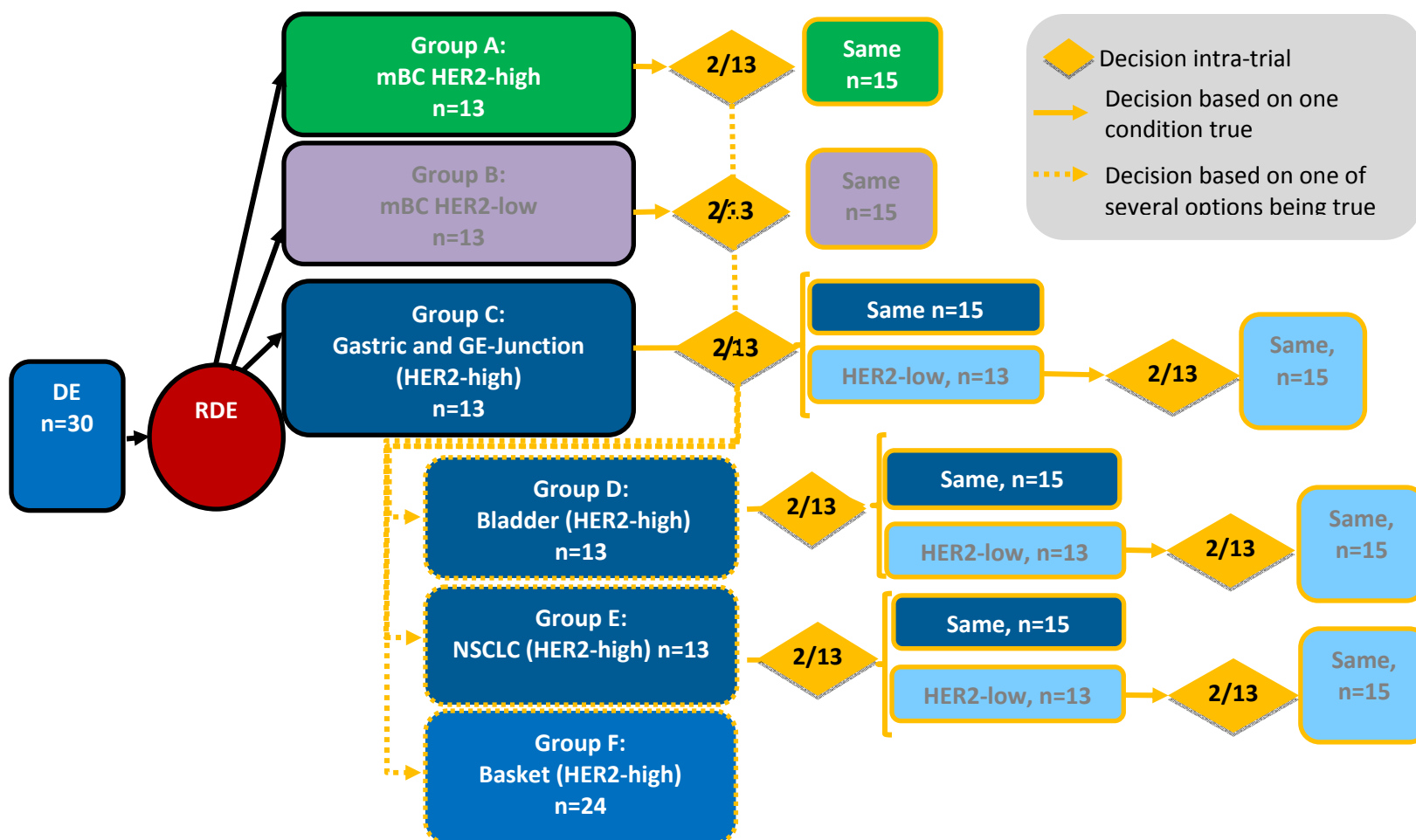
Part 1: The number of patients will depend upon the toxicities observed, the number of dose-level cohorts evaluated, and the number of dose-level cohorts expanded as the study progresses; approximately 30 patients are estimated. Overall sample size will be guided by the mCRM design.

Part 2: During the dose expansion phase of the study, up to 28 patients per each dose expansion cohort will be enrolled. Simon's two-stage design will be used. The null hypothesis that the true response rate is 7.5% will be tested against a one-sided alternative. In the first stage, 13 patients will be enrolled. If there are one (1) or fewer responses in these 13 patients, the

cohort will be closed. Otherwise, 15 additional patients will be enrolled for a total of 28 patients. The null hypothesis will be rejected if five (5) or more responses are observed in these 28 patients. This design yields a type I error rate of 0.05 (one-sided) and power of 80% when the true response rate is 25%.

In the basket group, up to 24 patients will be enrolled, with no more than 3 patients from each indication. If responses are observed, plans are described in the Interim Analysis [Part 2]).




Figure 1: ADCT-502-101 Study Schematic



Schedule of Events

Table 1: Schedule of Events

	Screening	Cycle 1					Cycle 2					Cycles 3, 4, 5, etc.		EOT	12-Week Follow-up ¹	Long-term Follow-up
	Days -28 to -1	Day 1	Day 2	Days 3 and 5	Day 8	Day 15	Day 1	Day 2	Days 3 and 5	Day 8	Day 15	Day 1	Day 8 ²			
Informed consent ³	X															
Demography ⁴	X															
Medical/Cancer history ⁵	X															
Available tumor tissue collection ⁶	X															
Physical examination ⁷	X	X ⁸			X	X	X ⁸			X	X	X ⁸		X		
ECOG PS ⁹	X	X					X					X		X		
Height	X															
Weight	X	X					X					X		X		
Vital signs ¹⁰	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG (triplicate) ¹¹	X	X	X				X	X				X		X		
ECHO or MUGA ¹²	X						X					X		X		
Disease assessments ¹³	X											X ¹⁴		X ¹⁵		X ¹⁶
β-HCG ¹⁷	X	X										X ¹⁸		X		
CBC with differential ¹⁹	X	X			X	X	X			X	X	X	X	X		

	Screening	Cycle 1					Cycle 2					Cycles 3, 4, 5, etc.		EOT	12-Week Follow-up ¹	Long-term Follow-up
	Days -28 to -1	Day 1	Day 2	Days 3 and 5	Day 8	Day 15	Day 1	Day 2	Days 3 and 5	Day 8	Day 15	Day 1	Day 8 ²			
Coagulation ¹⁹	X	X					X					X		X		
Chemistry ¹⁹	X	X			X	X	X			X	X	X	X	X		
Urinalysis ¹⁹	X	X					X					X		X		
PK sample ²⁰		X	X	X	X	X	X	X	X	X	X	X		X	X	
ADA sample ²⁰	X	X					X					X		X	X	
sHER2 sample ²⁰		X					X					X		X	X	
																
Concomitant medications ²¹	← X →															
Adverse events ²²	← X →															
ADCT-502 administration ²³		X					X					X				
1 st New anticancer treatment ²⁴															X	X
Survival																X ²⁵

Visit Scheduling Windows: For scheduling purposes, the following allowances will be made for Visits:

- Day 1: Cycles 2, 3, 4, etc. (excluding Cycle 1, Day 1): ± 3 days
- Days 8 and 15: ± 1 day
- EOT: As soon as possible after decision to discontinue the study drug AND prior to initiation of new anticancer treatment
- 12-Week Follow-up: ± 7 days after last dose of study drug
- Long Term Follow-Up (approx. every 12 weeks after last dose): ± 4 weeks

Refer to [Section 10.2](#) for details of CBC, coagulation, chemistry, and urinalysis panels.

- ¹ If possible, collection of pharmacokinetic (PK), soluble HER2, and anti-drug antibodies (ADA) samples will take place at the follow-up visit 12 weeks after the last dose of ADCT-502, unless a new anticancer treatment has been initiated.
- ² After completion of 6 treatment cycles, the Day 8 visit is not required unless clinically indicated.
- ³ A signed and dated Institutional Review Board (IRB) /Independent Ethics Committee (IEC) approved informed consent form (ICF) obtained prior to performing any study evaluations. Results (e.g., from laboratory tests or radiographic evaluations, etc.) obtained prior to the date of informed consent, but within the allowed timeframe for Screening may be used for determination of patient eligibility only if obtained as part of the patient's standard of care. Patients must meet entry criteria at Screening, and should continue to meet entry criteria at Cycle 1 Day 1 pre-dose. However, clinically acceptable variations, if they are in the opinion of the Investigator not compromising patient safety, may be allowed on that day.
- ⁴ Demography includes collection of date of birth, sex, and race.
- ⁵ Medical/Cancer history to include a complete history of all surgeries, significant diagnoses, and all cancer treatments. Results of testing for genetic abnormalities associated with the patient's tumor type (such as BRCA1, for example) will be recorded.
- ⁶ During Part 1, ship tissue sample to the central laboratory for **retrospective analysis of HER2**. An FFPE block (or slides) from any biopsy since initial diagnosis is acceptable, but if several are available, the most recent sample is preferred. Either tumor tissue block or freshly cut unstained slides (minimum 7; 10 preferred) is acceptable. During Part 2, ship tissue sample to the central laboratory for **prospective analysis of HER2** to confirm eligibility.
- ⁷ Physical examinations will include a complete review of body systems. Investigators should be cognizant of potential toxicities for ADCT-502 and similar compounds as described in the Investigator's Brochure (IB) and refer unexplained findings or abnormalities to a specialist accordingly (e.g., ocular toxicity to an ophthalmologist, etc.).
- ⁸ A physical examination does not need to be repeated if performed within 72 hours prior to Day 1 of any cycle.
- ⁹ Refer to [Appendix 18.2](#) for definitions of Eastern Cooperative Oncology Group (ECOG) Performance Status grades.
- ¹⁰ Refer to [Table 2](#) for timing of vital sign measurements. Vital sign measurements include arterial blood pressure, heart rate, respiratory rate, and body temperature.
- ¹¹ The Fridericia formula for rate correction of QT intervals should be used for all patients throughout the study. Refer to [Table 2](#) for timing of electrocardiogram (ECG) in relation to PK sample collection.
- ¹² Perform multiple-gated acquisition (MUGA) scan or echocardiogram (ECHO) at Screening, after Cycle 1, every 3 cycles (i.e., every 9 weeks), and at End of Treatment (EOT). All patients will have measurements of left ventricular ejection fraction (LVEF) via a consistent method (MUGA scan or ECHO), regardless of symptoms. If the LVEF is reported as a range, the average should be taken.
- ¹³ Screening (Baseline) imaging (computerized tomography [CT] or magnetic resonance imaging [MRI]) must be performed within 4 weeks prior to Day 1, Cycle 1. See [Section 10.3](#) for details.
- ¹⁴ Disease assessments will be conducted every 2 cycles \pm 1 week for the first 2 time points (e.g., after Cycles 2 and 4), and every 4 cycles thereafter (i.e., approximately every 12 weeks). Patients with metastatic breast cancer (MBC) enrolled in Groups A and B will have disease assessments every 4 cycles.


.....Footnotes continue on next page

- ¹⁵ Disease assessments do not need to be repeated at EOT if last assessment was performed within 6 weeks prior to the EOT visit, or if patient already has documented progression of disease (PD).
- ¹⁶ Any patients who discontinue treatment for any reason other than disease progression will continue to be followed by radiographic examination every 12 weeks until disease progression or initiation of new anticancer treatment. Once the final efficacy analysis for progression-free survival (PFS) is performed (Part 2), the frequency of tumor response assessment for patients remaining under treatment may be further decreased and/or performed according to standard of care.
- ¹⁷ Blood or urine pregnancy test for women of childbearing potential. For eligibility confirmation, a negative blood pregnancy test is required; the test does not need to be repeated if it was obtained within 7 days prior to Cycle 1, Day 1.
- ¹⁸ A pregnancy test will be repeated at Day 1 of every other cycle (every 6 weeks) and at EOT.
- ¹⁹ Does not need to be repeated if performed within 72 hours prior to Day 1 of any cycle.
- ²⁰ Refer to [Table 2](#) for timing of collection for PK and PD samples. PK and/or ADA samples may be collected at other time points if clinically indicated, e.g., at the time of other significant AE that are at least possibly related to ADCT-502.
- ²¹ Concomitant medications will include prescription and/or over-the-counter medication, herbal or naturopathic products within 14 days prior to Cycle 1, Day 1, during the treatment period, and within 30 days after the last dose of study drug, and will be recorded in the electronic case report form (eCRF).
- ²² For all patients, collection of adverse events (AEs) and serious adverse events (SAEs) will continue for 30 days after the last dose of study drug or initiation of new anticancer treatment.
- ²³ Volume of study drug administration should be recalculated if there is a weight increase or decrease $\geq 10\%$ compared to the weight used to calculate administration at Cycle 1, Day 1.
- ²⁴ The first new anticancer treatment should be documented for all patients.
- ²⁵ After documentation of disease progression or start of new treatment, all patients will be followed approximately every 12 weeks after the last dose of study drug to collect survival information. Follow-up for survival may continue for up to 2 years after treatment discontinuation.

Table 1: Summary of the 2019-2020 Season																				
Year	Month	Day	Weather Conditions											Temperature (°C)		Wind Speed (km/h)	Precipitation (mm)			
			Clear					Cloudy					Max	Min						
			Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast								
2019	Jan	1	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	15	5	10
		2	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	15	5	10
		3	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	15	5	10
		4	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	15	5	10
2020	Feb	1	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	15	5	10
		2	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	15	5	10
		3	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	15	5	10
		4	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	Sunny	Partly Sunny	Partly Cloudy	Cloudy	Overcast	15	5	10

List of Abbreviations

Abbreviation	Definition
ADA	anti-drug antibodies
ADC	antibody drug conjugate
ADL	activities of daily living
anti-HCV	antibody to hepatitis C virus
ASCO	American Society of Clinical Oncology
AUC	area under the concentration versus time curve
β-HCG	beta human chorionic gonadotropin
BID	twice a day (bis in die)
BSA	body surface area
CAT or CT	computerized tomography
CBC	complete blood count
cfDNA	circulating free DNA
CLIA	Clinical Laboratory Improvement Amendments
C _{max}	maximum serum concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CSF	cerebrospinal fluid
DAR	drug to-antibody ratio
DCR	disease control rate
DESC	dose escalation steering committee
DLT	dose limiting toxicities
DOR	duration of response
DSMB	data safety monitoring board
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOI	end of infusion
EOT	end of treatment
EWOC	escalation with overdose control
FDA	Food and Drug Administration
FIH	first-in-human
FISH	fluorescence <i>in situ</i> hybridization
FFPE	formalin-fixed paraffin-embedded
HBsAg	hepatitis B surface antigen
HER2/neu receptor	human epidermal growth factor receptor-2
HED	human equivalent dose
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	hazard ratio

		
G/GE	gastric/gastroesophageal	
GLP	good laboratory practices	
IB	Investigator's Brochure	
IHC	immunohistochemistry	
ISH	in situ hybridization	
IV	intravenous	
LHRH	luteinizing hormone-releasing hormone	
LVEF	left ventricular ejection fraction	
mAb	monoclonal antibody	
MBC	metastatic breast cancer	
mCRM	modified continual reassessment method	
MedDRA	Medical Dictionary for Regulatory Activities	
MI	myocardial infarction	
mPFS	median progression-free survival	
MRI	magnetic resonance imaging	
MTD	maximum tolerated dose	
MUGA	multigated acquisition	
mOS	median overall survival	
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events	
NGS	next generation sequencing	
NSCLC	non-small cell lung cancer	
ORR	overall response rate	
OS	overall survival	
PBD	pyrrolbenzodiazepine	
PD	pharmacodynamics	
PDX	patient derived xenograft	
PFS	progression-free survival	
PK	pharmacokinetic	
PO	per os	
PS	performance status	
RDE	recommended dose for expansion	
RECIST	Response Evaluation Criteria in Solid Tumors	
SAE	serious adverse event	
SCLC	small cell lung cancer	
sHER2	soluble HER2	
SUSARs	Suspected Unexpected Serious Adverse Reactions	
TEAE	treatment-emergent adverse event	
T _{max}	time to C _{max}	
U	United States	

1 Introduction and Background

1.1 HER2 and HER2 Targeting Therapies

The human epidermal growth factor receptor-2 (HER2/neu receptor), a member of the epidermal growth factor family of receptor tyrosine kinases (including EGFR/ErbB1/HER1, ErbB3/HER3, and ErbB4/HER4), is a 185 kDa transmembrane glycoprotein, which provides signal transduction for cell proliferation and differentiation. The HER2 monomeric protein has three main regions: the extracellular amino-terminal region comprising four subdomains (I-IV), the hydrophobic transmembrane domain and the carboxy-terminal kinase domain comprising the juxtamembrane domain, tyrosine kinase and C-terminal tail with autophosphorylation sites. HER2 has no known ligand, and it is activated by homodimerization or heterodimerization with other member of the ERBB family (Omar, 2015).

HER2 is over-expressed/amplified in several solid tumor types (Yan, 2015). Targeted HER2 therapies are approved for the treatment of breast and gastric/esophageal cancers that over-express or are gene-amplified for HER2.

Trastuzumab (Herceptin®), a humanized monoclonal antibody (mAb), binds to the HER2 receptor and downregulates its expression on the cell surface. Trastuzumab is approved in the United States (US) and in Europe for the treatment of HER2-positive breast cancer in the adjuvant and metastatic settings, defined as HER2 IHC (immunohistochemistry) 3+ or IHC 2+/ fluorescence in-situ hybridization (FISH)-amplification (Herceptin® [trastuzumab] US Prescribing Information, 2016). In the metastatic setting, trastuzumab is used in combination with chemotherapy regimens and/or in combination with pertuzumab in the first-line setting (CLEOPATRA study) (Swain, 2015) followed by ado-trastuzumab emtansine (T-DM1) after relapse or disease progression. Despite improved patient outcomes, acquired resistance affects the majority of patients previously exposed to trastuzumab, and the molecular mechanisms conferring trastuzumab resistance are likely to be multifactorial.

In addition, trastuzumab is indicated in combination with cisplatin and capecitabine or 5-fluorouracil for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease (ToGA trial) (Bang, 2010). Trastuzumab-based therapy significantly improved median overall survival (mOS) compared with the chemotherapy alone (hazard ratio [HR] 0.74; p=0.0046 and mOS: 13.8 months versus 11.1 months). However, acquired resistance to trastuzumab usually limits the duration of response to this treatment despite its improvement over the chemotherapy alone (duration of response [DOR] 6.9 months versus 4.8 months).

Ado-trastuzumab emtansine (Kadcyla®), also known as T-DM1, is an antibody-drug conjugate of trastuzumab containing a potent microtubule inhibitor, DM1 (a derivative of maytansine) approved in the US in 2013 for the treatment of HER2-positive metastatic breast cancer for patients who had previously been treated with trastuzumab and a taxane chemotherapy (EMILIA study) (Verma, 2012). Median progression-free survival (mPFS) was 9.6 months with T-DM1 versus 6.4 months with lapatinib plus capecitabine (HR for

progression or death from any cause, 0.65; $P < 0.001$), and mOS at the second interim analysis crossed the stopping boundary for efficacy (30.9 months versus 25.1 months; HR for death from any cause, 0.68; $P < 0.001$). Ado-trastuzumab emtansine (T-DM1) has also demonstrated the potential to prolong PFS in the third-line setting based on results from the Phase 3 TH3RESA study ([Krop, 2014](#)) (mPFS 6.2 months for T-DM1 versus 3.3 months for physician's choice). However, results from the Phase 3 MARIANNE study ([Perez, 2016](#)) indicate that median PFS in the frontline setting for patients with advanced breast cancer treated with T-DM1 was non-inferior, but not superior, compared to those treated with trastuzumab plus a taxane-based chemotherapy. Ado-trastuzumab emtansine is often accompanied by unacceptable thrombocytopenia and hepatotoxicity at doses higher than the approved regimen (3.6 mg/kg every 3 weeks), as well as reductions in left ventricular ejection fraction (LVEF), and peripheral sensory neuropathy. In preclinical gastric cancer models, T-DM1 has shown more potent antitumor activity than trastuzumab ([Barok, 2011](#)). However, the multicenter adaptive phase 2/3 of T-DM1 in HER2-positive patients with unresectable locally advanced or metastatic gastric or gastroesophageal (GE) junction cancer who progressed during or after first-line fluoropyrimidine plus platinum therapy with or without HER2-targeted therapy did not show a benefit of T-DM1 vs. taxane based chemotherapy ([Kang, 2016](#)).

The third HER2 targeting mAb based therapeutic modality currently approved in the oncology setting, is pertuzumab (PERJETA®). Pertuzumab is a HER2/neu receptor antagonist indicated for use in combination with trastuzumab and docetaxel for treatment of patients with HER2-positive metastatic breast cancer (MBC) who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. It is also approved in combination with trastuzumab and docetaxel as neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer as part of a complete treatment regimen for early breast cancer ([PERJETA® US Prescribing Information, 2012](#)).

In the Phase 3 randomized trial (CLEOPATRA study) ([Swain, 2015](#)) of pertuzumab plus trastuzumab and docetaxel vs. placebo plus trastuzumab and docetaxel, independent review indicated that the pertuzumab-treated group demonstrated an increase in mPFS of 6.3 months (18.7 months in the pertuzumab -treated group vs. 12.4 months in the placebo-treated group).

Approximately 20% of all cases of breast cancer have *HER2* gene amplification and high levels of HER2 protein expression that predict the response to trastuzumab. Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer-related deaths worldwide. HER2 over-expression/amplification occurs in 7–34% of gastric cancer and is associated with poor prognosis. While trastuzumab based therapy is the standard of care in both metastatic breast and gastroesophageal cancer, the known prevalence of HER2 over-expression/amplification across tumor types in general suggests that other patient populations may benefit from treatment with HER2 targeted agents. A number of smaller studies or case reports have demonstrated this, for example in patients with colorectal cancer (CRC) ([Sartore-Bianchi, 2016](#); [Harder, 2012](#); [Javle, 2015](#); [de Bono, 2007](#); [Bookman, 2003](#); [Fleming, 2010](#); [Oudard, 2015](#); [Limaye, 2013](#)).

In one of the largest studies to date, (Yan, 2015) HER2 expression status in diverse cancers was examined in approximately 38,000 patients. Indications planned for inclusion in this protocol were found to be positive in the range of 0.6% (prostate) to 12.4% (bladder carcinoma). Since these percentages of HER2 positive patients refer to what is termed HER2-high in this protocol, the percentage of patients anticipated to ultimately benefit from ADCT-502 may be higher, as patients with HER2-low expressing tumors were not evaluated but will be included in this protocol in a staggered fashion, depending on efficacy results in HER2-high expressing patients.

In certain malignancies, principally non-small cell lung cancer (NSCLC), the HER2 protein can be constitutively activated through genetic mutations; initial efficacy data suggest that HER2 targeting modalities can also be of therapeutic benefit for such patients (Mazieres, 2013).

1.2 Description of ADCT-502

ADCT-502 is an antibody drug conjugate (ADC) composed of an engineered version of the humanized monoclonal antibody trastuzumab, directed against the human HER2 receptor, site-specifically conjugated to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin, through a protease-cleavable valine-alanine linker. [REDACTED]

ADCT-502 specifically binds to HER2, and once internalized, releases the PBD dimer to allow cross-linking of DNA and eventually trigger cell death. ADCT-502 has demonstrated potent and specific in vitro and in vivo antitumor activity in [REDACTED] with differing levels of HER2 expression.

1.3 Nonclinical Efficacy and Toxicology of ADCT-502

In vitro studies support a mechanism of action whereby ADCT-502 binds to HER2, internalizes, and releases its cytotoxic payload. In preclinical in vivo xenograft experiments (including patient derived xenograft [PDX] models), ADCT-502 [REDACTED]

[REDACTED] The efficacy of ADCT-502 in these models is due to HER2-mediated delivery of the PBD cytotoxin SG3199.

ADCT-502 [REDACTED]

Additional details may be found in the current ADCT-502 Investigator's Brochure (IB).

2 Rationale

2.1 Study Rationale and Purpose

Three mAb-based therapies targeting HER2 are currently licensed across 2 indications, namely breast cancer and/or gastric/GE junction cancers. Use of any of these agents is limited to patients whose tumors are defined as HER2 positive, which in this protocol is specified as HER2-high. Until HER2 targeted therapies became available, HER2 expression was associated with worse prognosis compared to patients whose tumors did not over-express HER2.

Consequently, there is unmet medical need in those indications where HER2 is expressed at high levels, but for which the current treatments are not licensed. Also, there is high unmet medical need in breast and gastric/GE junction cancers in which HER2 expression is observed but below the defined thresholds for HER2 targeted therapy.

In addition, high unmet medical need exists in the licensed indications once current HER2 targeted therapy is no longer effective and patients relapse, or which are primary resistant to this therapeutic approach. For example, a substantial number of patients develop resistance to trastuzumab or T-DM1 ([Chung, 2013](#); [Barok, 2011](#)).

Finally, trastuzumab-based regimens are associated with significant side effects, largely because of the cytotoxic chemotherapy component ([Hernández-Blanquissett, 2016](#); [Chung, 2013](#); [Arteaga, 2011](#)). The effects of many of these drugs are short-lived, and a significant proportion of these patients still relapse and die of breast cancer. Thus, promising new approaches are being developed, such as antibodies linked to cytotoxic moieties, to enhance the risk-benefit ratio of drugs.

The mechanism of action and preclinical data of ADCT-502 supports its use in patients with relapsed or refractory metastatic breast and gastric cancer who have been previously treated with trastuzumab/T-DM1. Given the substantial prevalence of HER2 expression in a range of other advanced cancers, including NSCLC, bladder, biliary tract and ovarian cancer, ADCT-502 will be evaluated as an anticancer treatment in patients with such tumor types for which there is published clinical evidence of HER2 expression.

Results of preclinical studies in PDX models suggest that ADCT-502 may have potent clinical activity in both groups of patients, those with HER2-positive/high tumors as well as those with HER2 low-expressing and/or heterogeneous tumors, the latter being a patient population currently not served by approved HER2 targeting agents at all.

2.2 Rationale for Study Design

The dose escalation portion of this Phase 1, open-label, dose finding study is designed to establish a safe and tolerated dose of ADCT-502 for further testing in patients with solid tumors expressing HER2 (high and low expressers). Up to nine (9) groups are planned in the expansion portion to further characterize the safety and evaluate preliminary efficacy. As indicated in [Section 4.1](#), the enrollment of the groups is staggered in order to allow for an

evaluation of the therapeutic potential in a limited number of patients with breast and GE cancer prior to exposing patients with other tumor types to ADCT-502.

Part 1 will utilize a modified continual reassessment method (mCRM) to guide dose escalation and estimate the maximum tolerated dose (MTD) and/or determine the recommended dose for expansion (RDE) for ADCT-502. The mCRM and escalation with overdose control (EWOC) enables incorporation of available prior information and updates the model parameters based upon new information about observed dose limiting toxicities (DLT) seen in the clinical study. The dose recommended by the model at any stage of the trial is based on the entire history of all available DLT information from previous cohorts as opposed to only the number of DLTs observed in the last group of patients. Part 2 will utilize the Simon two-stage optimal design with a futility stop and staggered enrollment to minimize exposure of patients when evidence for efficacy is weak.

2.3 Starting Dose Justification

The starting dose of ADCT-502 in this study is based on the intravenous (IV) Good Laboratory Practice (GLP) toxicology study with once every 3 weeks dosing. Based on the ADCT-502-related effects observed in this GLP study, [REDACTED]

The starting dose for an ADC is based on the conversion of the HNSTD ([REDACTED]) to a Human Equivalent Dose (HED) based on body surface area (BSA) through multiplication with a species specific factor ([REDACTED]), which is followed by division with a standard safety factor of [REDACTED]

2.4 Plans and Justification for Provisional Dose Levels

Overall, approximately 10 dose levels are planned. An initial increase of 100% for lower dose levels is foreseen, resulting in provisional dose levels of 30, 60 and 120 µg/kg. Midstage escalation is somewhat more conservative to account for potential low-grade toxicity to become apparent, with dose level increases of 50%, 33% and 25%, resulting in doses of 180, 240 and 300 µg/kg. Subsequent levels are determined by a fixed dose increase of 50 µg/kg (i.e., 300, 350, 400, 450 and 500 µg/kg) as the highest dose level to be tested, if allowed by the mCRM with EWOC. The default dosing regimen is once every 3-week dosing. Clinical and pharmacokinetic (PK) data will be reviewed on an ongoing basis and may provide evidence to support interim dose levels. In addition, or as an alternative to decreasing doses to interim dose levels, the dosing interval may be extended (but not shortened), for example, to dosing every 4, 5 or 6 weeks instead of every 3 weeks. Once the dose interval is changed or an intermediate dose not predefined in the mCRM model is used, 3+3 design may be used for future dose escalation. One situation in which such approach may be advantageous is drug accumulation; implementation will need DESC approval (DESC, see [Section 4.6.1](#)) and may affect both ongoing patients as well as new cohorts. Similarly, it is at the discretion of the DESC to modify the dosing regimen that mandates omitting dosing of every n-th cycle, e.g. every 3rd cycle. Note: Scheduled visits will be kept,

except when C2 dosing is skipped; in that case C2D2-D5 would be omitted (respective assessment will not be done). This approach may be beneficial in balancing efficacy and adverse events. The cumulative dose of ADCT-502 in such a revised regimen can only be less than or equal to the cumulative dose of a dose-level that has been tested and found to be safe per mCRM.

3 Study Objectives and Endpoints

3.1 Objectives

3.1.1 Primary Objectives

- Evaluate safety, tolerability, and determine the MTD and/or RDE of single agent ADCT-502 in patients with advanced solid tumors with known HER2 status (IHC $\geq 1+$ or HER2 amplified/mutated) (Part 1).
- Further evaluate safety and tolerability at the dose level determined in Part 1 in patients with advanced solid tumors including breast cancer, lung, gastroesophageal, and bladder cancer or a basket of other solid tumors known to express HER2 (HER2-high or HER2-low status confirmed prospectively for study entry) (Part 2).

3.1.2 Secondary Objectives

- Evaluate the preliminary antitumor activity of ADCT-502.
- Characterize the PK profile of ADCT-502.
- Determine the immunogenicity of ADCT-502.

[REDACTED]

■ [REDACTED]

■ [REDACTED]

3.2 Endpoints

3.2.1 Primary Endpoints

- Frequency and severity of DLTs (Part 1 only), adverse events (AEs), serious adverse events (SAEs), laboratory abnormalities, physical examinations, ECOG performance status, vital signs, and 12-lead ECGs.

3.2.2 Secondary Endpoints

- Overall Response Rate (ORR), Disease Control Rate (DCR), Duration of Response (DOR), PFS, and OS.
- Determination of PK parameters for ADCT-502 (area under the concentration versus time curve (AUC) of total antibody, (drug to-antibody ratio [DAR] ≥ 0), PBD-conjugated antibody (DAR ≥ 1), and free warhead SG3199).
- Anti-drug antibody (ADA) titers to ADCT-502 before, during, and after treatment with ADCT-502.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4 Study Design

4.1 Overview

This is a first-in-human (FIH) Phase 1, multicenter, open-label study to evaluate the safety, tolerability, PK, pharmacodynamics (PD), immunogenicity, and preliminary antitumor activity of ADCT-502 used as a single agent in patients with advanced solid tumors with documented HER2 expression. The study consists of two parts (see [Figure 1](#)).

During Part 1 (Dose Escalation), patients will receive escalating doses of ADCT-502 according to a mCRM to determine the MTD and/or RDE.

Patients participating in Part 2 (Dose Expansion) will have their HER2 status prospectively measured to be classified as either HER2-high or HER2-low as defined for the study and assigned to 1 of 9 groups as follows:

- Group A: HER2-high breast cancer
- Group B: HER2-low breast cancer
- Group C: HER2-high gastric/GE cancer (and staggered HER2-low)
- Group D: HER2-high bladder cancer (and staggered HER2-low)
- Group E: HER2-high NSCLC (and staggered HER2-low)

- Group F: Basket of 8 HER2-high solid tumor indications (SCLC, CRC, pancreatic, biliary tract, prostate, ovarian, endometrial, or salivary gland)

The proposed indication for Group C (HER2-high gastric/GE cancer) may be exchanged with the indication of Group D or E (HER2-high bladder cancer or NSCLC), or one of the indications from the basket group, depending on emerging data from Part 1.

Simon's 2-Stage design will be used during Part 2. Enrollment will be paused and a futility analysis performed after Stage 1 (see [Section 12.2](#), Interim Analysis [Part 2]). If futility is not triggered, enrollment for that group will continue to Stage 2.

Groups A, B, and C will be opened for enrollment simultaneously. If for one or more of Groups A, B, or C futility is not triggered, Groups D, E, and F will be opened.

If futility for the HER2-high patients enrolled in Stage 1 of Groups C, D, or E is not triggered, enrollment of HER2-low expressing patients in the respective group will be opened.

This recruitment of HER2-low patients in indications of Groups C, D and E is also subject to a Simon 2-stage design.

4.2 Patient Selection and Evaluation of HER2 Expression/Amplification/Mutation

Five (5) types of patients, based on HER2 expression levels and mutations, are selected in this FIH study of ADCT-502:

1. Patients with indications and HER2 expression levels that qualified them for (prior) treatment with trastuzumab and/or ado-trastuzumab emtansine, e.g., HER2 positive BC and HER2 positive G/GE cancer.
2. Patients with BC or G/GE cancer with HER2 expression that is present, but at a level that is below the threshold qualifying them for Item Number 1.
3. Patients with HER2 expression levels equivalent to Item Number 1, but who have a tumor type other than BC or G/GE cancer (NSCLC, small cell lung cancer [SCLC], CRC, bladder, pancreatic, biliary tract, prostate, ovarian, endometrial, and salivary gland cancer).
4. Patients from the same indication list as in Item Number 3, except with HER2 expression levels present but lower than that, i.e. equivalent to expression levels in Item Number 2.
5. Patients with 1 of the 12 indications mentioned in Items 1–4 who have been shown to possess a *HER2* hotspot mutation; they are either classified as HER2-high if a concomitant amplification was demonstrated (or if they fulfill HER2-high criteria as per below definition), otherwise they are classified as HER2-low. Patients with such *HER2* genetic alteration pre-defined prior to study enrollment and not belonging to 1 of the 12 indications may be included in the dose escalation part after sponsor agreement.

HER2 status will be tested by IHC (HercepTest, Dako, Denmark) and scored as 0, 1+, 2+, or 3+, and/or FISH (HER2 FISH pharmDx, Dako). HER2 amplification testing may be performed according to applicable in situ hybridization (ISH) methods as described in the ASCO guidelines (e.g., amplification testing is not limited to FISH). Amplification testing can also be done via NGS (see below).

A HER2-high patient is defined as IHC 3+, or IHC 2+ with FISH amplification.

This definition is consistent with the approved indications for trastuzumab and ado-trastuzumab emtansine [T-DM1] (Kadcyla) based therapy.

A HER2-low patient is defined as IHC 1+, or IHC 2+ without FISH amplification.

Note: patients with IHC 0 / IHC 1+ with amplification is HER2-high for study purposes; a patient with IHC 3+ with negative amplification results is HER2-low for study purposes.

Mutational hotspots indicate selective pressure across a population of tumor samples ([Chang, 2016](#)). Therefore, even if not formally demonstrated for each instance, it is plausible to assume that such mutational hotspots in HER2 signify expression of the protein, at least at HER2-low levels, and thus ADCT-502 should be beneficial as per pre-clinical data in low-expressing HER2 models. Indeed, it was formally demonstrated that *HER2* somatic mutations are being expressed, at the RNA level for a subset of mutations listed in the appendix ([Bose, 2013](#)).

Furthermore, [Mazieres, 2013](#), has published supporting evidence with other HER2 targeting agents in a population with *HER2* mutations; hence, such patients are allowed into the study.

More recently, also HER2 amplification status was shown to be reliably determined by hybridization capture-based NGS methods; e.g., NGS fold change > 1.8 was equivalent to FISH > 2.0 ([Ross, 2017](#)).

Therefore, patients with results available from next generation sequencing (NGS) from a Clinical Laboratory Improvement Amendment (CLIA) certified laboratory will be assigned to these groups as follows:

For Part 1:

HER2 gene amplification irrespective of mutational status: HER2-high.

HER2 mutated in the absence of amplification: HER2-low. Refer to [Appendix 18.3](#) for genetic changes that constitute a mutation for purposes of this study.

Irrespective of NGS results, HER2 expression status will be confirmed retrospectively in a central laboratory.

For Part 2:

Assignment of HER2-high or –low status via NGS (as described above) must be prospectively confirmed centrally by IHC and FISH (if applicable).

Patients in Part 2 must have their HER2 status measured prospectively for study entry and be classified as either HER2-high or HER2-low as defined for the study.

The different level of scrutiny applied to HER2 testing (historic local vs. prospective central, allowing defined *HER2* mutations as a proxy for HER2 expression during dose escalation) corresponds to the different goals of the two phases of the study: Part 1 being primarily driven to establish a safe dose for expansion, and Part 2 assessing both tolerability as well as initial signs of efficacy.

4.3 Number of Patients

During Part 1, approximately 30 patients may be treated, depending on safety observations and number of dose levels tested.

In Part 2, the total number of patients will be determined by the number of responses for each tumor type stratified by the level of HER2 expression. Initially, 3 groups (Groups A, B, and C) with 13 patients in each group will be enrolled (39 patients). Depending on efficacy signals, up to approximately 248 patients across 9 different groups could be enrolled (i.e., between approximately 39 and 248 patients will be enrolled in Part 2).

The total number of patients will be between approximately 69 and 278.

4.4 Duration of Patient Participation

The duration of each patient's participation will be dependent on individual response to treatment and will include a Screening Period of up to 28 days, Treatment Period, and Follow-up Period. Patients may continue treatment until disease progression or unacceptable toxicity.

All patients will have an EOT visit as soon as possible after decision to discontinue ADCT-502 and prior to initiation of new anticancer treatment. If possible, collection of PK, soluble HER2, and ADA samples will take place at the follow-up visit 12 weeks after the last dose of ADCT-502, unless a new anticancer treatment has been initiated.

All patients will be followed approximately every 12 weeks after the last dose of study drug to collect survival information. Follow-up for survival may continue for up to 2 years after treatment discontinuation.

Any patients who discontinue treatment for any reason other than disease progression will continue to be followed by radiographic examination every 12 weeks until disease progression or initiation of new anticancer treatment.

The duration of the study participation for each patient is defined as the time from the date of

signed written informed consent through the completion of the follow-up period, or withdrawal of consent.

4.5 Duration of Study

Study duration will be dependent on overall patient tolerability and response to treatment. It is anticipated that the entire study (Part 1 and Part 2) could be approximately 3 years from first patient treated to last patient completed.

4.6 Description of Dose Escalation Process

Each cohort will consist of 2 patients. There will be a 24-hour observation before enrolling the second patient at Dose Level 1. The DLT observation period at each dose level is 1 cycle (3 weeks), after which it will be determined whether to escalate to the next dose level, stay at the current dose level, or de-escalate to the previous dose level for the next cohort. There will be no de-escalation from Dose Level 1. Inpatient dose escalation is not permitted.

Dose escalation is not permitted unless two or more patients have complete DLT information through the first cycle in any given dose level. Dose escalation will be determined by using a mCRM with a target DLT rate of 30% and an equivalence interval of 20% to 35%, and with dose escalation-with-overdose-control (EWOC) and no dose skipping.

The mCRM will be implemented in Part 1 under the oversight of a Dose Escalation Steering Committee (DESC). The DESC will confirm each escalating dose level after reviewing all available safety data. PK data from patients in that dose level and prior dose levels may also inform decision making. The DESC may halt dose escalation prior to determining the MTD based on emerging PK, PD, toxicity, or response data.

Additional patients may be included at any dose level to further assess the safety and tolerability if at least 1 patient in the study has achieved a partial response or better, or if further evaluation of PK or PD data is deemed necessary by the DESC to determine the RDE.

Furthermore, to better understand the potential efficacy of ADCT-502 in an indication approved for treatment with HER2 targeted antibodies, up to 3 additional breast cancer patients who have previously been treated with an approved HER2 targeted therapy may be enrolled per cohort at given dose levels ≥ 60 $\mu\text{g/kg}$ determined by the mCRM model to be safe.

Dose escalation will be stopped after the mCRM has assigned 3 cohorts consecutively to the same dose level.

If the MTD is not reached, the recommended dose(s) and schedule(s) for expansion (RDE) will be determined.

Once the Part 2 RDE(s) is/are determined, patients receiving lower or higher dose levels of ADCT-502 enrolled in part 1 may be offered continued treatment at the RDE(s).

4.6.1 Safety Oversight by the Dose Escalation Steering Committee

A DESC comprised of ADC Therapeutics and the investigators will review patient safety on an ongoing basis during Part 1 to determine if the dose escalation schedule prescribed by the mCRM warrants modification. In addition to safety observations, PK and/or PD data may also inform DESC decision making. Intermediate doses or extended dosing intervals may be assigned after agreement between ADC Therapeutics and the investigators. The DESC will continue to provide oversight during Part 2. No formal Data Safety Monitoring Board (DSMB) will be used.

4.6.2 Definition of Dose-Limiting Toxicities

A DLT is defined as any of the following events that occur during the 21-day DLT evaluation period, except those that are clearly due to underlying disease or extraneous causes.

A **hematologic** DLT is defined as:

Event	Severity
Febrile neutropenia or neutropenic infection	Grade 3 or 4
Neutropenia lasting > 7 days	Grade 4
Thrombocytopenia	Grade 4
Thrombocytopenia with clinically significant bleeding	Grade 3
Thrombocytopenia requiring a platelet transfusion	Grade 3
Anemia	Grade 4
Anemia requiring transfusion	Grade 3

A **non-hematologic** DLT is defined as:

Event	Severity
Hy's law case	AST and/or ALT > 3x ULN and bilirubin > 2x ULN, and without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity < 2x ULN) and no other reason that could explain the combination of increased transaminases and serum total bilirubin, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.
Hypersensitivity/infusion-related	Grade 3 or higher. A Grade 3 hypersensitivity /

reaction (regardless of premedication)	infusion-related reaction that resolves within 24 hours after onset with appropriate clinical management does not qualify as a DLT.
All other non-hematologic toxicity	Grade 3 & 4

The following conditions **are not considered** non-hematologic DLTs:

Event	Severity
Fatigue	Grade 3 for ≤ 7 days.
Diarrhea, nausea, or vomiting	Grade 3 in the absence of premedication that responds to therapy and improves by at least 1 grade within 3 days for Grade 3 events or to \leq Grade 1 within 7 days.
Serum lipase or serum amylase	Grade 3 for ≤ 7 days if without clinical signs or symptoms of pancreatitis.
Electrolyte abnormalities	\leq Grade 3 which normalize within 48 hrs (with or without medical intervention) and which do not manifest themselves clinically; in such instance, a follow-up sample MUST be taken within 48 hrs to check whether such normalization has occurred.

Patients who experience a DLT that resolves or stabilizes with appropriate medical management may continue treatment at the discretion of the Investigator in consultation with the Sponsor.

5 Management of Toxicity Including Dose Delays and Modifications

The Investigator may suspend ADCT-502 dosing for up to 1 cycle (i.e., 21 days of the default dosing schedule) for any patient who experiences a protocol-defined DLT. At the discretion of the Investigator, the dose may also be delayed for up to 21 days for any other toxicity of any grade.

Resumption of dosing with ADCT-502 after any suspension, even when longer than 21 days, is at the discretion of the Investigator, in consultation with the Sponsor, on assessment of the patient's clinical condition and whether or not the patient is deriving potential clinical benefit from treatment with ADCT-502.

5.1 ADCT-502 General Dose Modification Guidelines

Guidelines for management of specific toxicities are detailed in [Sections 5.2, 5.3, and 5.4](#). For management of events not specified in these sections, the following may serve as a guidance to investigators:

AE Grade	ADCT-502 Management Guideline
1	No dose adjustment is required.
2	<p><u>First Occurrence:</u></p> <p>Consider holding ADCT-502 until improvement to \leq Grade 1 or Baseline. Up to 1 dose of ADCT-502 may be skipped to permit improvement. If improvement to \leq Grade 1 or Baseline occurs within 21 days from the last scheduled (but missed) ADCT-502 dose, continue ADCT-502 at the original assigned dose level in subsequent treatment cycles.</p> <p>If improvement to \leq Grade 1 or Baseline does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Second Occurrence:</u></p> <p>Hold ADCT-502 until improvement to \leq Grade 1 or Baseline. Up to 1 dose of ADCT-502 may be skipped to permit resolution. If improvement to \leq Grade 1 or Baseline occurs within 21 days from the last scheduled (but missed) ADCT-502 dose, continue ADCT-502 at 1 dose level below the original assigned dose in subsequent treatment cycles. If improvement to \leq Grade 1 or Baseline does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Third Occurrence:</u></p> <p>Permanently discontinue ADCT-502.</p>
3	<p><u>First Occurrence:</u></p> <p>Hold ADCT-502 until improvement to \leq Grade 1 or Baseline. Up to 1 dose of ADCT-502 may be skipped to permit improvement, then continue ADCT-502 at 1 dose level below the original assigned dose in subsequent treatment cycles.</p> <p><u>Second Occurrence:</u></p> <p>Permanently discontinue ADCT-502.</p>
4	Permanently discontinue ADCT-502.

5.2 Guidelines for Dose Modification: Hematologic Toxicities

Adverse Event	Grade	ADCT-502 Management Guideline
Febrile neutropenia	3	Hold ADCT-502 until the patient recovers. Up to 1 dose of ADCT-502 may be skipped to permit improvement. Consider use of granulocyte colony stimulating factor (G-CSF) as per institutional guidelines or as per ASCO guidelines. G-CSF prior to ADCT-502 is not allowed unless approved by sponsor.

Adverse Event	Grade	ADCT-502 Management Guideline
		<p><u>First Occurrence:</u></p> <p>If patient recovers from febrile neutropenia prior to next scheduled dose or within 21 days from last scheduled (but missed) ADCT-502 dose, then continue ADCT-502 at 1 dose level below the original assigned dose in subsequent treatment cycles. If the patient does not recover within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Second Occurrence:</u></p> <p>Permanently discontinue ADCT-502 if febrile neutropenia recurs despite ADCT-502 dose reduction.</p>
Febrile neutropenia	4	Permanently discontinue ADCT-502.
Thrombocytopenia with significant bleeding or platelet transfusion required as per PI assessment	3	<p>Hold ADCT-502 until bleeding has stopped and improvement has occurred to \leq Grade 1. Up to 1 dose of ADCT-502 may be skipped to permit improvement.</p> <p><u>First Occurrence:</u></p> <p>Upon improvement to \leq Grade 1 within 21 days from last scheduled (but missed) ADCT-502 dose, continue ADCT-502 at 1 dose level below the original assigned dose in subsequent treatment cycles.</p> <p>If improvement to CTCAE \leq Grade 1 does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Second Occurrence:</u></p> <p>Upon improvement to \leq Grade 1 within 21 days from last scheduled (but missed) ADCT-502 dose, continue ADCT-502 at 2 dose levels below the original assigned dose in subsequent treatment cycles.</p> <p>If improvement to \leq Grade 1 does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Third Occurrence:</u></p> <p>Permanently discontinue ADCT-502.</p>
Thrombocytopenia (regardless of whether significant bleeding is present or not)	4	<p>Hold ADCT-502 until bleeding has stopped and improvement has occurred to \leq Grade 1. Up to 1 dose of ADCT-502 may be skipped to permit improvement.</p> <p><u>First Occurrence:</u></p> <p>Upon improvement to \leq Grade 1 within 21 days from last scheduled (but missed) ADCT-502 dose, continue ADCT-502 at 1 dose level below the original assigned dose in subsequent treatment cycles.</p> <p>If improvement to CTCAE \leq Grade 1 does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue</p>

Adverse Event	Grade	ADCT-502 Management Guideline
		<p>ADCT-502.</p> <p><u>Second Occurrence:</u></p> <p>Upon improvement to \leq Grade 1 within 21 days from last scheduled (but missed) ADCT-502 dose, continue ADCT-502 at 2 dose levels below the original assigned dose in subsequent treatment cycles.</p> <p>If improvement to \leq Grade 1 does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Third Occurrence:</u></p> <p>Permanently discontinue ADCT-502.</p>
Neutropenia or thrombocytopenia (in the absence of bleeding)	3	<p>Hold ADCT-502 until improvement to \leq Grade 1. Up to 1 dose of ADCT-502 may be skipped to permit improvement. Consider use of G-CSF as per institutional guidelines or as per ASCO guidelines. G-CSF prior to ADCT-502 is not allowed unless approved by sponsor.</p> <p><u>First Occurrence:</u></p> <p>If improvement to \leq Grade 1 within 21 days from last scheduled (but missed) ADCT-502 dose, then continue ADCT-502 at original assigned dose in subsequent treatment cycles.</p> <p>If improvement to \leq Grade 1 does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Second Occurrence:</u></p> <p>If improvement to \leq Grade 1 within 21 days from last scheduled (but missed) ADCT-502 dose, then continue ADCT-502 at 1 dose level below the original assigned dose in subsequent treatment cycles.</p> <p>If improvement to \leq Grade 1 does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Third Occurrence:</u></p> <p>Permanently discontinue ADCT-502</p>
Neutropenia	4	<p>Hold ADCT-502 until improvement to \leq Grade 1. Up to 1 dose of ADCT-502 may be skipped to permit improvement. Consider use of G-CSF as per institutional guidelines or as per ASCO guidelines. G-CSF prior to ADCT-502 is not allowed unless approved by sponsor.</p> <p><u>First Occurrence:</u></p> <p>If improvement to \leq Grade 1 within 21 days from last scheduled (but missed) ADCT-502 dose, then continue ADCT-502 at original assigned dose in subsequent treatment cycles. If improvement to \leq Grade 1 does not occur within 21 days from the last scheduled (but missed)</p>

Adverse Event	Grade	ADCT-502 Management Guideline
		<p>ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Second Occurrence:</u></p> <p>If improvement to \leq Grade 1 within 21 days from last scheduled (but missed) ADCT-502 dose, then continue ADCT-502 at 1 dose level below the original assigned dose in subsequent treatment cycles.</p> <p>If improvement to \leq Grade 1 does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Third Occurrence:</u></p> <p>Permanently discontinue ADCT-502.</p>
Anemia	3	<p>Hold ADCT-502 until improvement to \leq Grade 1 or Baseline.</p> <p>Up to 1 dose of ADCT-502 may be skipped to permit improvement.</p> <p>Consider use of erythropoietin (EPO) as per institutional guidelines.</p> <p><u>First Occurrence:</u></p> <p>If improvement to \leq Grade 1 or Baseline prior to next scheduled dose, continue ADCT-502 at the original assigned dose at the next scheduled treatment cycle. If improvement to \leq Grade 1 or Baseline within 21 days from last scheduled (but missed) ADCT-502 dose, then continue ADCT-502 at 1 dose level below the original assigned dose in subsequent treatment cycles. If improvement to \leq Grade 1 or Baseline does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Second Occurrence:</u></p> <p>If improvement to \leq Grade 1 or Baseline within 21 days from last scheduled (but missed) ADCT-502 dose, then continue ADCT-502 at 2 dose level below the original assigned dose in subsequent treatment cycles. If improvement to \leq Grade 1 or Baseline does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Third Occurrence:</u></p> <p>Permanently discontinue ADCT-502.</p>
Anemia	4	<p>Hold ADCT-502 until improvement to \leq Grade 1 or Baseline.</p> <p>Up to 1 dose of ADCT-502 may be skipped to permit improvement.</p> <p>Consider use of EPO as per institutional guidelines.</p> <p><u>First Occurrence:</u></p> <p>If improvement to \leq Grade 1 or Baseline within 21 days from last scheduled (but missed) ADCT-502 dose, then continue ADCT-502 at 1 dose level below the original assigned dose in subsequent treatment cycles. If improvement to \leq Grade 1 or Baseline does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose,</p>

Adverse Event	Grade	ADCT-502 Management Guideline
		<p>permanently discontinue ADCT-502.</p> <p><u>Second Occurrence:</u></p> <p>If improvement to \leq Grade 1 or Baseline within 21 days from last scheduled (but missed) ADCT-502 dose, then continue ADCT-502 at 2 dose level below the original assigned dose in subsequent treatment cycles. If improvement to \leq Grade 1 or Baseline does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Third Occurrence:</u></p> <p>Permanently discontinue ADCT-502.</p>

5.3 Guidelines for Dose Modification: Non-hematologic Toxicities

Adverse Event	Grade	ADCT-502 Management Guideline
Infusion-related reactions	1	<p>The infusion rate may be decreased by 50% or temporarily interrupted for up to 6 hours to permit resolution of the event.</p> <p>Acetaminophen (paracetamol) and/or H1- and H2-receptor antagonists (e.g., diphenhydramine, ranitidine) may be administered for symptomatic treatment per institutional standard at the discretion of the Investigator.</p> <p>Consider premedication (e.g., secondary prophylaxis) with acetaminophen (paracetamol) and/or H1- and H2-receptor antagonists at least 30 minutes prior to start of subsequent doses.</p>
	2	<p>Interrupt ADCT-502 infusion for up to 6 hours to permit resolution of the event. If the event resolves within 6 hours, resume ADCT-502 infusion at 50% of the prior infusion rate. Acetaminophen (paracetamol) and H1- and H2-receptor antagonists (diphenhydramine and ranitidine) should be administered for symptomatic treatment. If the patient experiences chest tightness, dyspnea, or shortness of breath, IV methylprednisolone 100 mg (or the equivalent) should be administered.</p> <p>If the event resolves within 6 hours and requires IV steroid treatment, pre-medicate (e.g., secondary prophylaxis) with acetaminophen (paracetamol), H1- and H2-receptor antagonists (e.g., IV diphenhydramine, and IV ranitidine), and IV methylprednisolone 100 mg (or the equivalent) at least 30 minutes prior to start of subsequent doses.</p> <p>If the event resolves within 6 hours and did not require IV steroid treatment, pre-medication (e.g., secondary prophylaxis), at least 30 minutes prior to start of subsequent doses may be considered.</p>

Adverse Event	Grade	ADCT-502 Management Guideline
Hypersensitivity and infusion-related reactions	3	Permanently discontinue ADCT-502 unless AE resolves within 24 hours after onset (with or without clinical management). Manage severe infusion-related reactions per institutional guidelines (i.e., treatment with IV diphenhydramine, IV ranitidine, and IV glucocorticoids). Intramuscular epinephrine should be used after failure of other therapeutic options.
Hypersensitivity and infusion-related reactions	4	Permanently discontinue ADCT-502.
Transaminase (AST/ALT) Abnormalities	2	No dose modification is required.
	3	<p>Hold ADCT-502 until improvement to \leq Grade 1 or Baseline. Up to 1 dose of ADCT-502 may be skipped to permit improvement.</p> <p><u>First Occurrence:</u></p> <p>If improvement to \leq Grade 1 or Baseline occurs prior to next scheduled dose, continue ADCT-502 at the original assigned dose at the next scheduled treatment cycle.</p> <p>If improvement to \leq Grade 1 or Baseline within 21 days from last scheduled (but missed) ADCT-502 dose, continue ADCT-502 at 1 dose level below the original assigned dose in subsequent treatment cycles. If improvement to \leq Grade 1 or Baseline does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Second Occurrence:</u></p> <p>If improvement to \leq Grade 1 or Baseline within 21 days from last scheduled (but missed) ADCT-502 dose, then continue ADCT-502 at 2 dose level below the original assigned dose in subsequent treatment cycles. If improvement to \leq Grade 1 or Baseline does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Third Occurrence:</u></p> <p>Permanently discontinue ADCT-502.</p>
Hyperbilirubinemia	2	<p>Hold ADCT-502 until improvement to \leq Grade 1 or Baseline.</p> <p>If improvement to \leq Grade 1 or Baseline occurs prior to next scheduled dose, continue ADCT-502 at the original assigned dose at the next scheduled treatment cycle.</p> <p><u>First Occurrence:</u></p> <p>If improvement to \leq Grade 1 or Baseline within 21 days from last scheduled (but missed) ADCT-502 dose, continue ADCT-502 at 1 dose</p>

Adverse Event	Grade	ADCT-502 Management Guideline
		<p>level below the original assigned dose in subsequent treatment cycles. If improvement to \leq Grade 1 or Baseline does not occur within 21 days from the last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p>Consider close monitoring as needed.</p> <p><u>Second occurrence:</u></p> <p>Permanently discontinue ADCT-502</p> <p>Permanently discontinue ADCT-502 for any case meeting Hy's Law criteria.</p>
	3	<p>Hold ADCT-502 until improvement to \leq Grade 1 or Baseline. Up to 1 dose of ADCT-502 may be skipped to permit improvement.</p> <p><u>First occurrence:</u></p> <p>If improvement to \leq Grade 1 or Baseline occurs prior to next scheduled dose, continue ADCT-502 at the original assigned dose at the next treatment cycle. If improvement to \leq Grade 1 or Baseline occurs within 21 days from the last scheduled (but missed) ADCT-502 dose, continue ADCT-502 at 1 dose level below the original assigned dose in subsequent treatment cycles. If improvement to \leq Grade 1 or Baseline does not occur within 21 days from last scheduled (but missed) ADCT-502 dose, permanently discontinue ADCT-502.</p> <p><u>Second occurrence:</u></p> <p>Permanently discontinue ADCT-502.</p>
Changes in LVEF	1-4	See Table 3

5.4 Guidelines for Dose Modifications: Left Ventricular Dysfunction

ADCT-502 should be discontinued in any patient who develops confirmed congestive heart failure (CHF) (i.e., Grade ≥ 3 left ventricular systolic dysfunction as defined by NCI CTCAE version 4.0). CHF should be treated and monitored according to standard medical practice.

If ADCT-502 is withheld due to clinically significant (e.g., \geq Grade 3 or per investigator judgement) left ventricular cardiac dysfunction and treatment is then resumed, left ventricular ejection fraction (LVEF) measurement must be repeated after every cycle for the next 2 cycles and then every 3 cycles and at End of Treatment (EOT).

ADCT-502 must be discontinued in all patients for whom a drop of LVEF to below 40% is documented (unless it is not confirmed with a repeat assessment within 21 days).

For patients whose LVEF drops to values between 40% and 45%, the decision to stop or continue ADCT-502 should be based on [Table 3](#). Additional evaluations to evaluate safety may be performed as clinically indicated.

Table 3: Dose Modification Guidelines for Left Ventricular Dysfunction

Symptomatic CHF	LVEF < 40% (Grade 3 or 4)	LVEF 40% to ≤ 45% and Decrease is ≥ 10% Points from Baseline (Grade 2)	LVEF 40% to ≤ 45% and Decrease is < 10% Points from Baseline (Grade 2)	LVEF > 45% (≤ Grade 2)
Discontinue ADCT-502	Do not administer ADCT-502. Repeat LVEF assessment within 3 weeks. If LVEF <40% is confirmed, permanently discontinue ADCT-502.	Do not administer ADCT-502. Repeat LVEF assessment within 3 weeks. If the LVEF has not recovered to within 10% points from Baseline, discontinue ADCT-502.	Continue treatment with ADCT-502. Repeat LVEF assessment within 3 weeks.	Continue treatment with ADCT-502.

CHF = congestive heart failure; LVEF = Left ventricular ejection fraction

6 Patient Population

6.1 Inclusion Criteria

1. Male or female age 18 years or older.
2. Refractory to or intolerant of existing therapy(ies) known to provide clinical benefit for their condition.
3. Eastern Cooperative Oncology Group (ECOG) performance status:
 - a. Part 1: 0-2
 - b. Part 2: 0-1
4. Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue block (or unstained slides (minimum 7; 10 preferred) if block is not available) to demonstrate HER2 expression.

Note: any biopsy since initial diagnosis is acceptable, but if several are available, the most recent sample is preferred.
5. Pathologic diagnosis of solid tumor malignancy that is locally advanced or metastatic at time of Screening:

Part 1 (Dose Escalation):

Advanced solid tumors with documented HER2 status of IHC ≥1+ or HER2

amplified/mutated by FISH or NGS (refer to [Section 4.2](#) and [Appendix 18.3](#)).

Note: Clinical pathology report of HER2 status must be available for review to confirm eligibility in Part 1.

Part 2 (Dose Expansion):

HER2-high* or HER2-low** advanced solid tumor belonging to one of the pre-specified indications for groups A – E (breast cancer, gastric & gastroesophageal cancer, bladder cancer, non-small cell lung cancer) or one of the eight pre-specified indications for the basket group (SCLC, CRC, pancreatic, biliary tract, prostate, ovarian, endometrial, or salivary gland) according to assigned treatment group for which HER2 status has been confirmed prospectively (HER2-high or HER2-low) for study entry.

* A HER2-high patient is defined as IHC 3+, or IHC 2+ with FISH amplification.

** A HER2-low patient is defined as IHC 1+, or IHC 2+ without FISH amplification.

Note: A patient with IHC 0 / IHC 1+ with amplification is HER2-high for study purposes; a patient with IHC 3+ with negative amplification results is HER2-low for study purposes.

6. Part 2/Dose Expansion Only: Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Note: 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 per RECIST.

7. Screening laboratory values within the following parameters:

- Absolute neutrophil count (ANC) $\geq 1500/\text{mm}^3$ ($\geq 1.5 \times 10^9/\text{L}$).
- Platelet count $\geq 100,000/\text{mm}^3$ ($\geq 100 \times 10^9/\text{L}$).
- Hemoglobin $\geq 9 \text{ g/L}$ ($\geq 5.6 \text{ mmol/L}$).
- Aspartate transaminase (AST) and alanine aminotransferase (ALT) $\leq 2.5 \times$ upper limit of normal (ULN); or $\leq 5.0 \times$ ULN if liver metastases are present.
- Total bilirubin $\leq 1.5 \times$ ULN (or $\leq 3 \times$ ULN, with direct bilirubin $\leq 1.5 \times$ ULN, in patients with known Gilbert syndrome).
- Serum/plasma creatinine $\leq 1.5 \times$ ULN; or, if creatinine $> 1.5 \times$ ULN, a measured creatinine clearance must be $> 60 \text{ mL/min}$ as calculated by the Cockcroft and Gault equation for patient to be eligible.

8. Women of childbearing potential* must agree to use a highly effective** method of contraception from the time of giving informed consent until at least 16 weeks after the last dose of ADCT-502. Men with female partners who are of childbearing potential must agree that they or their partners will use a highly effective method of contraception from the time of giving informed consent until at least 16 weeks after the patient receives his last dose of ADCT-502.

*Defined as: Sexually mature women who have not undergone bilateral tubal ligation, bilateral oophorectomy, or hysterectomy; or who have not been postmenopausal (i.e., who have not menstruated at all) for at least 1 year.

Defined as: Hormonal contraceptives (oral, injectable, patch, intrauterine devices), male partner sterilization, or total abstinence from heterosexual intercourse, when this is the preferred and usual lifestyle of the patient. **Note: The double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), periodic abstinence (such as calendar, symptothermal, post-ovulation), withdrawal (coitus interruptus), lactational amenorrhea method, and spermicide-only are not acceptable as highly effective methods of contraception.

6.2 Exclusion Criteria

1. Known history of \geq Grade 3 hypersensitivity to a therapeutic antibody.
2. Known history of positive serum human ADA to trastuzumab.
3. History of Stevens-Johnson syndrome or toxic epidermal necrolysis syndrome.
4. Major surgical procedure or significant traumatic injury, radiotherapy, chemotherapy, targeted therapy, hormone therapy (except for luteinizing hormone-releasing hormone (LHRH) agonists or denosumab) or other anticancer therapy within 21 days OR within 5 half-lives of the product, whichever is shorter, prior to the Cycle 1, Day 1 visit.

Note: cumulative dose of anthracycline >450 mg/m² is prohibited.

5. Failure to recover to Grade 0 or Grade 1 from acute non-hematologic toxicity due to previous therapy, prior to screening (with the exception of alopecia).
6. Central Nervous System (CNS) disease only.
7. Symptomatic CNS metastases or evidence of leptomeningeal disease (brain MRI or previously documented cerebrospinal fluid (CSF) cytology).

Previously treated asymptomatic CNS metastases are permitted provided that the last treatment (systemic anticancer therapy and/or local radiotherapy) was completed ≥ 8 weeks prior to Day 1 except usage of low dose of steroids on a taper (i.e. up to 10 mg on Day 1 and consecutive days is permissible if being tapered down). Patients with discrete dural metastases are eligible.

8. Active cardiac disease including any of the following:
- Angina pectoris that requires the use of anti-anginal medication.
 - Ventricular arrhythmias except for benign premature ventricular contractions.
 - Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication.
 - Clinically significant valvular disease with documented compromise in cardiac function.
 - Symptomatic pericarditis.
 - Congenital long QT syndrome or a corrected QTc interval ≥ 450 ms at Screening.
 - LVEF $< 50\%$ at Screening or a history of decrease in LVEF to $< 40\%$ during previous treatment with HER2 targeted therapy.
9. History of clinically significant cardiovascular dysfunction including any one of the following:
- History of myocardial infarction (MI) or recent MI documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of left ventricular function within 6 months prior to Day 1.
 - History of documented congestive heart failure (New York Heart Association functional classification III-IV).
 - Documented cardiomyopathy.
 - Uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 100 mm Hg).
10. Active ulceration of the upper gastrointestinal tract or gastrointestinal bleeding.
11. Active autoimmune disease, motor neuropathy considered of autoimmune origin, and other CNS autoimmune disease.
12. Patients receiving concomitant immunosuppressive agents or chronic corticosteroids use, at study entry except in cases outlined below:
- a. Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular), or as physiologic replacement are permitted.
13. Known human immunodeficiency virus (HIV) infection; known seropositive for hepatitis B surface antigen (HBsAg), or antibody to hepatitis C virus (anti-HCV) with confirmatory testing and requiring anti-viral therapy.

Note: Testing is not mandatory to be eligible. Testing for HCV should be considered if the patient is at risk for having undiagnosed HCV (e.g., history of injection drug use).

14. Any other malignancy within 3 years prior to Day 1, with the exception of adequately treated in-situ carcinoma of the cervix uteri, basal or squamous cell carcinoma or other non-melanomatous skin cancer.
15. Active bleeding diathesis or significant anticoagulation (such as with oral anti-vitamin K medication. Low-dose warfarin, aspirin, or equivalent, are permitted as long as the INR ≤ 2.0).
16. History of thromboembolic or cerebrovascular events within the last 6 months, including transient ischemic attack, cerebrovascular accident, deep vein thrombosis or pulmonary embolism.
17. Clinically significant third space fluid accumulation (i.e., ascites requiring tap or pleural effusion that is either requiring tap or associated with shortness of breath).
18. Breastfeeding or pregnant.
19. Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes mellitus, active untreated or uncontrolled infection including viral and systemic fungal infections, chronic obstructive or chronic restrictive pulmonary disease including dyspnea at rest from any cause) that could cause unacceptable safety risks or compromise compliance with the protocol.

6.3 Definition of HER2 Expression Levels

Expression levels for HER2 are classified as HER2-high or HER2-low for the purposes of this protocol. Please see [Section 4.2](#) for details.

7 Reasons for Withdrawal/Discontinuation

Patients may withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or others at the study site.

A patient may be withdrawn from treatment with ADCT-502 for any of the following reasons:

- Disease progression.
- AE.
- Withdrawal of consent.
- Major protocol deviation.
- Required treatment delay >21 days (except in case of potential patient benefit, which must be approved by the Sponsor).
- Non-compliance, including lost to follow-up.

- Pregnancy.
- Other (e.g., development of contraindications with use of the study drug).
- The Investigator determines that it is in the best interest of the patient to discontinue the patient's participation in the study.
- Discontinuation of the study by the Sponsor.
- Death.

7.1 Handling of Withdrawals

The Investigator will confer with the Sponsor if a patient experiences a serious or intolerable AE. If a patient discontinues from the study because of an AE, the patient will be followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

For each patient who discontinues study treatment and withdraws from the study, the Investigator will record the reason(s) for discontinuation on the relevant page of the electronic case report form (eCRF). Whenever possible, each patient who discontinues study treatment will undergo an EOT visit and all EOT assessments. Patients who fail to return for final assessments are to be contacted by the investigative site. Following a minimum of two, documented unsuccessful telephone calls, the investigative site will send a registered letter to the patient in a final attempt to ensure protocol compliance.

Note: Once discontinued from the study for any reason, patients are not permitted to be re-enrolled into the study.

7.1.1 Patient Replacements

Any patient in Part 1 who discontinues before completion of the first treatment cycle, for any reason other than a DLT, will be replaced.

8 Study Drug

8.1 ADCT-502 Drug Product

ADCT-502 is a sterile formulation containing PBD-conjugated humanized monoclonal IgG1 antibody [REDACTED] and engineered trastuzumab [REDACTED]. Refer to the current IB for additional information regarding formulation.

8.2 Packaging and Storage

ADCT-502 is formulated as a sterile liquid at 5 mg/mL in a 10 mL glass vial (2.0 mL nominal fill). The drug product is designed to deliver 10 mg ADCT-502 per vial and is intended for intravenous infusion following dilution in 0.9% sodium chloride.

The drug product storage temperature is $\leq -60^{\circ}\text{C}$.

8.3 Preparation and Administration

The study drug will be supplied by ADC Therapeutics through the designated packaging, labeling, and distribution center. After the vials have been completely thawed, the study drug may be prepared per the instructions provided in the ADCT-502 Pharmacy Manual. ADCT-502 must be diluted in 0.9% sodium chloride due to compatibility reasons and administered via a metered IV pump.

Patients will receive a 1-hour IV infusion of ADCT-502 on Day 1 of each 3-week (21-day) cycle. If ADCT-502 is well tolerated after the first cycle, the infusion duration may be shortened to 30 minutes for subsequent cycles for that patient at the discretion of the Investigator. Variations in infusion times due to minor differences in IV bag overfill/underfill and the institution's procedure for flushing chemotherapy lines will not result in protocol deviation.

Additional instructions regarding study drug shipment, handling, storage, and preparation are included in the pharmacy manual.

8.4 Study Drug Accountability

The Investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. All study drugs will be reconciled and retained or destroyed according to applicable regulations.

8.5 Treatment Compliance

Administration of ADCT-502 will be performed by the Investigator or a qualified designee. Compliance will be verified based on the source documentation of study drug administration information.

9 Concomitant Treatment

All medications used within 14 days prior to Cycle 1, Day 1, during the treatment period, and within 30 days after the last dose of study drug are recorded in the eCRF. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

9.1 Prophylaxis Mandated During the Study

Unless contraindicated, administer dexamethasone 4 mg PO BID the day before ADCT-502 administration (if possible/feasible), the day of ADCT-502 administration (give at least 2 hours prior to administration when not given the day before; otherwise any time prior to administration), and the day after ADCT-502 administration.

9.2 Prohibited During Study

- Other anticancer therapy.
- Other investigational agents.
- Chronic treatment with corticosteroids (prednisone ≥ 12.5 mg/day or dexamethasone ≥ 2 mg/day). Inhaled steroids, intraocular, joint injections, and nasal steroids, or as physiologic replacement, are permitted.
- Live vaccines.

9.3 Permitted Treatment During Study

After confirmation and documentation of eligibility, supportive care treatments (transfusions, etc.) can be prescribed as medically appropriate. Prophylactic treatment for hypersensitivity has not been prospectively mandated, but may become required as specified in [Section 9.4](#).

9.3.1 Palliative Radiotherapy

Local radiotherapy for analgesic/palliative purposes or for lytic lesions at risk of fracture may be carried out if required after completion of the DLT evaluation period. Whenever possible, these patients should have a tumor assessment of the lesion(s) before they receive radiotherapy to rule out progression of disease. No dose modification of study medication is needed during radiotherapy.

9.3.2 Oral Contraception

Oral contraception is allowed during the study. Refer to [Section 6.1](#) for contraception requirements.

9.3.3 Anti-emetics

Prophylactic anti-emetics will be withheld during the DLT observation period (i.e., Cycle 1). Subsequently, patients may receive (prophylactic) anti-emetics at the discretion of the treating physician.

9.3.4 Anti-diarrheal Treatment

Anti-diarrheal treatment is recommended at the first sign of diarrhea. As a recommendation, initial management of diarrhea should include dietary modifications, extra fluid, and loperamide.

9.3.5 Growth Factors

Hematopoietic growth factors are permitted as per American Society of Clinical Oncology guidelines ([Smith, 2006](#)); however, prophylactic use of growth factors is not allowed during the DLT observation period (first treatment cycle).

9.3.6 Steroids

Concomitant steroid use is permitted as follows:

- Replacement doses of steroids for patients with adrenal insufficiency
- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection)

9.3.7 Skin Toxicity Therapy

Appropriate skin toxicity therapy includes e.g. antihistamines, topical or systemic corticosteroids, , and should be used according to institutional guidelines (see also [Section 9.6](#) Other supportive care).

9.3.8 Bisphosphonates or Denosumab

Concomitant use of bisphosphonates or denosumab is allowed if started 12 weeks or more prior to first dose.

9.3.9 Androgen Deprivation Therapy

Androgen deprivation therapy (ADT) is permitted if its continuation is in the best interest in the patient as per investigator assessment unless prohibited above.

Any other concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator.

9.4 Prophylaxis for Hypersensitivity

If one patient experiences a Grade 2 or higher infusion-related hypersensitivity reaction ([Appendix 18.1](#)) at any time during Part 1 (Dose Escalation), all subsequent patients must receive prophylactic treatment per institutional standard of care or according to the guidelines below, to reduce the risk of hypersensitivity reactions:

- On Day 1 of each cycle, patients will be instructed to take 20 mg orally of dexamethasone at 12 and 6 hours before the start of ADCT-502 infusion. When necessary, 12 and 6 hours before the first infusion may be defined as “immediately before sleeping” and “immediately after waking up.”

- On Day 1 of each cycle, patients will be given 50 mg IV of diphenhydramine hydrochloride at 30 minutes before the start of ADCT-502 infusion.
- On Day 1 of each cycle, patients will be given 50 mg of ranitidine (or equivalent) IV at 30 minutes before the start of ADCT-502 infusion.
- For 2 days following administration of ADCT-502 on Day 1, all patients are to take dexamethasone 4 mg orally, twice per day.

Furthermore, prophylaxis for hypersensitivity will supersede prior stipulations on dexamethasone prophylaxis as mandated in [Section 9.1](#).

Treatment of hypersensitivity or infusion reactions may be administered according to standard treatment center protocols. Additional guidance is provided in [Section 5.3](#).

Medications for the treatment of severe hypersensitivity reactions, including anaphylaxis, should be available for immediate use.

9.5 Treatment of Edema and/or Pleural Effusion

Spironolactone, at standard doses, should be considered for patients with weight gain greater than 1 kg (2.2 pounds) from C1D1, new or worsening edema, and/or new or worsening pleural effusion. The dose of spironolactone may be titrated as clinically indicated. Additional diuretic support may be added if there is further increase in weight, edema, or pleural effusion. Additionally, patients are advised to monitor their weight on a daily basis, at around the same time (preferably in the morning), and to notify the study site if they gain >1 kg (2.2 pounds) over C1D1.

9.6 Other Supportive Care

The following supportive care needs to be considered:

- Because of non-clinical observations related to nephropathy, adequate patient hydration (e.g., 8 to 10 glasses of water or equivalent per day) is recommended for patients receiving ADCT-502.
- Skin rash has been reported with other investigational agents containing the same PBD warhead ([Rudin, 2016](#)). Although there have not been signals of photosensitivity in the rat and monkey toxicology studies with ADCT-502, it is recommended that precautions are taken to avoid prolonged exposure of skin to direct sunlight.

10 Description of Procedures

Patients will undergo the procedures at the time points specified in schedule of events ([Table 1](#) and [Table 2](#)). Any clinically significant abnormalities (including clinically significant laboratory abnormalities) that worsen from Baseline are to be recorded as AEs or SAEs and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

10.1 Triplicate 12-Lead ECGs

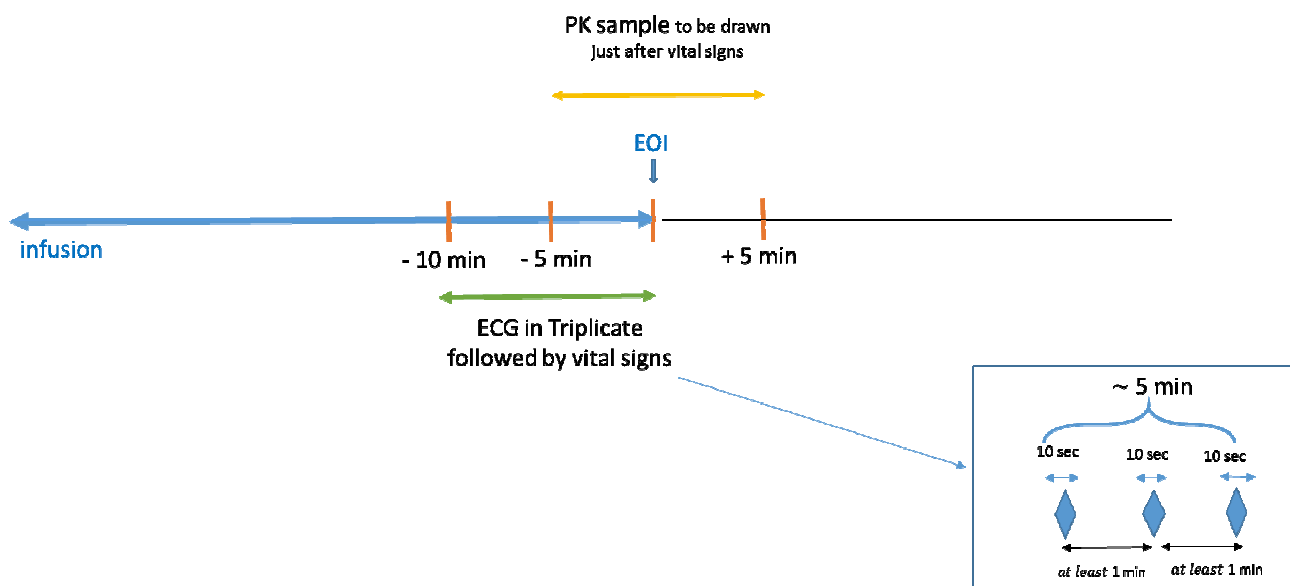
Three consecutive (also called triplicate) ECGs will be performed at defined timepoints throughout the study as per schedule of events ([Table 1](#) and [Table 2](#)).

ECG will be performed after patient is resting for at least 5-min.

At timepoints coinciding with ECG measurements, PK blood collection should occur immediately after the end of the ECG recording and, when applicable, after vital signs measurements (example in [Figure 2](#)).

If a patient experiences Torsade de Pointes, concomitant PK samples (e.g., unscheduled) should be collected.

Figure 2: Preferred sequence for triplicate ECG, vital signs, and PK sample assessments at end of infusion (EOI)



10.2 Laboratory Analyses (Safety)

10.2.1 Complete Blood Count with Differential

Complete blood count (CBC) includes white blood cells (WBC) with 5-part differential, platelet count, hemoglobin, hematocrit, and absolute neutrophil count.

10.2.2 Coagulation

Coagulation panel must include partial thromboplastin time (PTT) and International Normalized Ratio (INR) (prothrombin time (PT) expressed in seconds is optional). Patients taking coumarin-derivative anticoagulants should be monitored closely and their anticoagulant dose adjusted as needed.

10.2.3 Chemistry

Chemistry includes alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, amylase, lipase, total bilirubin, sodium, potassium, calcium, magnesium, blood urea nitrogen or urea, carbon dioxide/bicarbonate, chloride, creatinine, creatine phosphokinase, total protein, albumin, glucose, triglycerides, total cholesterol, phosphorus, and lactate dehydrogenase.

10.2.4 Urinalysis

Urinalysis includes pH, specific gravity, protein, white blood cells, hemoglobin, ketones, glucose and bilirubin. Urinalysis may be performed by dipstick.

Abnormal findings will be followed up with a microscopic evaluation and/or additional assessments as clinically indicated. A microscopic evaluation consists at a minimum of WBC and RBC quantitation per high power field, as well as semi-quantitative assessment of other cells and substances, if present, such as epithelial cells, bacteria, and crystals (“few,” “moderate,” “many”). Other evaluations depending on microscopic findings may be added.

10.3 Efficacy Assessments

Computerized tomography (CT) or magnetic resonance imaging (MRI) scans with contrast of the chest, abdominal and pelvic area or brain scans (CT or MRI with contrast), and bone scans or X-ray exam if clinically indicated, will be performed. For image acquisition specifications, including instruction in the event of allergy to contrast dye, refer to Appendix II of RECIST version 1.1 (Specifications for Standard Anatomical Radiological Imaging).

The same methods used at baseline that identify sites of disease should be used uniformly for all subsequent assessments. Response to treatment will be determined by the Investigator as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to RECIST version 1.1.

Images will be obtained according to local site imaging requirements and may be required to be submitted for a central/independent review. Submission instructions for the central/independent review will be provided in a separate manual.

Once the final efficacy analysis for progression-free survival (PFS) is performed (Part 2), the frequency of tumor response assessment for patients remaining under treatment may be further decreased and/or performed according to standard of care.

10.4.1 Pharmacokinetics

The PK profile of ADCT-502 (total antibody; $\text{DAR} \geq 0$), PBD-conjugated antibody ($\text{DAR} \geq 1$), and free warhead SG3199 will be assessed centrally. The PK profile will include determination of standard PK parameters (e.g., maximum concentration [C_{\max}], time to C_{\max} [T_{\max}], area under the curve [AUC]). PK samples may be collected at other time points if clinically indicated.

At timepoints coinciding with ECG measurements, PK blood collection should occur immediately after the end of the ECG recording and, when applicable, after vital signs measurements (example in [Figure 2](#)).

10.5 Sample Handling, Storage and Shipment

During this study, serum, whole blood and tissue samples will be collected and shipped to the central laboratory for analysis. Refer to [Table 2](#) for the sample collection schedule.

Serum isolated from whole blood will be collected for PK, ADA and sHER2 analysis. Serum samples should be clearly labeled with site number, patient ID and the sample collection time point prior to being stored. Once labeled, serum samples should be stored at $\leq -70^{\circ}\text{C}$ until shipment. Serum samples should be shipped according to the sample shipment schedule provided in the laboratory manual.

Whole blood will be collected and shipped to the central laboratory for cfDNA and gDNA extraction. The extracted cfDNA and gDNA will be stored for future analysis.

Instruction related to the collection and shipment of tumor tissue sample will be provided in separate laboratory manual(s). When sending tissue samples the patient ID and block ID (where appropriate) should be clearly indicated.

For detailed instructions related to central laboratory sample collection, labeling, processing, storage, or shipment refer to the appropriate laboratory manual(s).

Please note samples collected for local analysis (CBC, Coagulation, Chemistry, UA, etc.) should not be frozen. Local samples should be transferred ambient to the appropriate local laboratories.

Biological samples may be retained for up to 10 years to further address scientific questions as new information in regards to the disease or the study drug becomes available.

11 Adverse Events

11.1 Definitions of Adverse Events

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the Investigator at any time after ICF signature if any symptoms develop.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Hospitalization for elective procedures or for protocol compliance is not considered an SAE.

Important medical events that may not result in death, are life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, the event may jeopardize the patient or may require medical or surgical intervention to prevent any of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

11.2 Eliciting and Documenting Adverse Events

All AEs will be assessed from the time the patient signs the ICF until 30 days after the last dose of study drug or initiation of new anticancer treatment.

Any SAEs that occur more than 30 days after the last dose of study drug do not need to be

reported unless the Investigator considers them related to study drug.

At every study visit, patients will be asked a standard non leading question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs will be documented from any data collected on the AE page of the eCRF (e.g., clinically significant changes in laboratory values, physical examination, ECG changes, etc.) or identified from review of other documents that are relevant to patient safety.

11.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected will include event terminology, date of onset, CTCAE version 4.0 assessment of severity, relationship to and action taken with the study drug, date of resolution of the event, seriousness, any required treatment or evaluations, and outcome. With the exception of disease progression, AEs resulting from concurrent illnesses, reactions to concurrent illnesses, and reactions to concurrent medications also must be reported. All AEs will be followed to adequate resolution.

Any AE that meets SAE criteria ([Section 11.1](#)) must be reported to the contract research organization (CRO) immediately (i.e., within 24 hours after the time site personnel first learn about the event) through the EDC system. In case the EDC system is down or for SAE reporting questions, the following contact information may be used:

Pharmacovigilance Department

SAE Hotline: +1 (800) 772-2215

SAE Fax line: +1 (888) 772-6919

SAE Email Mailbox: CHOsafety@PRAHS.com

11.4 Assessment of Severity

Adverse events will be graded according to CTCAE version 4.0. For events not included in the CTCAE criteria, the severity of the AE is graded on a scale of 1 to 5 as shown in [Table 4](#).

Table 4: Definition of Severity Grades for Common Terminology Criteria for Adverse Events (CTCAE)

Grade	Definition
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). ^a
3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. ^b
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to adverse event.

^aInstrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^bSelf-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

11.5 Assessment of Causality

The Investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the eCRF. All adverse events, regardless of assessment of causality, are reported on the eCRF.

All SAEs considered at least possibly related to the study drug will be considered unexpected; and therefore, reported as Suspected Unexpected Serious Adverse Reactions (SUSARs).

11.6 Follow-Up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

11.7 Overdose

An overdose is any dose of study treatment given to a patient that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the Sponsor. There are no data available to determine what the effects of overdose are and whether they can be reversed. Symptomatic treatment and standard supportive care measures for the management of any observed toxicity should be applied.

11.8 Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical study Pregnancy Report Form. To ensure patient safety, each pregnancy must be reported as described for reported SAEs in [Section 11.3](#), upon learning of its occurrence. The pregnancy must be followed to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient discontinued from the study. The outcome of the pregnancy will be reported on the Pregnancy Outcome Form. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy that is brought to the Investigator's attention after the patient has completed the study and considered by the Investigator as possibly related to the study treatment must be promptly reported in the same manner.

12 Statistical Methods

Full details of the analysis plan, including a more technical and detailed elaboration of the statistical analyses will be provided in the statistical analysis plan (SAP). Results for the exploratory/correlation analyses may be reported separately.

12.1 Sample Size Calculations

Part 1: The number of patients will depend upon the toxicities observed, the number of dose-level cohorts evaluated, and the number of dose-level cohorts expanded as the study progresses; approximately 30 patients are estimated. Overall sample size will be guided by the mCRM design.

Part 2: During the dose expansion phase of the study, up to 28 patients per each dose expansion cohort will be enrolled. Simon's two-stage design ([Simon, 1989](#)) will be used. The null hypothesis that the true response rate is 7.5% will be tested against a one-sided alternative. In the first stage, 13 patients will be accrued. If there are one (1) or fewer responses in these 13 patients, the cohort will be closed. Otherwise, 15 additional patients will be accrued for a total of 28 patients. The null hypothesis will be rejected if five (5) or more responses are observed in 28 patients. This design yields a type I error rate of 0.05 (one-sided) and power of 80% when the true response rate is 25%.

In the basket group, up to 24 patients will be enrolled, with no more than 3 patients from each indication. If responses are observed, plans are described in [Section 12.2](#) (Interim Analysis [Part 2]).

12.2 Interim Analysis (Part 2)

According to the Simon 2-Stage design, interim futility analyses will be performed separately for each expansion group.

Patients will be enrolled in Groups A, B, and C first.

When 13 evaluable patients have been accrued in any of these 3 groups, enrollment will be paused and the futility analysis will be performed after the 13th patient has completed two post-baseline assessments. If futility is not triggered, the enrollment for that cohort will continue until the enrollment of 28 patients is complete and Groups D, E, and F will be open for enrollment.

Similarly, if futility for the HER2-high patients enrolled in Stage 1 of Groups C, D, or E is not triggered, enrollment of HER2-low expressing patients in the same respective group will be started. This recruitment of HER2-low patients in Groups C, D and E is subject to a Simon 2-stage design, and enrolment of all approximate 28 patients per group is only opened if futility is not triggered in the respective group after 13 patients have been accrued and evaluated. Statistical parameters for any further evaluation of a tumor type(s) identified via the basket Group F will be proposed under protocol amendment or evaluation in a new protocol.

12.3 Analysis Populations

- Safety Population: All patients who receive at least 1 dose of ADCT-502 will be evaluable for safety.
- DLT Evaluable Population: All patients in Part 1 who receive study drug, except patients who discontinue study drug during Cycle 1 without experiencing a DLT.
- Efficacy Population: All patients who:
 - receive at least 1 dose of ADCT-502, have valid baseline disease assessment(s), and at least one valid post-baseline disease assessment, unless
 - disease progression and death is documented at any time after receiving ADCT-502
- PK, PD, and Exploratory Evaluable Population: All patients who receive at least 1 dose of ADCT-502 with valid samples collected.

12.4 Safety Analyses

The safety objective will be evaluated by summarization of AEs, SAEs, and changes in laboratory parameters, vital signs, ECGs, and MUGA/echocardiograms. Dose interruptions, reductions, and relative dose intensity will also be summarized.

12.4.1 Adverse Events

The focus of adverse event summarization will be on treatment-emergent adverse events. A treatment-emergent adverse event is defined as an adverse event that occurs or worsens in the period extending from the first dose of study drug to 30 days after the last dose of study drug in this study.

Treatment-emergent adverse events will be summarized. Summary tables will be presented to show the number of patients reporting treatment-emergent adverse events by severity grade

and corresponding percentages. A patient who reports multiple treatment-emergent adverse events within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade.

Separate summaries will be prepared for treatment-emergent adverse events classified as severe or life-threatening (Grade 3 or higher); study-drug-related adverse events; adverse events leading to treatment interruption, modification, or discontinuation; serious adverse events and death.

12.4.2 Clinical Laboratory Results

Clinical hematology, coagulation panel, biochemistry, and urinalysis data will be summarized at each scheduled assessment. All results will be summarized using shift from baseline. Shifts for clinical laboratory results that can be graded according to CTCAE version 4.0 will be summarized by CTCAE grade. Shifts for other numeric laboratory results will be by high/normal/low flag. Shifts for all other laboratory results will be by normal/abnormal flag.

Summaries by visit will include data from scheduled assessments, and all data will be reported according to the nominal visit date for which it was recorded. Unscheduled data will be included in “worst-case post-Baseline” summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. Further details will be provided in the SAP.

12.4.3 Additional Safety Assessments

The results of scheduled assessments of vital signs, physical examinations, ECOG performance status, and 12-lead ECGs will be summarized. All data will be reported according to the nominal visit date for which it was recorded (i.e., no visit windows will be applied). Unscheduled data will be included in “worst case” summaries, which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. All data will be listed. Further details will be provided in the SAP.

12.5 Efficacy Analyses

Efficacy objectives to assess preliminary anti-tumor activity will be summarized in terms of ORR, DCR, DOR, PFS and OS. Analyses will be based on response as determined by the investigator per RECIST version 1.1. The potential impact of level of HER2 expression and potentially other biomarkers on clinical efficacy will also be explored.

12.5.1 Overall Response Rate

ORR will be defined as the proportion of patients with a best overall response of CR or PR at the time each patient discontinues ADCT-502. The percentage of ORR with its 80% confidence interval (CI) will be presented.

12.5.2 Disease Control Rate

DCR will be calculated to facilitate comparison and to help with future publications. DCR will be defined as the proportion of patients with a best overall response of CR or PR, or SD. Percentage of DCR with its 80% CI will be presented.

12.5.3 Duration of Response

DOR will be defined among responders (CR or PR) as the time from the earliest date of first response until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of disease progression as assessed by the Investigator using RECIST version 1.1 for response. For patients who have not progressed or died at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. The data will be analyzed by Kaplan-Meier method. The median duration of response and 80% CI will be presented. Further details will be outlined in the SAP.

12.5.4 Progression-Free Survival

PFS will be defined among the efficacy population as the time from first dose of study drug until the first date of either disease progression or death due to any cause. The date of disease progression will be defined as the earliest date of radiological disease progression as assessed by the Investigator using RECIST version 1.1, or death. For patients whose disease has not progressed at the time of the analysis, censoring will be performed using the date of the last valid disease assessment. The data will be analyzed by Kaplan-Meier method. The median PFS time and 80% CI will be presented. Further details will be outlined in the SAP.

12.5.5 Overall Survival

Median OS will be defined as the time from the beginning of study drug treatment until death due to any cause. For patients who have not died at the time of the analysis, censoring will be performed using the date the patient was last known to be alive. The data will be analyzed by Kaplan-Meier method. The median OS and 80% CI will be presented. Further details will be outlined in the SAP.

12.6 Pharmacokinetic and Pharmacodynamic Analyses

PK parameters will be determined for all PK-evaluable patients using non-compartmental method(s) using Phoenix (Cetara USA, Inc., Princeton, NJ, USA) or other appropriate software. All data will be summarized with respect to demographic, baseline characteristics and safety observations using descriptive statistics (quantitative data) and contingency tables (qualitative data). In addition, the influence of ADCT-502 and free warhead SG3199 concentrations on the QTc interval or LVEF values will also be explored.

12.7 Study Drug Exposure

Study drug exposure will be summarized by dose level and overall. Duration of treatment, total number of cycles dosed, and total dose received will be summarized. The number of patients dosed by cycle will also be summarized using frequency counts and percentages.

Duration of treatment will be calculated as date of last dose of study drug minus date of first dose of study drug plus 1.

13 Data Quality Assurance

13.1 Data Management

As part of the responsibilities assumed by participating in the study, the Investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, and patient diaries.

Investigative site personnel will enter patient data into an electronic data capture system. The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

Clinical data management will be performed in accordance with applicable CRO standards and data cleaning procedures to ensure the integrity of the data (e.g., removing errors and inconsistencies in the data). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded using WHO Drug Dictionary.

After database lock, each study site will receive information about all of their site-specific eCRF data as entered into electronic data capture system for the study, including full discrepancy and audit history. Additionally, a copy of all of the study site's data from the study will be created and sent to the Sponsor for storage. The CRO will maintain a duplicate copy for its records. In all cases, patient initials will not be collected or transmitted to the Sponsor.

14 Study Conduct and Administration

14.1 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

14.2 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an institutional review board (IRB)/independent ethics committee (IEC) before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with the current version of the ICH harmonised tripartite guideline E6: Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the Sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The Investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The Investigator must supply the Sponsor or its designee with written documentation of continued review of the clinical research.

14.3 Patient Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the Sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the Investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all patients on-study must sign the revised form, unless otherwise indicated by the IRB/IEC (local or global, as applicable). In such case, the reason for not re-consenting the patient should be documented.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the Investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study, and that additional exploratory studies can be done with collected blood/serum, by signing the ICF.

14.4 Investigator's Obligations

The following administrative items are meant to guide the Investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC, but will not result in protocol amendments.

14.4.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA, or the IRB/IEC.

The Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

14.4.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54 and local regulations. In addition, the Investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor the CRO is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor the CRO is financially responsible for further treatment of the patient's disease.

14.4.3 Adverse Events and Study Report Requirements

By participating in this study, the Investigator agrees to submit reports of SAEs to the Sponsor according to the time line and method outlined in the protocol. In addition, the Investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

The Sponsor will ensure that all relevant safety information (SAEs and SUSARs) is reported to the FDA and competent authorities of EU Member States, and to the IEC, in accordance with current legislation (US 21CFR.316 and EU Directive 2001/20/EC).

14.4.4 Investigator Documentation

Prior to beginning the study, the Investigator will be asked to comply with the current version of ICH E6 8.2, Title 21 of the CFR, and local regulations by providing the following essential documents, including but not limited to:

- IRB/IEC approval.
- Original Investigator-signed Investigator agreement page of the protocol.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572 or equivalent (where applicable).
- Curriculum vitae for the Investigator and each sub-Investigator listed on Form FDA 1572 or equivalent (where applicable).
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian.

14.4.5 Study Conduct

The Investigator agrees that the study will be conducted according to the principles of the current version of ICH E6. The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical study registers before enrollment of patients begins.

14.4.6 Adherence to Protocol

The Investigator agrees to conduct the study as outlined in this protocol in accordance with the current version of ICH E6 and all applicable guidelines and regulations.

14.4.7 Investigator's Final Report

Upon completion of the study, where applicable, the Investigator should provide the IRB/IEC with a summary of the study outcome and the Sponsor and regulatory authority(ies) with any reports required.

14.4.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period; however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

15 Study Management

15.1 Monitoring

15.1.1 Monitoring of the Study

The clinical monitor, as a representative of the Sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the Investigator and study site at periodic intervals, in addition to maintaining necessary telephone and written contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and personnel.

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

15.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the Investigator agrees to allow the Sponsor, representatives of the Sponsor, or a regulatory agency access to all study records.

The Investigator should promptly notify the Sponsor and the CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

15.2 Management of Protocol Amendments and Deviations

15.2.1 Modification of the Protocol

Any change in the study plan requires a protocol amendment. All amendments to the protocol must be reviewed and approved following the same process as the original protocol before the amended protocol can be implemented.

Only protocol amendments intended to eliminate an apparent immediate hazard to patient(s)

may be implemented immediately, i.e., without IRB/IEC and Sponsor approval, but the circumstances of the change must be documented and submitted to the IRB/IEC and to the Sponsor for further evaluation.

15.2.2 Protocol Deviations

The Investigator will make every attempt to avoid deviations from the protocol, except in medical emergencies. In the event of a medical emergency, the Medical Monitor must be notified as soon as possible. The Investigator will inform the governing IRB/IEC of all protocol changes issued by the Sponsor in accordance with the IRB/IEC's established procedure.

15.3 Study Termination

The Sponsor has every intention of completing the study; however, the Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last patient completes the last visit to the study site (includes any EOT visit to the site and any visit to the site to obtain confirmatory scan of response).

15.4 Final Report

Whether the study is completed or prematurely terminated, the Sponsor will ensure that the clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s).

An Investigator will be identified to act as the signatory for the clinical study report. The Investigator will be provided access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

16 Publications

Following completion of the study, the results from the study may be reported publicly by making any oral public presentation and/or submitting or presenting a manuscript, abstract, or other materials relating to the Study at scientific meetings and/or to a publisher, reviewer, or other outside person in scientific journals (“Publication”), provided however that Publication of the results of the Study conducted at a site shall not be made before the first multi-site Publication by Sponsor. The Sponsor shall coordinate the drafting, editing, authorship, and other related activities of such Publication and shall mutually agree with the Investigator(s) on the number, medium, forum and timing for Publication. Sponsor shall solicit input regarding contents of the Publication from all Investigators and in consultation with all sites. The Sponsor acknowledges the right of the Investigator(s) to publish the results of this study after the entire study has completed, but also reserves the right to a window to review the Publication for regulatory compliance as well as for protection of its intellectual property. In particular, Sponsor may request to remove Sponsor’s confidential information and suspend Publication for a certain period of time to protect Sponsor’s intellectual property interest, as further set forth in the Clinical Trial Agreement with the clinical study site(s) and Investigator(s).

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18 Appendices

18.1 CTCAE Immune System Hypersensitivity Grades

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Allergic reaction = A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis = A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis, and loss of consciousness and may lead to death.					
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Autoimmune disorder = A disorder resulting from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, intravenous fluids); prophylactic medications indicated for ≤24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Cytokine release syndrome = A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or intravenous fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
Serum sickness = A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately 6 to 21 days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort, and dyspnea.					
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

ADL = Activities of daily living; NSAIDs = non-steroidal anti-inflammatory drugs.

Adapted from CTCAE version 4.0 – June 14, 2010, Immune system disorders.

18.2 Eastern Cooperative Oncology Group Performance Status

Performance status will be assessed using the ECOG performance status grades as indicated below:

Grade	Definition
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., 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.
Oken, 1982	

18.3 Somatic Mutations Observed via Next Generation Sequencing

[Table 5](#) lists somatic *ERBB2/HER2* mutations obtained from the cbiportal database (<http://www.cbiportal.org>, accessed 20 December 2016), which were identified as recurrent hotspots (statistically significant) in a population-scale cohort of tumor samples of various cancer types using methodology based on [Chang, 2016](#).

Table 5: List of Somatic *ERBB2/HER2* Mutations Obtained from the Cbiportal Database

Amino Acid Position	Mutation Type
L755M	Single Residue Change
L755P	Single Residue Change
L755S	Single Residue Change
L755W	Single Residue Change
S310F	Single Residue Change
S310Y	Single Residue Change
V777L	Single Residue Change
V777M	Single Residue Change
V842I	Single Residue Change
D769H	Single Residue Change
D769N	Single Residue Change
D769Y	Single Residue Change
R678Q	Single Residue Change

Additional *ERBB2/HER2* mutations, which are known to be oncogenic based in part on [Bose, 2013](#); [Hyman, 2016](#); and [Gonzalvez, 2016](#), are listed below in [Table 6](#).

Table 6: List of *ERBB2/HER2* Mutations Known to be Oncogenic

Amino Acid Position	Mutation Type
G309A	Single Residue Change
G309E	Single Residue Change
V842I	Single Residue Change
R896C	Single Residue Change
Y772_V773insRDGE	Insertion
Y772_A775dup synonymous 772-775, in-frame indel	Duplication
G778_S779insLPS	In frame insertion
P780-Y781insGSP synonymous G778_p780dup	In frame Insertion
L869R	Single Residue Change

Most of the *HER2* mutations observed in lung cancer to date have been insertions within a small stretch of exon 20 on the *ERBB2/HER2* gene. Such aberrations are likely oncogenic and are displayed in [Table 7](#) ([Mazieres, 2013](#); [Buttitta, 2006](#); [Shigematsu, 2005](#)).

Table 7: Insertional *HER2* Mutations Predominantly Identified in Lung Cancer

Amino Acid Position	Mutation Type
G776_777insVC synonymous G776>VC synonymous G776delinsVC	In frame insertion
A775 or G776	Any in frame insertion/duplication at this position, including but not limited to A775_G776insYVMA e.g. 776–779 (YVMA) qualifies as well
GSP 781-783 ins	In frame insertion
G776V	In frame codon insertion
G776L	In frame codon insertion

It is plausible to assume that all listed mutations are likely to have a tumor promoting impact on the *HER2* protein, and that tumor cells therefore express such altered protein in order to gain a growth and/or survival advantage over neighboring cells.

Moreover, *HER2* hotspot mutations are a good predictor for functional relevance ([Bose, 2013](#)), and hence all mutations listed in this section including the ones from cBioportal listed in [Table 8](#) qualify for participation in Part 1 of the study. Additionally, patients with mutations that are reported with variation in terminology on the corresponding NGS report, but that have the same meaning as those listed here, will be permitted into the study.

Table 8: List of Mutations from Cbioportal

Amino Acid Position	Mutation Type
G776S	Single Residue Change
G660D	Single Residue Change
G660R	Single Residue Change
T733I	Single Residue Change
T862A	Single Residue Change
T862S	Single Residue Change

18.4 Appendix: Modified Continual Reassessment Method of Dose Escalation

18.4.1 Overview

Planned dose levels for ADCT-502 are shown below in [Table 9](#). Dose escalation will be conducted according to a mCRM, with dose EWOC and no dose skipping.

A recommendation to escalate, stay, or deescalate the dose level for the next 2 patient cohorts will be made according to the planned dose scheme in [Table 9](#).

The study will be continuously monitored for safety and early stopping for successfully identifying the MTD. Dose escalation will be stopped when 3 cohorts are consecutively assigned to the same dose level, which will be identified as the MTD.

Table 9: Planned Dose Levels for ADCT-502

Dose Level	Dose of ADCT-502	Dose Level	Dose of ADCT-502
1	30 µg/kg	7	240 µg/kg
2	60 µg/kg	8	300 µg/kg
3	120 µg/kg	9	350 µg/kg
4	150 µg/kg	10	400 µg/kg
5	180 µg/kg	11	450 µg/kg
6	210 µg/kg	12	500 µg/kg

18.4.2 Model and Priors

Dose escalation in this study will be conducted using the mCRM.

For each dose, $d = 1, \dots, n$, we model the binary outcome of non-DLT, or a DLT.

The log odds of a DLT are modeled as

$$\theta_d = \log\left(\frac{\pi_{DLT}}{1 - \pi_{DLT}}\right)$$

with a 2-parameter model

$$\theta_d = \alpha + \exp(\beta) \log(d_i / d^*)$$

where d^* is the reference dose, which is used to standardize the dose d_i and allows for the interpretation of α as the odds of a DLT at d^* . $\exp(\beta)$ is positive, ensuring a monotonically increasing dose-toxicity relationship.

[Neuenschwander, 2008](#) placed a bivariate lognormal prior on the two parameters and proposed eliciting information on the risk of DLT at two (2) or more doses to obtain prior means and variances. Several articles have examined the specification of priors. When there are no previous historical clinical data available, it is possible to use uninformative prior. For this purpose, the above model can be re-parametrized in terms of (ρ_0, γ) , where ρ_0 is the probability of a DLT at the starting dose d_1 and γ is the MTD, the dose expected to produce DLT at 0.3 probability in this study, with

$$\gamma = \exp(-\beta) * (\log(\theta_d) - \log(1 - \theta_d) - \alpha)$$

and placing the following independent prior distributions on the parameters.

$$\rho_0 \sim \text{Uniform}(0, 0.30)$$

$$\gamma \sim \text{Uniform}(d_1, d_n).$$

18.4.3 Dose Escalation Rule and Choice of Cohort Size

Dose escalation will begin with 2 patients enrolled at the initial starting dose. The cohort size is 2, which means that 2 patients will be assigned to escalate to the next dose level, de-escalate to the prior dose level, or, stay at the current dose level.

On the completion of each cohort (i.e., 2 patients treated and assessed for DLT after 1-cycle), the posterior distributions of $\theta(d)$ are summarized for each dose level by the probabilities of under-dosing, targeted toxicity, or excessive/unacceptable toxicity. These 3 probabilities are defined as:

$$\text{Under-dosing: } \theta_d \in (0, 0.20)$$

$$\text{Targeted Toxicity: } \theta_d \in [0.20, 0.35]$$

$$\text{Excessive or Unacceptable Toxicity: } \theta_d \in (0.35, 1]$$

The dose which maximizes the probability of targeted toxicity while controlling the probability of excessive or unacceptable toxicity to $\leq 25\%$ will be recommended for the next cohort of 2 patients. The model has the flexibility for a larger cohort size if additional patient are available.

18.4.3.1 Stopping Rules

Patients will continue to be recruited into the study until 3 cohorts of patients are consecutively assigned to the same dose level, which will be identified as the MTD.

18.4.4 Interim Monitoring

The study will be continuously monitored for safety and for success in identifying the MTD. If dose escalation is not stopped for either safety or success in identifying the MTD, it will continue to enroll to the maximum sample size.

18.4.4.1 Safety Monitoring

The lowest dose (the initial starting dose) will be considered unsafe if the probability of excessive or unacceptable toxicity is $> 25\%$. The trial will stop, and no MTD found, if the lowest dose is considered unsafe (hence all doses are considered unsafe).

18.4.5 Operating Characteristics

Different dose-toxicity scenarios were simulated to evaluate how the dose escalation design will perform ([Figure 1](#)). The operating characteristics of the study are based on 1,000 simulations per scenario. For each scenario, the mean probability of selecting the dose as MTD is plotted versus dose, number of patients at the target dose, lower dose, high dose, and number of DLTs.

18.4.5.1 Scenarios

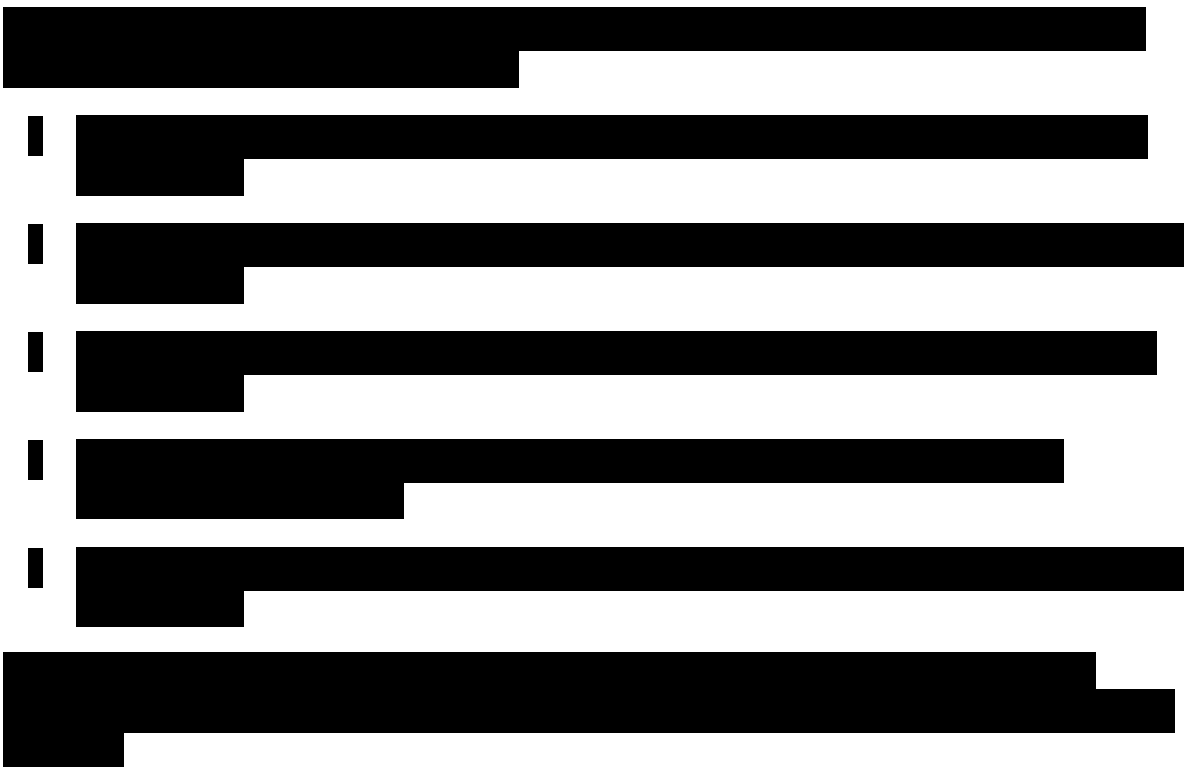
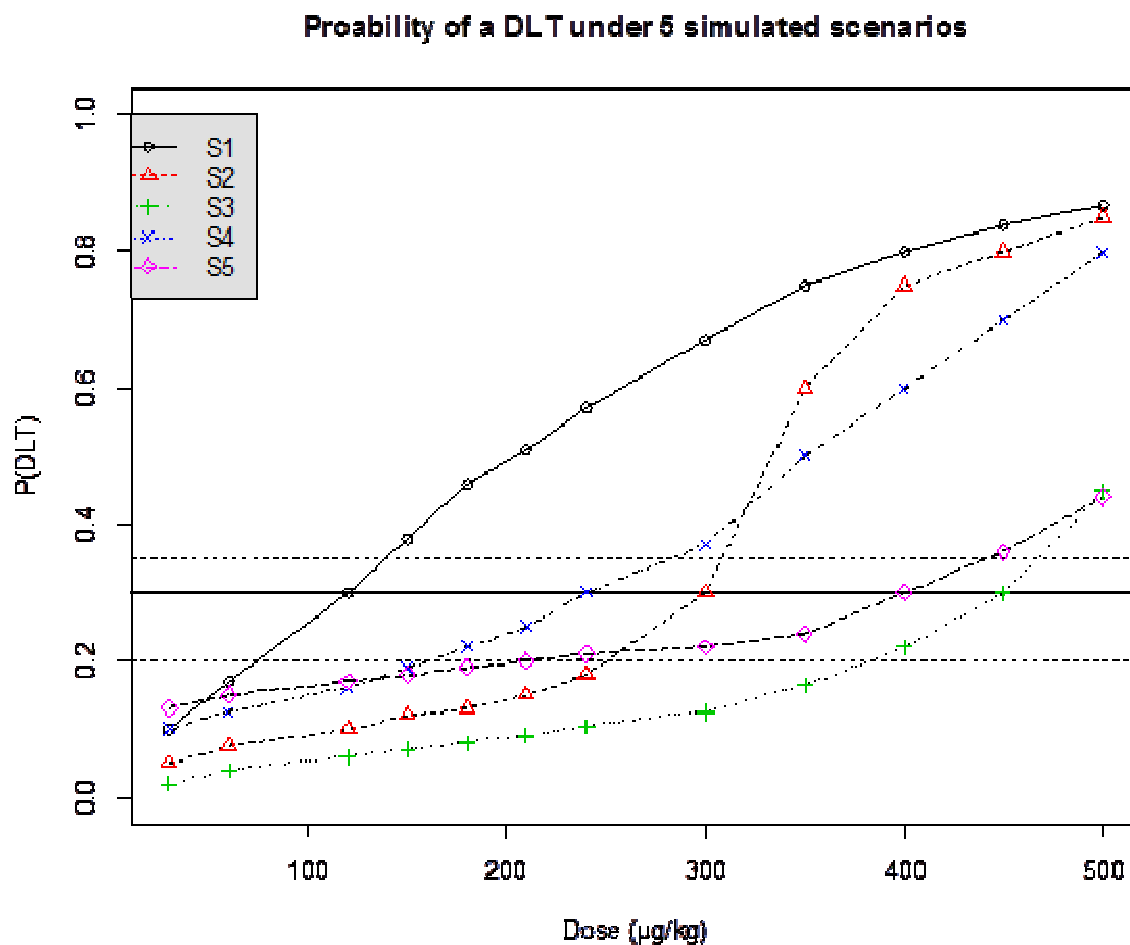
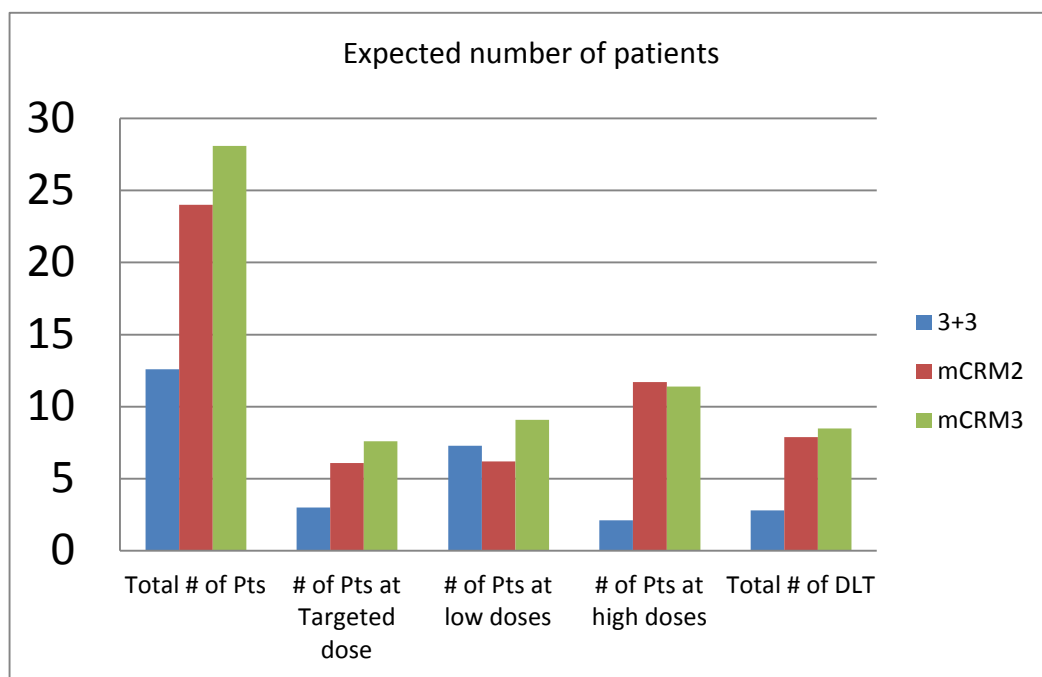
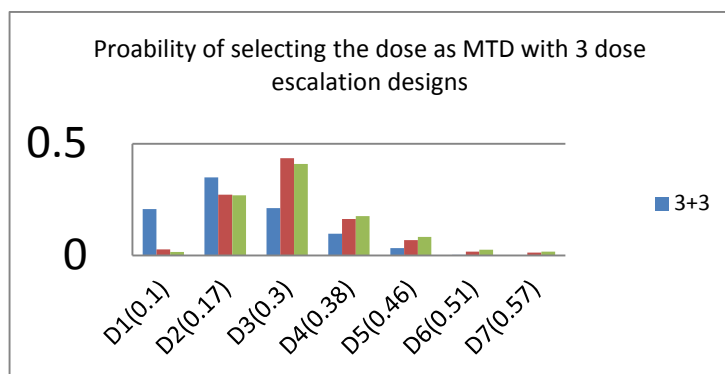
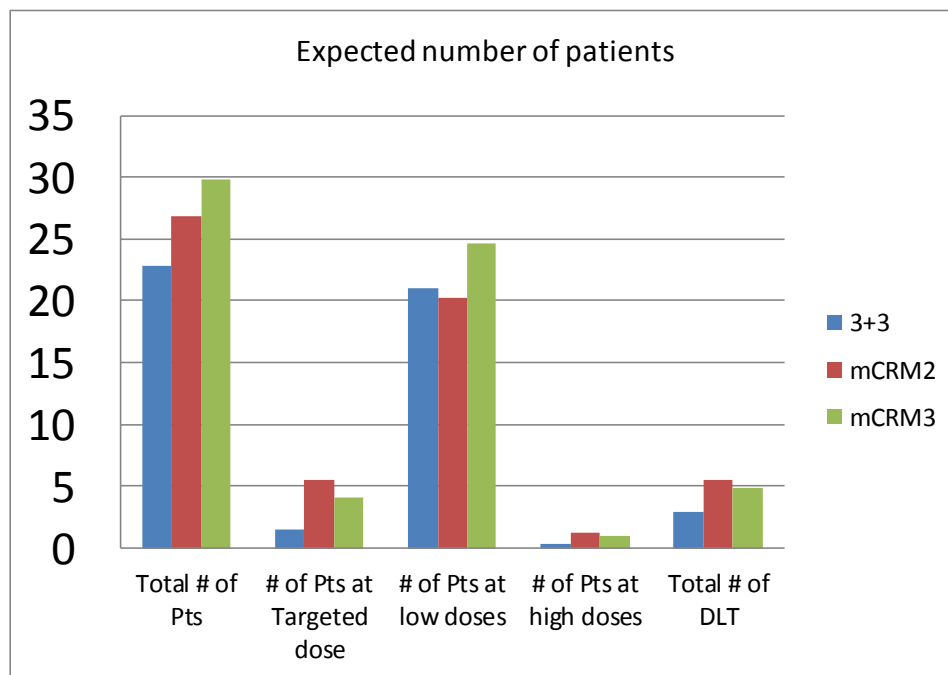
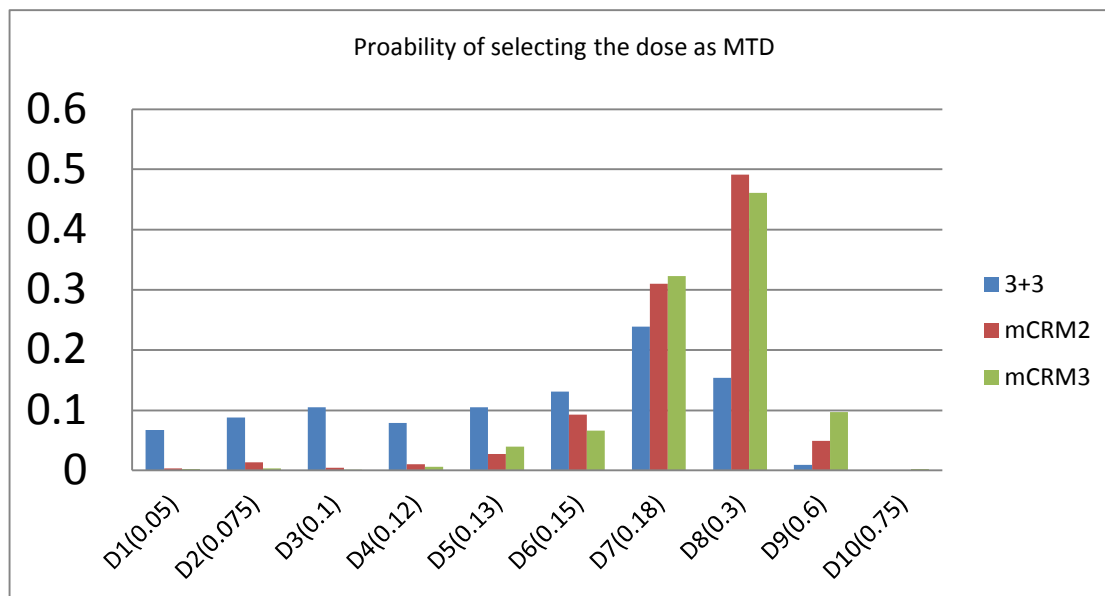
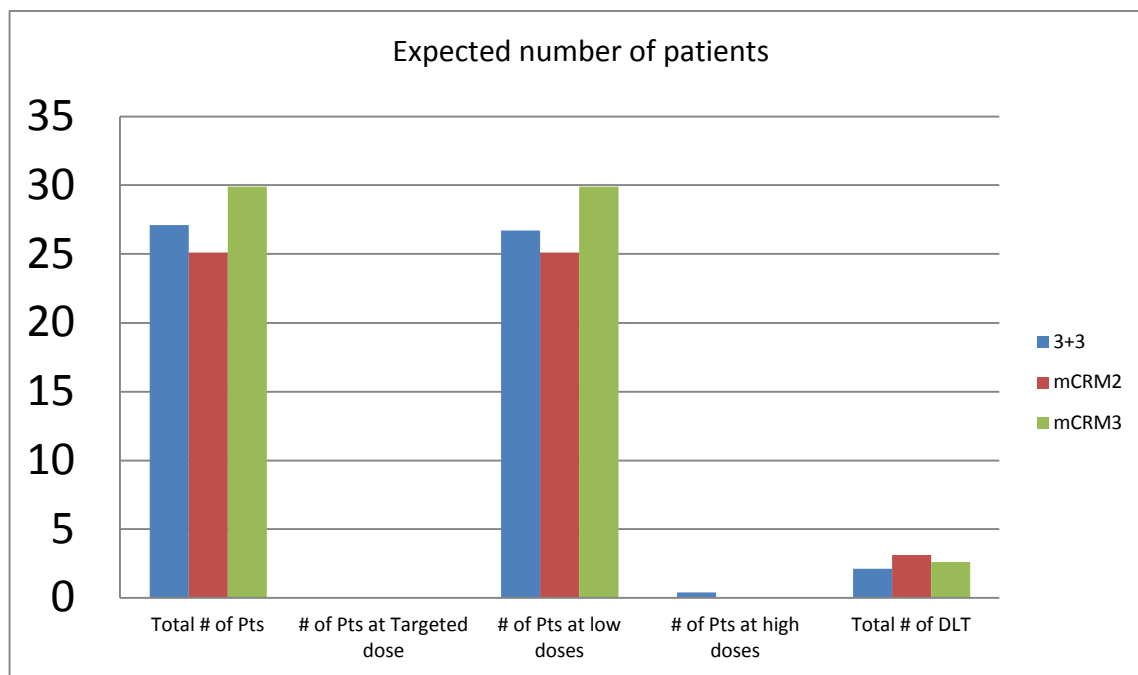
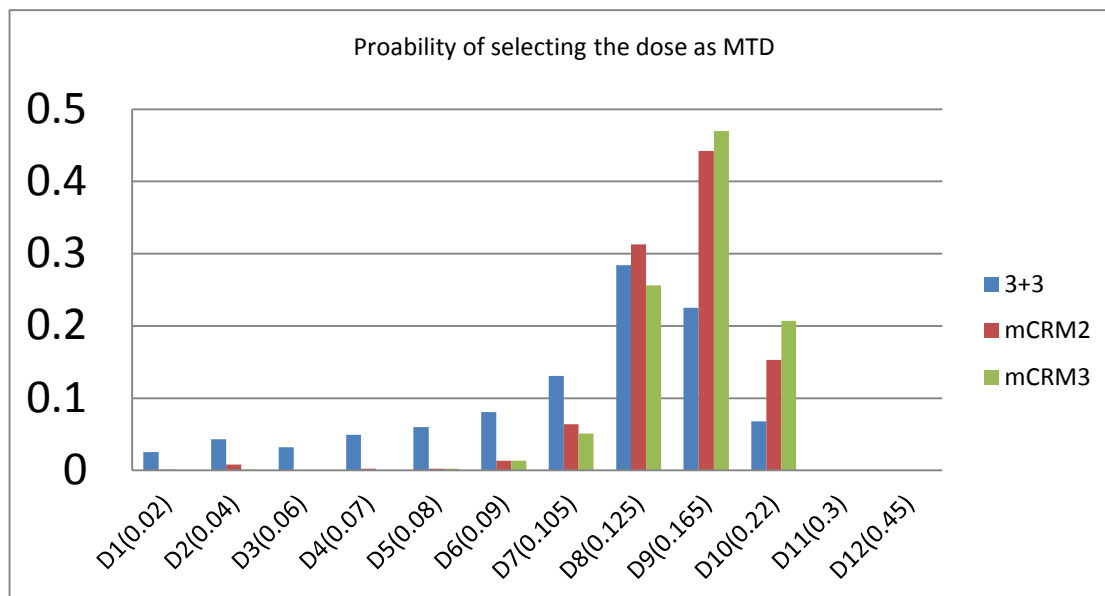


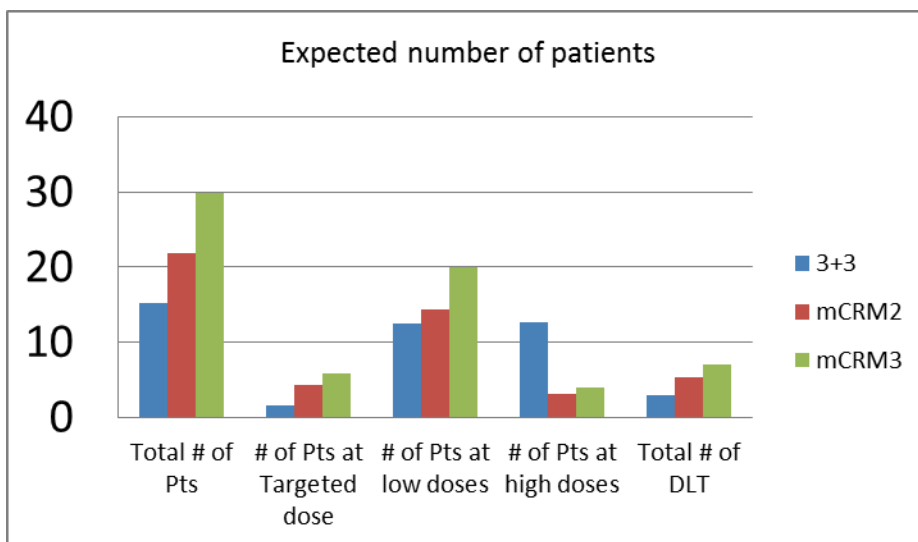
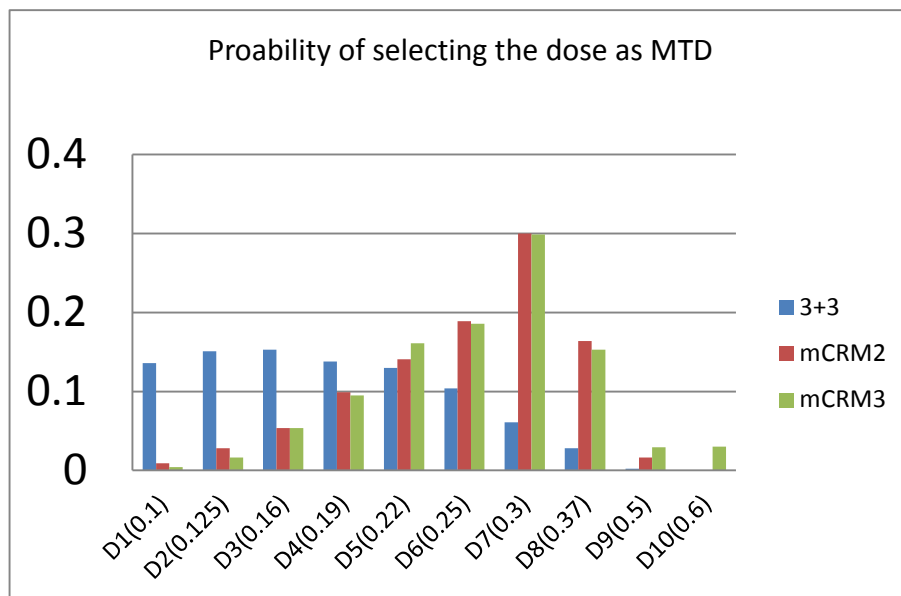
Figure 3: Probability of a DLT Under 5 Simulated Scenarios

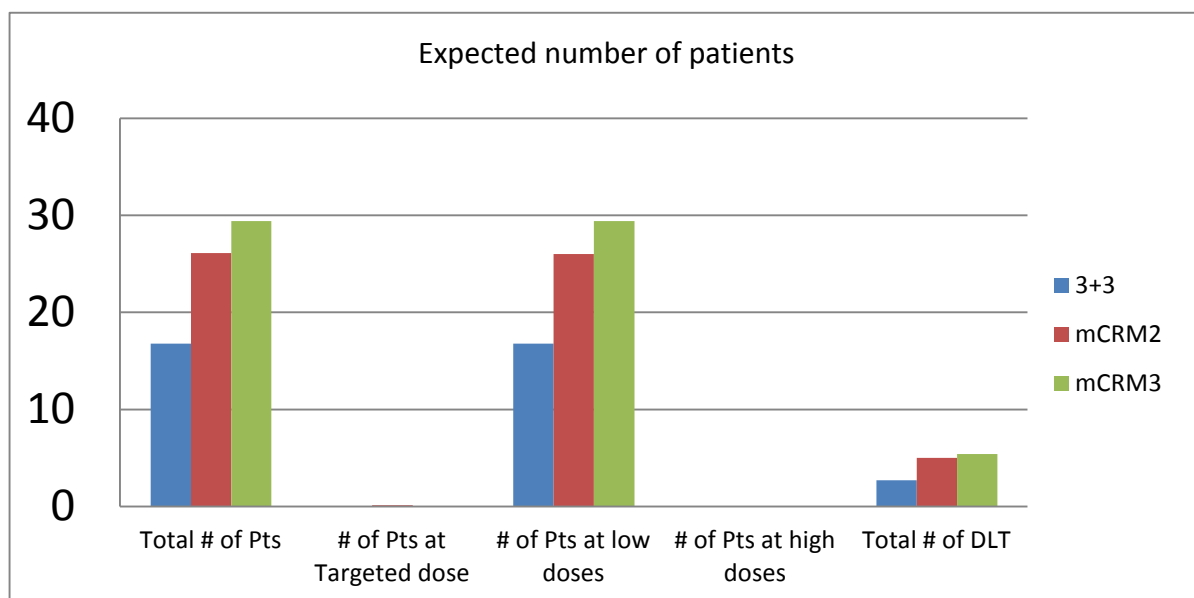
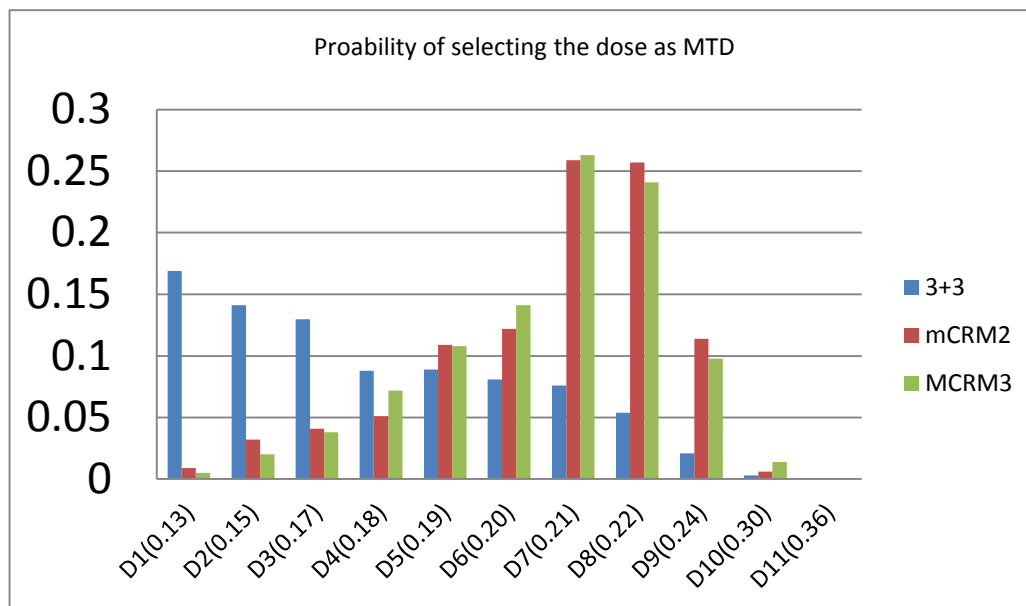
Scenario 1: True Probability of a DLT (with 0.1, 0.17, 0.3, 0.38, 0.46, 0.51, 0.57, 0.67, 0.75, 0.8, 0.84, 0.87)



Scenario 2: True Probability of a DLT (with 0.05, 0.075, 0.1, 0.12, 0.13, 0.15, 0.18, 0.3, 0.60, 0.75, 0.8, 0.85)

Scenario 3: True Probability of a DLT (with 0.02, 0.04, 0.06, 0.07, 0.08, 0.09, 0.105, 0.125, 0.165, 0.22, 0.3, 0.45)

Scenario 4: True Probability of a DLT (with 0.10, 0.125, 0.16, 0.19, 0.22, 0.25, 0.30, 0.37, 0.5, 0.6, 0.7, 0.8)

Scenario 5: True Probability of a DLT (with 0.13, 0.15, 0.17, 0.18, 0.19, 0.20, 0.21, 0.22, 0.24, 0.30, 0.36, 0.44)

Clinical Protocol Amendment 2 Summary of Changes

A Phase 1, Open-Label, Dose-Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of ADCT-502 in Patients with Advanced Solid Tumors with HER2 Expression

The primary reasons for Protocol Amendment 2 (17 August 2017) were to revise the modified continual Reassessment Method (mCRM) model and include additional flexibility around provisional dose levels and dosing regimen; as well as to incorporate revisions and clarifications throughout the document following increasing scientific knowledge, such as HER2 amplification status measured by next-generation sequencing (NGS).

Summary of Substantial Changes:

- Since there is no mathematical model which could accurately correlate DLT rate when the dose interval is changed or intermediate doses not predefined in the mCRM model are used, the possibility to use a 3+3 design has been introduced in Section 2.4 to cover for these situations.
- A new potential dosing schedule consisting in omitting dosing every n-th cycle (e.g. every 3rd cycle) has been introduced in Section 2.4. This approach is being employed in a clinical trial with an antibody-drug conjugate (ADC) with the identical linker and warhead as ADCT-502 (NCT03033511) and may have the potential to optimize anti-tumor activity while limiting adverse events.
- Section 4.2 has been revised to:
 - clarify that any immunohistochemistry (IHC) result can be overruled by contemporaneous or subsequent amplification results for the purpose of this study.
 - clarify that NGS (hybridization capture-based NGS) can also be used for determination of HER2 amplification.
 - clarify for Part 1 that a retrospective confirmation of HER2 expression is needed when NGS is used for HER2 classification, irrespective of NGS results.
 - update Inclusion criterion 5 and Appendix 18.3 accordingly.
- Clarified and revised time windows for visits and assessments in Schedule of Events (SoE) Table 1 and Table 2, and Section 4.4.
- It has been clarified in Section 4.4 and footnote 16 and 24 of the SoE that the Follow-up period is applicable for the whole study, i.e., both Part 1 and Part 2, including the follow-up by radiographic examination for any patients who discontinue treatment for any reason other than disease progression.
- The possibility to enroll additional breast cancer patients in cohorts of Part 1 to better understand the potential efficacy of ADCT-502 in an indication approved for treatment with HER2 targeted antibodies has been implemented in Section 4.6.

- Intra-patient escalation in Part 1 was made possible once the recommended dose(s) has been identified in Part 2, Section 4.6.
- Resuming dosing for drug delays longer than 21 days are also permitted for DLTs as long as the patient can potentially benefit from ADCT-502. This is supported by the fact that patients treated with different ADCs with the same warhead (e.g. ADCT-402) have demonstrated long-lasting tumor suppression during prolonged (> 1 month) drug holidays, Section 5.
- The recommendation of G-CSF use in case of (febrile) neutropenia was revised for clarification with additional reference to ASCO guidelines, Section 5.2.
- Inclusion criterion 4 was further clarified to provide more accurate information on the tumor tissue that is expected to be received for demonstrating HER2 expression. The number of slides had to be increased in case retesting is needed. The SoE Table 1 was revised accordingly.
- The unit of creatinine clearance was corrected in Inclusion criterion 7.
- Exclusion criterion 15 was revised for clarification.
- Prophylaxis with dexamethasone (Section 9.1), recommendations for treatment of edema and/or pleural effusion (Section 9.5), and other supportive care (Section 9.6) were added based on emerging safety data of other investigational agents containing the same pyrrollobenzodiazepine warhead.
- ECG will be recorded in triplicate in order to more robustly investigate the ECG-PK relationship. Associated instructions, e.g., sequence of assessments, are provided in SoE Table 1 and Table 2, Section 10.1, and 10.4.1.
- Section 10.3 indicates that imaging central review will be used.
- Sections 10.3, 10.4, and 10.4.2 were revised to include the instructions already present in footnotes of the SoE Table 1.
- PK, soluble HER2, and ADA samples will not be collected beyond starting new anticancer treatment due to practicality issues, e.g., when patients would enter a new oncology clinical study, SoE Table 1 and Section 10.4.2.
- In order to prevent stability issues with PK samples, the storage temperature has been set strictly to $\leq -70^{\circ}\text{C}$, Section 10.5.
- Revised instruction for AE reporting in Section 11.1 to start from ICF signature for consistency with Section 11.2.
- Additional dose levels (150 and 210 mg) have been implemented in the mCRM, Table 9 of Appendix 18.4. Therefore, the number of dose levels has not been limited to 10 in the statistical model in 18.4.2, and Figure2 and the graphical representations of Scenarios 1 to 5 have been updated.

In addition, administrative and editorial changes have been performed and revisions to the protocol text have also been applied to the synopsis section.