CLINICAL TRIAL PROTOCOL

Trial Title:	An Open-label, Multicenter, Phase 1a/2a Trial Investigating the Safety, Tolerability and Antitumor Activity of Multiple Doses of Sym013 (Pan-HER), a Monoclonal Antibody Mixture Targeting EGFR, HER2 and HER3, in Patients with Advanced Epithelial Malignancies
Short Title:	Sym013 (Pan-HER) in Patients with Advanced Epithelial Malignancies
Sponsor:	Symphogen A/S [redacted]
Sponsor's Medical Expert:	[redacted]
Coordinating Investigator:	[redacted]
Trial ID:	Sym013-01
Trial Phase:	Phase 1a/2a
EudraCT number:	*Pending*
IND Number:	116334
Protocol Version/Date:	7.0 / 14-Jun-2018 (Amendment 6)
Previous Protocol Versions/Dates:	6.0 / 23-Jan-2018 (Amendment 5) 5.0 / 04-May-2017 (Amendment 4) 4.0 / 26-Apr-2017 (Amendment 3) 3.0 / 14-Nov-2016 (Amendment 2) 2.0 / 03-Oct-2016 (Amendment 1) 1.0 / 13-Jun-2016

Sponsor Declarations

This confidential document is the property of Symphogen A/S. No unpublished information contained herein may be passed on, reproduced, published or used without prior written approval from Symphogen A/S. Access to this document must be restricted to relevant parties.

The trial will be conducted in compliance with this clinical trial protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6(R2): Guideline for Good Clinical Practice (GCP) (EMA/CHMP/ICH/135/1995), the Declaration of Helsinki, and applicable regulations.

The Sponsor has appointed a Coordinating Investigator for the trial. This Coordinating Investigator will provide input to the trial design and act as overall coordinator for Investigators across all sites. The Coordinating Investigator will furthermore sign off the Clinical Trial Report on behalf of all Investigators.

Lists of Investigators responsible for conducting the trial, medically qualified physicians responsible for all site-related medical decisions (if other than the Investigators), monitors, clinical laboratories, and other medical and/or technical departments and/or institutions involved in the trial are provided as separate documents.

Sponsor Signature Page

I hereby approve this clinical trial protocol as suitable and appropriate for use.

See attached electronic signature and date
Ulla Holm Hansen
Senior Clinical Trial Manager
Symphogen A/S

See attached electronic signature and date
Ivan D. Horak, MD, FACP
Chief Scientific and Medical Officer
Symphogen A/S

See attached electronic signature and date
Cliff Ding, PhD
Executive Director, Biostatistics and Data Management
Symphogen A/S

See attached electronic signature and date
Angela Hu, PhD
Director of Global Regulatory Affairs
Symphogen A/S

Principal Investigator Signature Page

I, the undersigned, am responsible for the conduct of the trial at this site and agree:

- To assume responsibility for the proper conduct of the clinical trial at this Investigational Site.
- Not to implement any changes to the clinical trial protocol without agreement from the Sponsor and prior review and written approval from the Institutional Review Board/Ethics Committee, except where necessary to eliminate an immediate hazard to the patients.
- That I am aware of and will comply with "Good Clinical Practice" (ICH E6(R2) GCP) (EMA/CHMP/ICH/135/1995) and all applicable regulatory requirements.
- That all site staff to which I have delegated tasks for this clinical trial are appropriately selected and adequately informed about the investigational product(s) and of their trial-related duties and functions as described in the clinical trial protocol.

_____ _____

Signature Date of Signature

Name: _____

Academic Degree: _____

Function: _____

Institution: _____

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1. SYNOPSIS

Item	Summary
Trial Title	An Open-label, Multicenter, Phase 1a/2a Trial Investigating the Safety, Tolerability and Antitumor Activity of Multiple Doses of Sym013 (Pan-HER), a Monoclonal Antibody Mixture Targeting EGFR, HER2 and HER3, in Patients with Advanced Epithelial Malignancies
Trial ID	Sym013-01
Investigational Medicinal Product	The investigational medicinal product (IMP) tested in this trial is Sym013, referenced as Pan-HER. Pan-HER is a recombinant antibody mixture containing 6 humanized immunoglobulin G1 (IgG1) monoclonal antibodies (mAbs), which bind specifically to non-overlapping epitopes on the epidermal growth factor receptor (EGFR), and the human epidermal growth factor receptors (HER) HER2 and HER3.
Overall Trial Design	This is an open-label, multicenter trial composed of 2 parts in which Pan-HER will be evaluated when administered by the intravenous (IV) route to patients with advanced epithelial malignancies without available therapeutic options. • Part 1 is a Phase 1a dose-escalation evaluating weekly (Q1W) and every second week (Q2W) schedules of administration in separate dose-escalation cohorts to determine the recommended phase 2 dose (RP2D) and regimen of Pan-HER. • Part 2 is a Phase 2a dose-expansion at the RP2D and regimen. Four (4) dose-expansion cohorts will be evaluated in this part of the trial and will be selected based upon findings from Part 1, additional preclinical data, and additional clinical data available at that time from other agents inhibiting these targets. Patients will be entered, depending upon either a defined molecular profile or profiles, or their underlying malignancy, to 1 of 4 corresponding expansion cohorts: Cohort A (HER2+ solid tumor malignancy Basket Cohort), Cohort B (pancreatic carcinoma), Cohort C (to be determined [TBD]), or Cohort D (TBD). The RP2D and regimen ultimately identified for use in Part 2 may be comprised of a fixed dose and schedule, a combination of doses to be administered on either a Q1W or Q2W schedule, or a combination dose and regimen. The RP2D and regimen will be selected based on tolerability demonstrated with Q1W and Q2W dosing during Part 1, as well as available pharmacokinetic (PK) and target engagement results, as applicable. Doses lower than the maximum tolerated dose(s) (MTD(s)) but between doses investigated in Part 1 may be selected if data indicate them to be optimal. **As of Amendment 6** At the time of Amendment 3 to this protocol, a total of 6 patients had been entered to Part 1; 1 patient each at Dose Levels 1 and 2 (1 mg/kg and 2 mg/kg, respectively), and 4 patients at Dose Level 3 (4 mg/kg) had been treated weekly (Q1W; 4 doses equaling 1 cycle). Due to the occurrence of Grade 1-2 oral mucositis, rash, and diarrhea at the 4 mg/kg Q1W dose, Q1W dosing was halted, and the dosing interval was changed to every second week (Q2W; 2 doses equaling 1 cycle). Dose Levels 4 and 5 (6 mg/kg and 9 mg/kg, respectively) were evaluated on the Q2W schedule. Due to the occurrence of Grade 3 infusion-related reaction (IRR) and oral mucositis at the 9 mg/kg Q2W dose, a mandatory prophylaxis regimen was implemented. Per Amendment 5, all patients must receive intensive prophylaxis, as defined herein, on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis, and must receive Pan-HER infusions over a fixed (at minimum) 4-hour (+10 min) period unless further prolongation is required for an individual patient due to the occurrence of an IRR. The dose of 9 mg/kg Q2W was further evaluated with these modifications in place, and found to be tolerated; dose-escalation under these conditions continues. With Amendment 6, Q1W dosing is reintroduced under the prophylaxis and infusion duration conditions outlined in Amendment 5. Since Dose Level 3 (4 mg/kg) was previously evaluated on the Q1W schedule, reevaluation of Q1W dosing will resume at the next higher Dose Level 4 (6 mg/kg); however, lower doses may be explored if indicated based on tolerability.

Part 1/Dose-escalation

The starting dose of Pan-HER will be 1 mg/kg Q1W. The following dose levels of Pan-HER are planned to be evaluated:

Q1W

- Dose Level 1: 1 mg/kg Q1W
- Dose Level 2: 2 mg/kg Q1W
- Dose Level 3: 4 mg/kg Q1W
- *Dose Level 4P: 6 mg/kg Q1W + P (lower doses with prophylaxis may be explored, if indicated)
- *Dose Level 5P: 9 mg/kg Q1W + P
- *Dose Level 6P: 12 mg/kg Q1W + P
- *Dose Level 7P: 15 mg/kg Q1W + P
- *Dose Level 8P: 18 mg/kg Q1W + P (highest potential dose allowed per protocol)

Q2W

- Dose Level 4: 6 mg/kg Q2W
- Dose Level 5: 9 mg/kg Q2W
- *Dose Level 5P: 9 mg/kg Q2W + P
- *Dose Level 6P: 12 mg/kg Q2W + P
- *Dose Level 7P: 15 mg/kg Q2W + P
- *Dose Level 8P: 18 mg/kg Q2W + P (highest potential dose allowed per protocol)

*Mandatory intensive IRR and oropharyngeal mucositis prophylaxis; 4-hour infusion (designated "P")

Initially, one patient will be treated at each dose level until the occurrence of a toxicity* during Cycle 1 that activates the stopping rule of the single-patient cohort titration design. The cohort will expand to 3 patients and the design will switch to a classical 3+3 dose-escalation design.

*Grade 2 toxicity, assessed by the Investigator as possibly, probably, or related to Pan-HER with the exception of Grade 2 alopecia, nausea, anemia, lymphopenia, and/or eosinophilia. Toxicity grading will be according to the Common Terminology Criteria for Adverse Events (Version 4.03) (CTCAE v4.03).

If such a toxicity has not occurred in the first 3 cohorts (i.e., 1 mg/kg, 2 mg/kg, and 4 mg/kg, Q1W), the next cohort to open will be a 3-patient cohort and the design will switch to the 3+3 design.

Further dose-escalation will follow a standard 3+3 design with a target toxicity level of < 33% as determined by dose-limiting toxicities (DLTs).

Note: The transition from single patient cohorts to 3+3 dose-escalation design occurred beginning with Dose Level 3 (4 mg/kg; Q1W). All Dose Levels evaluated thereafter are to be comprised of a minimum of 3 patients.

Staggered Dosing: Enrollment will be staggered between the first and second patient in each new dose level tested. The first patient must have completed and tolerated the first 2 doses with Q1W dosing, or the first dose with Q2W dosing, including follow-up until Day 15 of Cycle 1 (C1/D15) in order to allow for review of clinical and laboratory assessments. Thereafter, patients within a cohort may be added concurrently.

Escalation Rules: Escalation from a current dose level to the next will only proceed following evaluation of tolerability of the current dose level. Thus, dosing of the first patient at any new dose level will commence only after all patients to be treated at the current dose level have completed Cycle 1, and the current dose level has been found to be tolerable. The dose-escalation decision points are listed below:

- If no DLTs are encountered in any of the first 3 patients completing Cycle 1 within a dose level, dose-escalation may continue to the next level.

	• If 1 of 3 patients within a dose level experiences a DLT, 3 more patients will be enrolled at the same dose level (to a total of 6 patients). If no DLTs are encountered in the 3 additional patients, dose-escalation may continue to the next level when all patients have completed and tolerated Cycle 1. • If ≥ 2 patients within a dose level (of up to 6 patients) experience a DLT, then that dose will be considered to have exceeded the MTD and the dose level just below this maximum administered dose (MAD) will be considered to be the potential MTD. • Once the potential MTD has been declared, the MTD dose level will be completed to a total of 6 patients, if not already accomplished. In order to confirm the MTD, ≤1 of 6 patients within the dose level may have experienced a DLT. • An MTD may or may not be found within the dose levels tested. Dose-escalation may be stopped due to toxicity observations other than DLTs and/or results from PK and/or target engagement analyses. During Part 1, intermediate dose level(s) between 2 planned dose levels may be evaluated to further characterize safety and tolerability of Pan-HER, if indicated based on toxicity observations and/or results from PK and/or target engagement analyses. **RP2D:** The RP2D may include a dose or a combination of doses (e.g., initial loading dose followed by a lower maintenance dose) equal to or lower than the MTD for the Q1W and/or Q2W dosing regimens. A dose or doses between tolerated doses investigated in Part 1 may also be selected if data indicate this to be optimal. Further, the RP2D and regimen ultimately identified for use in Part 2 of this trial may be a dose or a combination of to be administered on a Q1W schedule, a Q2W schedule, or a combination thereof. The selection will be based on tolerability demonstrated with Q1W and Q2W dosing, as well as available PK and target engagement results, as applicable. **Part 2/Dose-expansion** Once the RP2D and regimen have been established during dose-escalation, enrollment into the 4 separate dose-expansion cohorts will commence (Cohort A, Cohort B, Cohort C, or Cohort D). All patients enrolled will be treated with Pan-HER at the established RP2D and regimen.
Trial Sites	**Part 1/Dose-escalation:** Approximately 3 investigational trial sites, hereafter called "trial sites" **Part 2/Dose-expansion:** Approximately 25 trial sites
Planned Trial Period	Part 1 of the trial is expected to begin Q4 2016. Patients will be sequentially enrolled to dose-escalation cohorts on either a Q1W or a Q2W schedule until establishment of a RP2D and regimen, expectedly Q1 2019. Enrollment to the expansion cohorts in Part 2 of the trial will commence upon approval of a protocol amendment defining the expansion cohorts to be further explored. Enrollment to Part 2 is expected to be from Q1 2019 to Q3 2020.
Primary and Secondary Objectives	**Primary objective of Part 1/Dose-escalation:** To assess the safety and tolerability of Pan-HER when administered either Q1W or Q2W by IV infusion to separate dose-escalation cohorts of patients with advanced epithelial malignancies without available therapeutic options. **Secondary objectives of Part 1/Dose-escalation:** 1. To determine a RP2D and regimen of Pan-HER 2. To evaluate the PK profile of Pan-HER 3. To evaluate the immunogenicity of Pan-HER 4. To evaluate target engagement in skin biopsy tissue (EGFR and HER3) and tumor biopsy tissue (EGFR, HER2 and HER3), if available 5. To evaluate other potential pharmacodynamic biomarkers of Pan-HER action, and estimate, if feasible, the magnitude of biological activity in peripheral blood and in skin biopsy (and tumor biopsy, if available) tissue 6. To make a preliminary evaluation of the antitumor effect of Pan-HER

	Primary objective of Part 2/Dose-expansion: To evaluate the antitumor effect of Pan-HER when administered at the RP2D and regimen to patients with advanced epithelial malignancies without available therapeutic options. Four (4) dose-expansion cohorts will be evaluated. **Secondary objectives of Part 2/Dose-expansion:** 1. To further evaluate the safety and tolerability of Pan-HER 2. To further evaluate the PK profile of Pan-HER 3. To further evaluate the immunogenicity of Pan-HER 4. To further evaluate target engagement in skin biopsy tissue (EGFR and HER3) and tumor biopsy tissue (EGFR, HER2 and HER3) (tumor biopsy required) 5. To further evaluate other potential pharmacodynamic biomarkers of Pan-HER action, and estimate, if feasible, the magnitude of biological activity in peripheral blood and in skin and tumor biopsy tissue (tumor biopsy required)
Primary Endpoints	**Primary endpoint of Part 1/Dose-escalation:** The occurrence of DLTs during Cycle 1 for each of the Pan-HER dosing regimens. **Primary endpoint of Part 2/Dose-expansion:** Documented objective response (OR), defined as documented partial response (PR) or complete response (CR) assessed by Response Evaluation Criteria in Solid Tumors (Version 1.1) (RECIST v1.1) at any time during trial participation, with radiologic evaluation to be performed locally.
Trial Periods	**Screening period:** After providing informed consent, the eligibility of patients will be established according to the protocol-defined inclusion and exclusion criteria. **Treatment period:** Patients in the trial will receive either Q1W or Q2W IV infusions of Pan-HER, depending upon cohort assignment, until occurrence of any of the following: unacceptable toxicity or other conditions preventing further treatment, disease progression, termination of the trial, or patient's decision to withdraw. **End of treatment/follow-up:** Once Pan-HER has been discontinued, an End of Treatment (EOT) visit will be performed within 10 days following the decision to withdraw treatment. A follow-up visit will be performed 30 (+7) days after the last dose of Pan-HER. This 1-Month Follow-up (1M FUP) visit constitutes the end of trial participation for the patient. **Part 2 ONLY, continued follow-up for response and/or overall survival:** After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or overall survival (OS) every 2 months. Response assessment follow-up is required in the event of an ongoing stable disease (SD) or OR (defined as PR or CR), as per RECIST v1.1 at the 1M FUP Visit, until progressive disease (PD) or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, or termination of the trial. This continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation.
Number of Patients	In total, approximately 134 patients will be included in this trial. It is estimated that approximately 34 patients will be enrolled to receive increasing doses of Pan-HER during Part 1. The exact number of patients will depend upon the observed tolerability of Pan-HER and the potential for adding additional patients to a cohort to ensure a sufficient number of evaluable patients per cohort. It is planned to enroll and treat approximately 100 patients during Part 2.
Main Inclusion and Exclusion Criteria	**Main inclusion criteria all patients, Part 1 and Part 2:** • Male or female, at least 18 years of age at the time of informed consent • Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 • Life expectancy >3 months assessed during Screening • Documented (histologically- or cytologically-proven) epithelial malignancy that is locally advanced or metastatic, having received all therapy known to confer clinical benefit **Additional inclusion criteria applicable to Part 2 <u>ONLY</u>:** • Epithelial malignancy (HER2+ solid tumor malignancies, pancreatic carcinoma, and 2 other tumor

types to be specified in a protocol amendment), measurable according to RECIST v1.1 that has been confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) within 4 weeks prior to C1/D1

- Willingness to undergo a pre-and post-dosing biopsy (total of 2 biopsies) from primary or metastatic tumor site(s) considered safe for biopsy

Main exclusion criteria:

- Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 4 weeks or 5 plasma half-lives, whichever is shortest, prior to C1/D1except:
  a. Nitrosoureas and mitomycin C within 6 weeks prior to C1/D1
- Part 2 ONLY: Radiotherapy against target lesions within 4 weeks prior to C1/D1, unless there is documented progression of the lesion following the radiotherapy
- Immunosuppressive or systemic hormonal therapy within 2 weeks prior to C1/D1, with allowed exceptions
- Use of hematopoietic growth factors within 2 weeks prior to C1/D1
- Active second malignancy or history of another malignancy within the last 3 years, with allowed exceptions
- Central nervous system (CNS) malignancies including:
  a. Primary malignancies of the CNS
  b. Known, untreated CNS or leptomeningeal metastases, or spinal cord compression; patients with any of these not controlled by prior surgery or radiotherapy, or symptoms suggesting CNS metastatic involvement for which treatment is required
- Inadequate recovery from an acute toxicity associated with any prior antineoplastic therapy
- Major surgical procedure within 4 weeks prior to C1/D1 or inadequate recovery from any prior surgical procedure
- Non-healing wounds on any part of the body
- Active thrombosis, or a history of deep vein thrombosis or pulmonary embolism, within 4 weeks prior to C1/D1, unless adequately treated and stable
- Active uncontrolled bleeding or a known bleeding diathesis
- Significant gastrointestinal abnormalities
- Significant cardiovascular disease or condition
- Abnormal hematologic, renal or hepatic function as defined by the following criteria:
  a. Absolute neutrophil count (ANC) $<1.5 \times 10^9$/L ($1500/mm^3$)
  b. Hemoglobin ≤8 g/dL
  c. Platelet count $<100 \times 10^9$/L ($100{,}000/mm^3$)
  d. Serum creatinine >1.5 × upper limit of normal (ULN) for the institution
  e. Aspartate aminotransferase (AST) >3.5 × ULN for the institution or AST >5 × ULN for the institution in case of known liver metastases
  f. Alanine aminotransferase (ALT) >3.5 × ULN for the institution or ALT >5 × ULN for the institution in case of known liver metastases
  g. Total bilirubin >1.5 × ULN for the institution
  h. Prothrombin time (PT) as assessed by International Normalized Ratio (INR) >1.5 × ULN for the institution*
  i. Partial thromboplastin time (PTT) >1.5 × ULN for the institution*

  *Unless on a stable dose (per the Investigator's discretion) of anticoagulant therapy for a prior thrombotic event
- Any of the following within 2 weeks prior to C1/D1:
  a. Any serious or uncontrolled infection
  b. Any infection requiring parenteral antibiotics
  c. Unexplained fever >38.0 °C

Investigational Medicinal Product: **Dose(s) and Treatment Schedule**	Pan-HER will be initiated on C1/D1 and, based on cohort assignment, will be administered either Q1W or Q2W to separate dose-escalation cohorts of patients by IV infusion in cycles of treatment: • Q1W: Dosing on Day 1, 8, 15, and 22 of each 28-day cycle (±2 days) • Q2W: Dosing on Day 1 and 15 of each 28-day cycle (±2 days) All patients will receive the allocated dose and schedule of Pan-HER until treatment withdrawal. There will be no intra-patient dose-escalation. Dose-delays of Pan-HER and/or intra-patient dose-reduction(s) may be required upon occurrence of specific toxicities. For Part 1 of the trial, Pan-HER will be administered following delivery of intensive prophylaxis, as defined herein, on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis. For Part 2, IRR and oropharyngeal mucositis prophylaxis is mandatory during Cycle 1 and Cycle 2. If the patient is without evidence of IRRs or oropharyngeal mucositis after Cycle 2, the Investigator may choose to withdraw related medications with subsequent dosing. Gradual withdrawal of medications is recommended. The duration of infusion will be (effective with Amendment 5): • Minimum of 4 hours (+10 min) for all infusions. Titrated rate increases during infusions, and infusion duration reductions after C1/D1, will no longer be allowed. Patients will be carefully observed for a minimum of 2 hours following completion of the first infusion and a minimum of 1 hour following completion of subsequent infusions. Recommended guidelines for management of IRRs are provided.
Dose-Limiting Toxicities (Part 1 only)	The decision to dose-escalate will be based on monitoring of safety during Cycle 1. A minimum of 4 infusions with Q1W dosing, and 2 infusions with Q2W dosing must have been administered at the assigned dose for a patient to have completed the DLT-observation period. All applied DLT criteria are provided.
Trial Assessments	**Safety Assessments:** • Medication survey • (Serious) Adverse Event ([S]AE) survey • DLT evaluation during Cycle 1, applicable for Part 1 • Vital signs and body measurements • ECOG PS • Physical examination • Electrocardiogram (ECG) • Transthoracic echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan • Safety blood samples • Urinalysis • Pregnancy test • Complement Panel, applicable for Part 2 **Disease Assessments:** • Disease status evaluation by CT or MRI according to RECIST v1.1 • Tumor marker evaluation, as indicated by tumor type, if applicable • Archival tumor tissue, for local assessment of EGFR and HER2 status, applicable for Part 1 (only if tissue is available) **Additional Assessments:** • PK sampling with extended PK-profiling after the first and fourth infusion of Pan-HER (C1/D1 and

	C1/D22, respectively) for Q1W dosing, and after the first and third infusion of Pan-HER (C1/D1 and C2/D1, respectively) for Q2W dosing • Anti-drug antibody (ADA) testing • Skin biopsy for biomarker analysis • Tumor biopsy for biomarker analysis: Optional for Part 1, Mandatory for Part 2 • Peripheral blood sample for biomarker analysis
Safety Surveillance	A safety monitoring committee (SMC) will be established. This committee will include Investigator(s), Medical Monitor(s), and Sponsor's medical representatives. The SMC will review clinical and laboratory safety data regularly throughout the trial and make decisions regarding the advisability of continuing accrual to a particular dose cohort, and/or escalating the dose and allowing accrual to a higher dose cohort. In order to do so, the Investigator must ensure to report safety data to the Sponsor or designee in a timely manner. Regular safety teleconferences will be held between the trial site(s) and the Sponsor and/or designee. Such safety teleconferences may fluctuate in frequency based on accrual and trial activity, as indicated. Patients will be carefully evaluated for evidence of all AEs, including potential cumulative and/or delayed toxicities throughout the duration of their time in the trial.
Statistical Methods and Sample Size Considerations	The primary endpoint of Part 1 of the trial is the occurrence of DLTs during Cycle 1 for each of the Pan-HER dosing regimens. The number of enrolled patients will depend on the extent of observed DLTs independently in each cohort. Based on the dose-escalation design, it is planned to enroll approximately 34 patients during the first part of the trial. All DLT events will be listed by dose cohort and patient. A summary table of DLTs across dose cohorts by System Organ Class (SOC) and preferred term will be presented, if applicable. The summaries will include number of DLTs and number and percentages of patients experiencing a DLT. The MTD is defined as the highest dose with a maximum of 1 out of 6 patients experiencing a DLT. The MTD may or may not be found within the dose levels tested. Based on an overall evaluation of the dose-escalation part of the trial, the RP2D to be used in Part 2 will be selected. In Part 2 of the trial, the primary endpoint is documented OR, defined as documented PR or CR assessed by RECIST v1.1 at any time during trial participation, with radiologic evaluation to be performed locally. It is planned to enroll and treat approximately 100 patients during Part 2. The planned number of patients to be enrolled may be adjusted when the 4 expansion cohorts (i.e., based on defined molecular profile(s) and tumor types) have been selected. The protocol amendment defining the expansion cohorts will contain a detailed sample size calculation covering the four expansion cohorts, including the expected range of OR.

2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

1M FUP	1-Month Follow-up
ADA	Anti-Drug Antibody
ADC	Antibody Drug Conjugate
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
C#/D#	Cycle # / Day #
CDC	Complement-Dependent Cytotoxicity
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
CT	Computed Tomography
CTCAE v4.03	Common Terminology Criteria for Adverse Events (Version 4.03)
CTR	Clinical Trial Report
DLT	Dose-Limiting Toxicity
DMP	Data Management Plan
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EOI	End of Infusion

EOT	End of Treatment
EU	European Union
^{18}F-FDG	Fluorine-18 Radiolabeled Fluorodeoxyglucose
FAS	Full Analysis Set
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
GnRH	Gonadotropin-Releasing Hormone
G2T	Grade 2 Toxicity
HA	Health Authority
hCG	Human Chorionic Gonadotropin
HER	Human Epidermal Growth Factor Receptor
HIV	Human Immunodeficiency Virus
HRT	Hormone Replacement Therapy
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IgG1	Immunoglobulin G1
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
ISF	Investigator Site File
IV	Intravenous
KRAS	Kirsten Rat Sarcoma Viral Oncogene Homolog
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MAD	Maximum Administered Dose
MAPK	Mitogen-Activated Protein Kinase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Image/Imaging
MTD	Maximum Tolerated Dose
MUGA	Multi-Gated Acquisition

NE	Not Evaluable
NOAEL	No Observed Adverse Event Level
NRAS	Neuroblastoma *RAS* Viral Oncogene Homolog
NSAID	Nonsteroidal Anti-Inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
OR	Objective Response
OS	Overall Survival
PD	Progressive Disease
PDF	Portable Document Format
PDX	Patient-Derived Xenograft
PET	Positron Emission Tomography
PI3K	Phosphoinositide 3-Kinase
PK	Pharmacokinetic(s)
PO	Orally, by mouth
PR	Partial Response
PS	Performance Status
PSA	Prostate-Specific Antigen
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
q.s.	Quantum Sufficit (as much as suffices)
Q1W	Every week, weekly
Q2W	Every second week
RAS	Rat Sarcoma
RECIST v1.1	Response Evaluation Criteria in Solid Tumors (Version 1.1)
RP2D	Recommended Phase 2 Dose
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
SMC	Safety Monitoring Committee
SOC	System Organ Class

SOI	Start of Infusion
SOP	Standard Operating Procedure(s)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBD	To Be Determined
TEAE	Treatment Emergent Adverse Events
TKI	Tyrosine Kinase Inhibitor
ULN	Upper Limit of Normal
WHO	World Health Organization
WT	Wild-Type

3. BACKGROUND AND TRIAL RATIONALE

3.1 Disease and Treatment

3.1.1 Solid Tumor Malignancies

Cancers are caused by malignant tumors formed by an abnormal growth of cells and tissue leading to organ failure. They fall into two categories: solid and hematological cancers. Solid tumors are formed by an abnormal growth of body tissue cells other than blood, bone marrow or lymphatic cells. A solid tumor consists of an abnormal mass of cells, which may stem from different tissue types such as lung, breast, colon, prostate, stomach and liver, and which initially grows in the organ of its cellular origin. In advanced stages of the disease, solid tumors may spread to other organs through metastatic tumor growth.

Cancer is the second-leading cause of death and disability in the world, only surpassed by heart disease. In 2012, 14.1 million people were diagnosed with cancer worldwide. An estimated 8.2 million people died from the disease. The World Health Organization (WHO) projected that by 2035, these figures could increase to 24 million new cases and 14.6 million cancer deaths worldwide. Lung, breast, colorectal, prostate and stomach cancer are the most common malignancies (1).

3.1.2 Epithelial Malignancies and the Role of the HER Family of Receptors

Epithelial malignancies or carcinomas are derived from tissues lining both the external (skin) and internal (mucosal) surfaces of the body. Carcinomas may differ based on their tissue origin and include: (a) adenocarcinomas; (b) squamous cell carcinomas; (c) basal cell carcinomas; and (d) transitional cell carcinomas. A variety of inherited or acquired genetic abnormalities may underlie the transformation of normal epithelial tissues to *bona fide* malignancies.

Although a wide variety of abnormalities may be involved in the genesis or maintenance of epithelial malignancies, the human epidermal growth factor receptor (HER) family has been shown to be involved in many cases. The HER family consists of four members: EGFR-ErbB1-HER1, ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4. These receptors play an important role in normal cell growth, metabolism, proliferation, survival, and differentiation. However, deregulation through mutation, overexpression, or gene amplification of HER family members (or their ligands) is commonly associated with development, progression, or acquired resistance of many human cancers. Homo- or hetero-dimerization induced by binding of ligands within the EGF family of growth factors results in cross-phosphorylation of the dimerization partners, ultimately triggering intracellular signaling (2,3).

Epidermal Growth Factor Receptor (EGFR) and HER2 are clinically validated targets with agents targeted to EGFR active in squamous cell carcinoma of the head and neck (SCCHN), colorectal, and squamous cell histology non-small cell lung cancers (NSCLC), and agents targeting HER2 approved for the treatment of breast and gastric cancers. There is also preclinical evidence suggesting that antibodies to HER3 may prove to be a clinically relevant target in combination with agents active against other HER family members (3,4,5,6). In contrast, the role of HER4 in cancer pathogenesis is less clear.

Accumulating evidence shows that the HER family displays a high degree of plasticity and the multiple members provide compensatory signaling leading to acquired resistance in response to therapeutic intervention to a single target (7,8). Simultaneous targeting of more than one HER family receptor is frequently able to reverse the resistance to the initial drug and is often more efficacious than single-receptor targeting alone (9,10,11). Inhibiting more than one HER family member may thus be critical to limiting acquired resistance and more effectively treating cancer.

In addition, the cells within a tumor may display extensive heterogeneity and therefore do not respond equally to individual therapies. This intra-tumor heterogeneity comprises not only clinically important traits such as ability to metastasize and resist therapy, but these cells may also express biomarkers suggesting potential alternative therapeutic targets, including the members of the HER family (12,13).

3.1.3 Current Treatment of Epithelial Malignancies with HER Family Inhibitors

Both small molecule tyrosine kinase inhibitors (TKI), targeting individual or multiple members of the HER family, and therapeutic monoclonal antibodies (mAbs) have been approved for treatment of various epithelial tumors. A number of additional therapeutic agents, including small molecules, antibody-drug conjugates, bispecific antibodies, and antibody mixtures are also being investigated in clinical trials. However, most of these approaches, including bi- or dual-specific antibody formats currently in development, fail to capture the full complexity of the HER family plasticity as only two of the receptors at the most are targeted simultaneously. Although small molecule TKIs are often capable of inhibiting multiple kinases simultaneously, they are unable to directly address HER3 since very limited kinase activity is associated with this member of the HER family.

HER-targeting TKIs are small molecules that bind either reversibly or irreversibly. They inhibit receptor signaling by competing with adenosine triphosphate for binding to the intracellular catalytic kinase domain of the receptor, thereby preventing autophosphorylation and activation of several downstream signaling pathways (4,5).

First-generation EGFR TKIs, such as erlotinib and gefitinib, are oral reversible inhibitors that have been shown to be effective in specific subsets of patients with NSCLC. Erlotinib is approved for second or third line therapy of NSCLC, for first line therapy of EGFR-activating mutation-positive NSCLC and maintenance therapy after first line therapy of this patient population. Erlotinib is also approved in combination with gemcitabine for treatment of pancreatic carcinoma. Gefitinib is approved for treatment of metastatic NSCLC with activating mutations of EGFR. Afatinib is a second generation oral TKI that irreversibly inhibits EGFR, HER2 and HER4. Due to the additional activity against HER2, afatinib is being investigated for breast cancer as well as other EGFR and HER2 driven cancers. Gefitinib and afatinib are both approved for treatment of patients with activating mutations of EGFR, and afatinib has also been approved for the treatment of patients with squamous cell histology NSCLC. Osimertinib, a third generation EGFR TKI has been approved for the treatment of patients who have developed resistance to previous treatment with erlotinib, gefitinib, or afatinib, including patients who express EGFR T790M mutations (25). It has recently been approved for first line therapy of patients with activating mutations of EGFR who have not developed resistance to first or second generation therapies (26,27).

Lapatinib is an oral TKI with activity against EGFR and HER2 that has been approved in combination with capecitabine for therapy of HER2-overexpressing advanced or metastatic breast cancer patients who have received and progressed after prior therapy including trastuzumab, an anti-HER mAb. It is also approved in combination with letrozole, an aromatase inhibitor, for HER2 overexpressing patients for whom hormonal therapy is indicated. Neratinib is an irreversible TKI with activity against EGFR, HER2, and HER4 (28). It was recently approved for adjuvant therapy of HER2-positive breast cancer following therapy with trastuzumab (29).

Since HER3 has only limited kinase activity, it is not effectively targeted directly by TKIs. For this reason, therapeutic antibodies are being explored to target HER3 for cancer therapy.

Therapeutic antibodies are large molecules (proteins) that are designed specifically for binding to epitopes displayed on the surface of cells. Antibodies against targets such as the HER family act mainly through two mechanisms. They may a) interfere with signal transduction from the cell surface and induce cellular events such as growth arrest or apoptosis, or they may b) induce effector functions such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) that kill the targeted cell (14).

Three anti-EGFR mAbs have received regulatory approval. Cetuximab, a chimeric mouse-human anti-EGFR antibody is approved alone and in combination with certain chemotherapy regimens for the treatment of first and later lines of therapy of advanced or metastatic Kirsten rat sarcoma (*KRAS*) viral oncogene homolog and neuroblastoma rat sarcoma (*NRAS*) viral oncogene homolog wild-type (WT) colorectal carcinoma. Cetuximab is also approved alone and in combination with either radiotherapy or chemotherapy for the treatment of SCCHN. Panitumumab is a human anti-EGFR mAb indicated as a single agent for patients with advanced or metastatic *RAS* WT colorectal cancer (CRC) refractory to prior treatment with a fluoropyrimidine, irinotecan, and oxaliplatin as well as in combination with FOLFOX for first line treatment of *RAS* WT advanced or metastatic CRC. Necitumumab is a recombinant human anti-EGFR antibody that is indicated for first line therapy of squamous cell NSCLC in combination with gemcitabine plus cisplatin.

Trastuzumab is an anti-HER2 mAb indicated for the treatment of patients with HER2-overexpressing breast cancer as well as HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. Trastuzumab is approved in a variety of settings alone and in combination with chemotherapy for patients with breast carcinoma. Pertuzumab is another anti-HER2 antibody that is approved in combination with trastuzumab and docetaxel for patients with treatment-naïve HER2-overexpressing metastatic breast cancer. It has also been approved in combination with trastuzumab and docetaxel for neoadjuvant treatment of patients with locally advanced, inflammatory, or early breast cancer based on improvement of pathological complete responses. Ado-trastuzumab emtansine is an antibody drug conjugate (ADC) composed of trastuzumab conjugated to a microtubule inhibitor. This ADC is indicated for patients with HER2-overexpressing metastatic breast cancer who had recurred within six months of having received prior therapy with a taxane and trastuzumab. Additional novel agents targeting HER2 are currently in development including mAbs, bispecific antibodies, and ADCs.

There is currently no approved HER3 targeting therapeutic antibody, but a variety of anti-HER3 antibodies are at different stages of clinical development. Based on preliminary data, most HER3 targeting antibodies have limited activity as single agents and are therefore being investigated in combination with other HER targeting agents and/or with chemotherapy (6).

3.2 Investigational Medicinal Product

3.2.1 Sym013 (Pan-HER)

The investigational medicinal product (IMP) tested in this trial is Sym013, referenced as Pan-HER.

Pan-HER is a recombinant antibody mixture containing 6 humanized immunoglobulin G1 (IgG1) mAbs, which bind specifically to non-overlapping epitopes on the EGFR (Hu1277 and Hu1565), HER2 (Hu4384 and Hu4517) and HER3 (Hu5038 and Hu5082).

Pan-HER IMP is a clear to opalescent, colorless to slightly yellow liquid to be administered as an intravenous (IV) infusion through a peripheral line or indwelling venous access device.

3.2.2 Mechanism of Action

The two antibodies against each receptor in Pan-HER bind to non-overlapping epitopes on their target receptor. This allows the pairs of antibodies to bind simultaneously to the receptor and effectively induce receptor internalization and degradation thereby inhibiting downstream signaling pathways that regulate growth, metabolism, proliferation, and survival. The removal of the receptors from the cell surface also prevents interactions between the receptors and other proteins, including ligands, and Pan-HER is consequently capable of effectively blocking HER ligand-induced proliferation in cancer cell lines (15). Unlike antibodies targeting a single member of the HER family, Pan-HER effectively prevents compensatory receptor up-regulation, which may allow tumor cells to initiate compensatory signaling and escape treatment. Pan-HER also mediates secondary effector functions, such as ADCC and CDC, which may contribute to the activity observed *in vivo*.

3.2.3 Summary of Non-clinical Findings

Results from a number of *in vitro* experiments demonstrate that Pan-HER effectively inhibits proliferation of a range of different cancer cell lines originating from various malignant human tissues, including cell lines with intrinsic and acquired resistance to existing HER-targeted therapies, such as cetuximab, trastuzumab, or pertuzumab. The fact that not all tested cell lines are inhibited to the same degree demonstrates that the activity is not due to a general cytotoxic effect (15).

The superior ability of Pan-HER to down-regulate EGFR, HER2, and HER3 simultaneously in cancer cells *in vitro* also translates into broad and efficacious tumor growth suppression *in vivo.* Pan-HER strongly suppressed tumor growth in seven cell-line based xenograft models of human cancer with varying dependency on EGFR, HER2, and HER3. In addition, Pan-HER effectively suppressed tumor growth in patient-derived xenograft (PDX) models of various tissue origin, including pancreatic, head and neck, squamous lung, ovarian, breast, and colorectal cancer. The majority of the models had documented resistance to targeted therapeutics and/or carried mutated *KRAS* and were considered hard-to-treat. Across all indications, Pan-HER had a measurable

effect in 81 of the 96 PDX models tested, and induced tumor regression in 23 models of the 96 tested.

Collectively, the xenograft studies have shown that there is a clear benefit of combining HER family target specificities as compared to single-receptor targeting. All three target specificities have been demonstrated to contribute to the efficacy of Pan-HER. The *in vivo* tumor growth inhibition by Pan-HER was superior or equal to that of cetuximab and/or trastuzumab in the models where these comparators were included.

In vivo safety and pharmacokinetics (PK) of Pan-HER were evaluated in non-human primates. EGFR, HER2 and HER3 are evolutionarily conserved between cynomolgus monkeys and humans, and Pan-HER recognizes both the human and cynomolgus targets with similar, high affinity. Thus, the cynomolgus monkey is considered a pharmacologically relevant model in which to study toxicity and PK.

Once-weekly IV infusion of Pan-HER at 3, 6, 12, 18, 24 and 36 mg/kg (non-GLP studies) and at 5, 10 and 15 mg/kg (pivotal study) was evaluated in the cynomolgus monkeys.

Following the first administration of Pan-HER in monkeys, Pan-HER showed a rapid clearance from serum with short half-lives ($T_{½}$) ranging from 1 to 3 days over the dose levels tested. A trend of increasing half-life with increasing dose was observed.

Dose-limiting toxicities (DLTs) in the form of diarrhea, dehydration and weight loss as well as skin sores/lesions were recorded after the second infusion of Pan-HER at 24 mg/kg and after one infusion at 36 mg/kg. The toxicity profile and PK profile indicate target engagement and that the toxicity is exaggerated pharmacology reflecting the mode of action of Pan-HER.

In the pivotal toxicology study, once-weekly IV infusions of Pan-HER to cynomolgus monkeys for six weeks at dose levels of 15 mg/kg/week or below were tolerated with no adverse signs of toxicity. Microscopically, there were no systemic findings, but locally thrombus formation and intimal proliferation within the saphenous veins were observed, and an increase in the inflammatory response in and around the infusion sites. These findings are considered as secondary toxicity features related to nonclinical immunotoxicity and not a direct target mediated toxicity.

Tissue cross reactivity studies showed specific positive staining with Pan-HER in the majority of human and cynomolgus monkey tissues examined. Specific positive staining with Pan-HER was observed mainly in tissues with epithelial and/or endothelial components and/or in the connective tissue.

An *in vitro* safety study (i.e., a human whole blood activation assay using blood from six healthy donors) indicated that Pan-HER has a low risk of triggering acute immune toxicity in human blood as no significant increase in cytokine release was observed.

In conclusion, data from toxicology, tissue cross reactivity, PK and the *in vitro* safety study in human whole blood indicate that Pan-HER can be safely tested in human cancer patients. Based on the data described in the pivotal study, the No Observed Adverse Event Level (NOAEL) is considered to be 15 mg/kg.

For further information, refer to the Investigator's Brochure.

3.2.4 Summary of Clinical Findings

3.2.4.1 Protocol Sym013-01

This is the first clinical trial to study Pan-HER. As of Amendment 6, a total of 19 patients have been entered to Part 1 of this trial: 1 patient each at 1 mg/kg and 2 mg/kg weekly (Q1W), 4 patients at 4 mg/kg Q1W, 3 patients at 6 mg/kg every second week (Q2W), 7 patients at 9 mg/kg Q2W, and with Amendment 5, 3 patients at the recently initiated cohort of 9 mg/kg Q2W + mandatory intensive prophylaxis for infusion-related reactions (IRRs) and oropharyngeal mucositis. Adverse events (AEs) observed at the 4 mg/kg Q1W dose activated the stopping rule of the single-patient dose cohort titration and resulted in transition to a 3+3 trial design. Effective with Amendment 3, due to Grade 1-2 oral mucositis, rash, and diarrhea at the 4 mg/kg Q1W dose, the dosing interval in this trial was changed from Q1W to Q2W for doses of 6 mg/kg and higher. Overall, the most frequently occurring, treatment-related AEs have been IRRs, oral mucositis, rash, and diarrhea.

Regarding IRRs, despite required premedication with a glucocorticoid and an antihistamine, 2 of 4 patients at 4 mg/kg Q1W experienced Grade 1-2 events, and 2 of 3 patients at 6 mg/kg Q2W experienced Grade 2 events. Per protocol, the occurrence of 2 IRRs in the 6 mg/kg Q2W cohort resulted in prolongation of infusion from a minimum duration of 2 hours to 2.5 hours, beginning with the 9 mg/kg cohort. Two (2) of the first 4 patients at 9 mg/kg Q2W experienced Grade 1-2 IRRs, and a fifth patient experienced a Grade 3 IRR. The Grade 3 event met the protocol-specified DLT criteria and was reported as a study drug-related serious adverse event (SAE). The patient was discontinued from study and the 9 mg/kg Q2W cohort was expanded. In addition, the minimum duration of infusion for subsequent patients was once again extended, from 2.5 hours to 3 hours, and as allowed per protocol, additional premedications were recommended for all future patients, to include predosing with montelukast and oral

dexamethasone, and day-of-dosing administration of an H2 antagonist and acetaminophen. No IRRs were observed in the subsequent 2 of 7 total patients entered to the 9 mg/kg cohort, and one Grade 1 IRR has been observed in a patient entered to the 9 mg/kg Q2W + prophylaxis cohort. Overall, IRRs have occurred on Day 1 of treatment (7 of 16 patients total), with 2 patients at 9 mg/kg Q2W experiencing a repeat Grade 1 to Grade 2 IRR with the 2nd and 5th dose of Pan-HER, respectively.

Regarding mucositis, Grade 1-2 events were observed in 4 of 4 patients at 4 mg/kg Q1W, in 2 of 3 patients treated at 6 mg/kg Q2W following recommended prophylaxis (1 patient also with anal mucositis), and in 5 of 7 patients at 9 mg/kg Q2W following recommended prophylaxis. Furthermore, 1 patient (who had not been premedicated) at 9 mg/kg Q2W experienced Grade 3 oropharyngeal mucositis meeting the protocol-specified DLT criteria. The event was also reported as a study drug-related SAE. Symptomatic treatment resulted in symptom resolution, and the patient was retreated with a reduced dose without recurrence. Since implementation of mandatory prophylaxis, a single case of mucositis, Grade 2, has been observed in the 9 mg/kg Q2W + prophylaxis cohort.

Regarding rash and diarrhea, Grade 1-2 acneiform/maculopapular rash has been reported in 11 patients at doses of 2 mg/kg and above; and Grade 1-2 diarrhea has been reported in 4 patients (i.e. 2 patients at 4 mg/kg Q1W and 2 patients at 6 mg/kg Q2W).

While data in this ongoing clinical trial have not been fully verified, other study drug-related AEs have included Grade 1-2 fatigue, epistaxis, dry skin, and flushing (each in 2 to 3 patients), as well as single episodes of nausea, vomiting, dyspepsia, anorexia, weight loss, blurred vision, dry eye, paronychia, oral candidiasis, dysgeusia, arthralgia, dysesthesia, and alopecia. A single episode of Grade 3 asymptomatic lipase elevation occurred at the 2 mg/kg Q1W. Dose-escalation and accrual to Part 1 continues, under the conditions set forth with Amendment 5; Pan-HER is being delivered by 4-hour infusion, and with mandatory intensive prophylaxis to reduce the risk of IRRs and oropharyngeal mucositis.

As of Amendment 5: As described, 2 events meeting the protocol DLT criteria occurred in the 9 mg/kg Q2W cohort, IRR and mucositis, and while increased prophylaxis for each was recommended, it was not fully implemented in advance of these events. For this reason, intensive prophylaxis for both toxicities was made mandatory in an effort to facilitate a more accurate evaluation of the safety and tolerability of Pan-HER at dose levels likely to be therapeutically active. Per amendment, patients entered to receive 9 mg/kg Q2W in Dose Level 5P (P=prophylaxis) and patients entered thereafter must receive intensive prophylaxis, as defined herein, on a mandatory basis to reduce the risk of IRRs and oropharyngeal

mucositis. Further, to reduce the risk of IRRs the infusion duration of Pan-HER was further prolonged, with delivery over a fixed 4-hour period (unless further prolongation is required for an individual patient due to the occurrence of an IRR). Titrated rate increases during infusions and infusion duration reductions after C1/D1 were no longer allowed.

As of Amendment 6: With Amendment 3, Q1W dosing was halted; with Amendment 6, Q1W dosing is reintroduced under the prophylaxis and infusion duration conditions outlined in Amendment 5. All patients must receive intensive prophylaxis, as defined herein, on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis, and must receive Pan-HER infusions over a fixed (at minimum) 4-hour (+10 min) period, unless further prolongation is required for an individual patient due to the occurrence of an IRR. Reevaluation of Q1W dosing will begin at the 6 mg/kg dose; however, lower doses may be explored if indicated based on tolerability.

3.2.4.2 Other Anticipated Clinical Findings

Dermatological toxicities, such as acneiform rash, dry skin, fissures, and paronychia are common AEs associated with EGFR inhibitors, in particular EGFR targeting antibodies, such as cetuximab and panitumumab (16). Other common side effects often associated with anti-EGFR mAbs are electrolyte disturbances, in particular hypomagnesemia, and IRRs.

Cardiotoxicity in the form of left ventricular dysfunction has been observed in association with HER2 inhibition, in particular with trastuzumab treatment (16). The risk increases in combination with anthracyclines.

Diarrhea is a common side effect of many cancer treatments, including chemotherapeutic agents and targeted therapeutics (16,17). EGFR-targeted TKIs are associated with high frequencies of clinically important diarrhea. Diarrhea is also common with several multi-agent HER2-directed regimens used in the treatment of HER2-positive breast cancer. HER3 targeting antibodies do not seem to induce much diarrhea or other severe AEs on their own, but increased frequencies of diarrhea have been observed in combination with EGFR targeted therapeutics such as erlotinib and cetuximab (18,19). Prophylaxis with agents that decrease intestinal motility, such as loperamide, appears to effectively reduce the incidence and severity of diarrhea caused by HER family targeting (17,20).

Based on nonclinical results, the AE most likely to be seen with Pan-HER is diarrhea.

3.3 Trial Rationale

As outlined in the previous sections, HER family expression heterogeneity and plasticity in response to therapeutic intervention are important drivers of primary and acquired drug resistance and pose challenges to effective cancer treatment in the clinic. By targeting three receptors of the HER family, Pan-HER effectively inhibits a range of cancers of various tissue origin and genetic background, including cell lines and xenograft models with acquired resistance to therapeutic antibodies. Importantly, by down modulating all three targets simultaneously, Pan-HER prevents compensatory receptor up-regulation and renders the receptors unavailable for ligand binding and activation. Pan-HER represents a novel strategy to deal with primary and acquired resistance and thus may provide a clinically relevant effect in patient populations for which few therapeutic options exist.

Pan-HER will be developed for the treatment of patients with resistant or refractory epithelial malignancies. Initially, the safety and efficacy of Pan-HER will be investigated in advanced epithelial malignancies. Future development of Pan-HER may include pancreatic, esophageal, gastric, CRC, NSCLC, advanced ovarian, and HER2-postive breast cancer having failed HER2 targeted therapy.

3.4 Dose Rationale

Data from toxicology, tissue cross reactivity, PK and *in vitro* safety study in human whole blood indicate that Pan-HER can be safely tested in human cancer patients.

Based on the observed NOAEL (15 mg/kg) during the pivotal toxicology study in monkeys, a starting dose of Pan-HER at 1.0 mg/kg in cancer patients has been selected. A safety factor of 15 is implemented to counterbalance a possible underestimation of the dose-toxicity relationship due to the immunogenicity in monkeys.

3.5 Overall Benefits/Risk

As limited clinical information is available for patients treated with Pan-HER (see **Section 3.2.4.1**), the benefits and the safety profile of Pan-HER have not been fully established. However, definite antitumor activity has been reported in many Phase 1 trials, including trials of HER family targeting agents. Results from preclinical studies indicate that Pan-HER may have a clear benefit against a number of different cancers, including those with primary or acquired resistance to HER family targeted therapeutics. Pan-HER has also been shown to be efficacious in preclinical models at dose levels that are well tolerated in cynomolgus monkeys.

During this trial, there will be an ongoing assessment of the risks with periodic evaluation of safety data. The trial will be discontinued in the event of any new finding indicating a risk that would render continuation of the trial unjustifiable.

In order to mitigate potential risks, the trial is designed to detect DLTs, if any, and to define a maximum tolerated dose (MTD) in accordance with the dose-escalation scheme planned for the trial. Enrollment will be staggered by 2 weeks between the first and second patient in each new dose level tested where more than 1 patient is to be entered, in order to ensure safety, before allowing concurrent enrollment of further patients at the given dose level. If the dose administered in a cohort is well tolerated, dose-escalation may proceed, and enrollment of subsequent cohorts may occur in order to establish a recommended phase 2 dose (RP2D). The options to slow infusions, interrupt dosing, decrease the dose administered, and discontinue administration of Pan-HER in the event of specific AEs is outlined in this clinical trial protocol. In addition, steps to prevent IRRs, and measures to intervene in the event of their occurrence, are specified.

4. TRIAL OBJECTIVES

4.1 Objectives of Part 1, Dose-Escalation

4.1.1 Primary Objective (Part 1)

To assess the safety and tolerability of Pan-HER when administered either Q1W or Q2W by IV infusion to separate dose-escalation cohorts of patients with advanced epithelial malignancies without available therapeutic options.

4.1.2 Secondary Objectives (Part 1)

1. To determine a RP2D and regimen of Pan-HER
2. To evaluate the PK profile of Pan-HER
3. To evaluate the immunogenicity of Pan-HER
4. To evaluate target engagement in skin biopsy tissue (EGFR and HER3) and tumor biopsy tissue, if available, (EGFR, HER2 and HER3)
5. To evaluate other potential pharmacodynamic biomarkers of Pan-HER action, and estimate, if feasible, the magnitude of biological activity in peripheral blood and in skin biopsy (and tumor biopsy, if available) tissue
6. To make a preliminary evaluation of the antitumor effect of Pan-HER

4.2 Objectives of Part 2, Dose-Expansion

4.2.1 Primary Objective (Part 2)

To evaluate the antitumor effect of Pan-HER when administered at the RP2D and regimen to patients with advanced epithelial malignancies without available therapeutic options.

Four (4) dose-expansion cohorts will be evaluated: Cohort A (HER2+ solid tumor malignancy Basket Cohort*), Cohort B (pancreatic carcinoma), Cohort C (to be determined [TBD]), or Cohort D (TBD).

**A Basket Cohort is designed to evaluate the potential antitumor effects of a targeted therapy by enriching for patients with a defined genetic alteration (e.g., mutations in or overexpression of a specific gene(s)) regardless of the tumor histotype of the enrolled patients' tumors.*

4.2.2 Secondary Objectives (Part 2)

1. To further evaluate the safety and tolerability of Pan-HER
2. To further evaluate the PK profile of Pan-HER

3. To further evaluate the immunogenicity of Pan-HER

4. To further evaluate target engagement in skin biopsy tissue (EGFR and HER3) and tumor biopsy tissue (EGFR, HER2 and HER3) (tumor biopsy required)

5. To further evaluate other potential pharmacodynamic biomarkers of Pan-HER action, and estimate, if feasible, the magnitude of biological activity in peripheral blood and in skin and tumor biopsy tissue (tumor biopsy required)

5. TRIAL DESIGN

5.1 Overall Design and Plan

This is an open-label, multicenter trial composed of 2 parts in which Pan-HER will be evaluated when administered by IV to patients with advanced epithelial malignancies without available therapeutic options:

- Part 1 is a Phase 1a dose-escalation evaluating Q1W and Q2W schedules of administration in separate dose-escalation cohorts to determine the recommended phase 2 dose (RP2D) and regimen of Pan-HER
- Part 2 is a Phase 2a dose-expansion at the RP2D and regimen. Four (4) dose-expansion cohorts will be evaluated in this part of the trial and will be selected based upon findings from Part 1, additional preclinical data, and additional clinical data available at that time from other agents inhibiting these targets. Patients will be entered, depending upon either a defined molecular profile or profiles, or their underlying malignancy, to 1 of 4 corresponding expansion cohorts: Cohort A (HER2+ solid tumor malignancy Basket Cohort), Cohort B (pancreatic carcinoma), Cohort C (TBD), or Cohort D (TBD).

During Part 1, cohorts of patients will receive increasing doses of Pan-HER on either a Q1W or a Q2W schedule until establishment of the following for each schedule:

- A maximum administered dose (MAD), the highest dose level administered (in mg/kg).
- An MTD; a dose level below the MAD, which is evaluated to have a toxicity level of <33%. An MTD may or may not be found within the dose levels tested. Dose-escalation may be stopped due to toxicity observations other than DLTs and/or results from PK and/or target engagement analyses.
- A RP2D; the RP2D may be equal to or lower than the MTD for the Q1W and/or Q2W dosing regimens.

During Part 2, expansion cohorts of patients will receive the RP2D and regimen. The RP2D and regimen ultimately identified for use in this trial may be comprised of a fixed dose and schedule, a combination of doses to be administered on either a Q1W or Q2W schedule, or a combination dose and regimen.

The RP2D and regimen will be selected based on tolerability demonstrated with Q1W and Q2W dosing during Part 1, as well as available PK and target engagement results, as applicable. Doses

lower than the MTD(s) but between doses investigated in Part 1 may be selected if data indicate them to be optimal.

The Part 1 starting dose of Pan-HER will be 1 mg/kg Q1W. The following dose levels of Pan-HER are planned to be evaluated:

Q1W

- Dose Level 1: 1 mg/kg Q1W
- Dose Level 2: 2 mg/kg Q1W
- Dose Level 3: 4 mg/kg Q1W
- *Dose Level 4P: 6 mg/kg Q1W + P (lower doses with prophylaxis may be explored, if indicated)
- *Dose Level 5P: 9 mg/kg Q1W + P
- *Dose Level 6P: 12 mg/kg Q1W + P
- *Dose Level 7P: 15 mg/kg Q1W + P
- *Dose Level 8P: 18 mg/kg Q1W + P (highest potential dose allowed per protocol)

Q2W

- Dose Level 4: 6 mg/kg Q2W
- Dose Level 5: 9 mg/kg Q2W
- *Dose Level 5P: 9 mg/kg Q2W+ P
- *Dose Level 6P: 12 mg/kg Q2W+ P
- *Dose Level 7P: 15 mg/kg Q2W + P
- *Dose Level 8P: 18 mg/kg Q2W + P (highest potential dose allowed per protocol)

*Mandatory intensive IRR and oropharyngeal mucositis prophylaxis; 4-hour infusion (designated "P")

Note: Patients entered to Dose Levels 1, 2 and 3 were treated Q1W. As of Amendment 3, the dosing schedule in this trial was changed to Q2W. Patients entered to the trial prior to implementation of this amendment could continue to be treated Q1W.

Note: As of Amendment 5, patients entered to Dose Level 5P and all patients thereafter must receive intensive prophylaxis on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis, and must receive Pan-HER over a fixed (at minimum) 4-hour (+10 min) period unless further prolongation is required for an individual patient due to the occurrence of an IRR. For patients entered to the trial prior to Amendment 5, these changes could be implemented at the Investigator's discretion based on the individual patient's prior experience with Pan-HER dosing.

Note: As of Amendment 6, Q1W dosing is reintroduced under the prophylaxis and infusion duration conditions outlined in Amendment 5. All patients must receive intensive prophylaxis, as defined herein, on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis, and must receive Pan-HER infusions over a fixed (at minimum) 4-hour (+10 min) period, unless further prolongation is required for an individual patient due to the

occurrence of an IRR. Reevaluation of Q1W dosing will begin at the 6 mg/kg dose; however, lower doses may be explored if indicated based on tolerability.

Initially, one patient will be treated at each dose level until the occurrence of a toxicity during Cycle 1 that activates the stopping rule of the single-patient cohort titration design. If such a toxicity has not occurred in the first 3 cohorts (i.e., cohorts of 1 mg/kg, 2 mg/kg, and 4 mg/kg Q1W), the next cohort to open will be a 3-patient cohort and the design will switch to the 3+3 design.

Further dose-escalation will follow a standard 3+3 design with a target toxicity level of < 33% as determined by DLTs.

During Part 1, intermediate dose level(s) between 2 planned dose levels may be evaluated to further characterize safety and tolerability of Pan-HER, if indicated based on toxicity observations and/or results from PK and/or target engagement analyses.

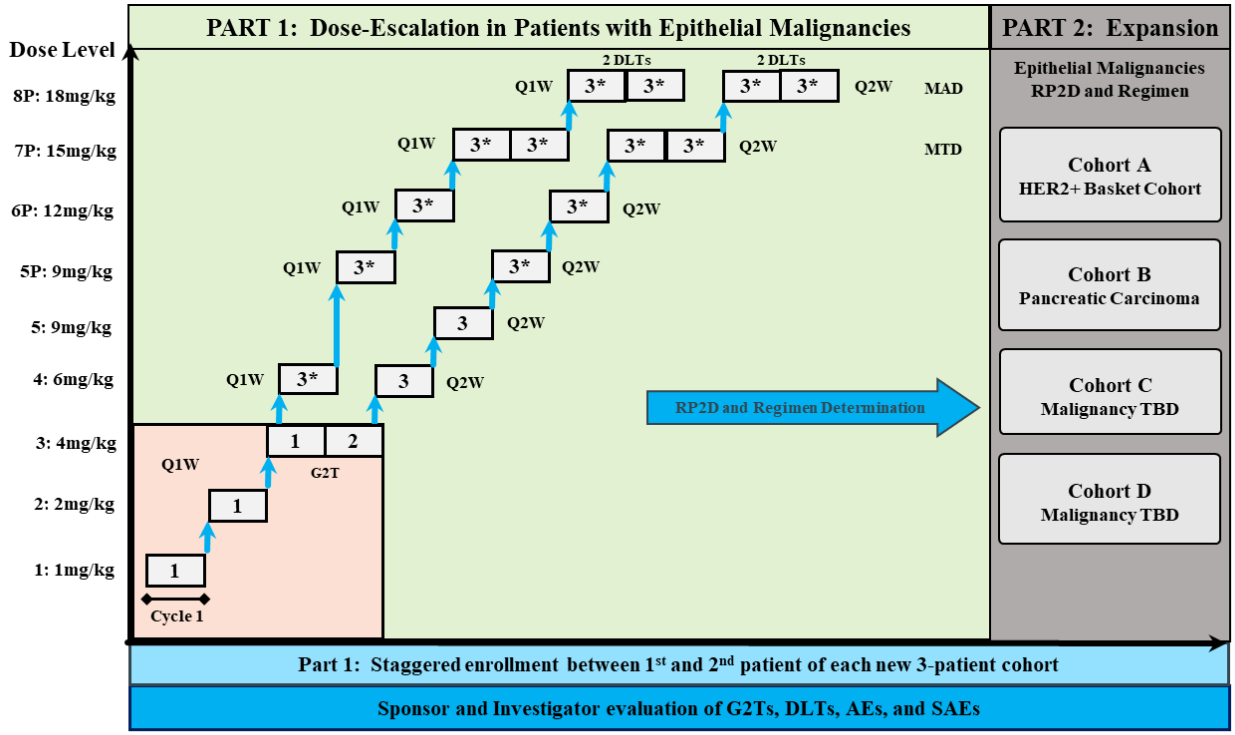
A safety monitoring committee (SMC) will be established and will include Investigator(s), Medical Monitor(s) and Sponsor's medical representatives. The SMC will review clinical and laboratory safety data regularly throughout the trial and will select the RP2D and regimen to be used in Part 2 based on safety data, as well as available PK and target engagement results.

During Part 2, the RP2D and regimen will be evaluated in 4 dose-expansion cohorts of patients (Cohort A, Cohort B, Cohort C, or Cohort D). A protocol amendment will be submitted specifying the inclusion and exclusion criteria related to each dose-expansion cohort.

Patients enrolled to dose-expansion cohorts will be treated with IV doses of Pan-HER at the RP2D and regimen to investigate the antitumor activity of Pan-HER and to further evaluate safety and tolerability.

The trial design is shown in **Figure 1**.

Figure 1 Overall Trial Design



Abbreviations: DLT: dose-limiting toxicity; G2T: grade 2 toxicity; MAD: maximum administered dose; MTD: maximum tolerated Dose; P(*): prophylaxis; RP2D: recommended phase 2 dose; Q1W: every week; Q2W: every second week

The number of investigational trial sites, hereafter called "trial sites", expected to participate will be approximately 3 in Part 1 and 25 in Part 2.

5.2 Discussion of Trial Design

5.2.1 Rationale for Trial Design

During Part 1 of this trial, patients will be enrolled to single-patient cohorts until occurrence of a toxicity that triggers switching to a standard 3+3 dose-escalation design (21). The trial is designed to select a safe and well-tolerated dose of Pan-HER during Part 1 and to investigate the selected dose in 4 groups of patients with epithelial malignancies without available therapeutic options during Part 2 of the trial. Four (4) dose-expansion cohorts to be evaluated in Part 2 will be selected based upon findings from Part 1, additional preclinical data, and additional clinical data from other agents inhibiting these targets available at that time. A protocol amendment will be submitted specifying the inclusion and exclusion criteria related to each dose-expansion cohort.

5.2.2 Rationale for Trial Population

In Part 1, patients with epithelial malignancies without available therapeutic options will be entered to evaluate the safety, tolerability and preliminary antitumor effect of Pan-HER. Results from preclinical studies indicate that Pan-HER is likely to be efficacious in this population. The patient population has been selected to optimize conditions for selecting tumor types for Part 2. In addition, it offers an opportunity to observe clinical benefit, if any, in patients during the initial escalation portion of the study.

In Part 2, the RP2D and regimen will be investigated in patients with epithelial malignancies without available therapeutic options (4 cohorts; patients to be entered to Cohort A [HER2+ solid tumor malignancy Basket Cohort], Cohort B [pancreatic carcinoma], Cohort C [TBD], or Cohort D [TBD], collectively called "dose-expansion cohorts"). The selection of expansion cohorts in Part 2 will be based upon findings from Part 1, additional preclinical data, and additional clinical data from other agents inhibiting these targets available at that time. A rationale for the 4 tumor types selected will be provided prior to opening Part 2 of the trial.

5.3 Schedule of Events

The overall trial plan is introduced in **Table 1** and further defined in the following sections.

Table 1 Overall Trial Plan

Screening Period	
Screening	14 days within first dose of Pan-HER
Treatment Period	
Treatment Allocation	The allocated dose and schedule of Pan-HER will depend upon cohort assignment and will be confirmed by Sponsor or designee on the Screening and Allocation Form.
Pan-HER	Pan-HER will be initiated on C1/D1 and, based on cohort assignment, will be administered either Q1W or Q2W to separate dose-escalation cohorts of patients by IV infusion in cycles of treatment: • Q1W: Dosing on Day 1, 8, 15, and 22 of each 28-day cycle (±2 days) • Q2W: Dosing on Day 1and 15 of each 28-day cycle (±2 days) The duration of infusion will be (effective with Amendment 5): • Minimum of 4 hours (+10 min) for all infusions. Titrated rate increases during infusions, and infusion duration reductions after C1/D1, will no longer be allowed For Part 1 of the trial, Pan-HER will be administered following delivery of intensive prophylaxis, as defined herein, on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis. For Part 2, IRR and oropharyngeal mucositis prophylaxis is mandatory during Cycle 1 and 2. If the patient is without evidence of IRRs or oropharyngeal mucositis after Cycle 2, the Investigator may choose to withdraw related medications with subsequent dosing. Gradual withdrawal of medications is recommended.
Discontinuation of Pan-HER	Treatment will continue until unacceptable toxicity or other conditions preventing further treatment, PD, termination of the trial, or patient's decision to withdraw.
End of Treatment	
End of Treatment Visit	Within 10 days after the decision to discontinue Pan-HER, an EOT Visit should be performed.
Follow-up	
1-Month Follow-up Visit	Follow-up continues until 1 month (30+7 days) after the last dose of Pan-HER. At that time, a 1M FUP Visit should be performed. This visit constitutes the end of trial participation for the patient.
Part 2 ONLY: Continued follow-up for response and/or for OS	After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS every 2 months. Response assessment follow-up is required in the event of an ongoing SD, PR or CR at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, or termination of the trial. The continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation.

Abbreviations (in alphabetical order): C1/D1, Cycle1/Day1; CR, complete response; EOT, End of Treatment Visit; IRR, infusion related reaction; IV, intravenous; 1M FUP, 1-Month Follow-up Visit; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease

5.3.1 Screening

When the trial site identifies a patient suitable for screening, the Sponsor or designee should be contacted to ensure that a cohort is open for inclusion. Once confirmed, the patient may be approached for informed consent. Screening activities may begin only once written informed consent has been obtained.

All patients giving informed consent to participate in the trial will receive a unique patient number. This number is composed of a five-digit prefix (which identifies the country and site), and a three-digit number, allocated sequentially starting from 001 for the first patient screened at the site, 002 for the second patient screened, etc.

The trial site staff must complete a Screening and Allocation Form, stating the allocated patient number along with the planned dates of screening and first scheduled Pan-HER administration (Cycle 1/Day 1, in the following C1/D1). The planned date of C1/D1 will need to be agreed upon in collaboration with the Sponsor or designee for the dose-escalation cohorts in order to ensure adequate time between dosing of the first patient and dosing of any subsequent patients within each cohort. The completed Screening and Allocation Form will then be sent to the Sponsor or designee prior to or on the day of Screening.

All screening activities must be performed within 14 days prior to C1/D1, unless otherwise specified. Individual screening assessments may be repeated prior to C1/D1, if justified and documented by the Investigator.

Once eligibility has been confirmed in accordance with the inclusion and exclusion criteria (**Sections 6.1** and **6.2**, respectively), the Screening and Allocation Form will be fully completed and signed by the Investigator and resent to the Sponsor or designee. Sponsor or designee will approve each patient for start of treatment. A copy of the fully executed Screening and Allocation Form will be returned to the trial site for archiving. This form documents the allocated dose and schedule of Pan-HER.

Furthermore, once eligibility is confirmed:

- All patients in Part 1 and 2 will have a blood sample taken for exploratory biomarker analysis
- All patients in Part 1 and 2 will have a skin biopsy performed
- Patients included in Part 1 of the trial and consenting to the optional tumor biopsy procedure will have a tumor biopsy performed, unless it is confirmed that suitable archival tissue is available for central analysis.

- All Patients in Part 2 will have a tumor biopsy performed, unless it is confirmed that suitable archival tissue is available for central analysis

5.3.2 Screening Failures

A patient found not eligible for the trial after giving informed consent is considered a screening-failure. The Screening and Allocation Form must be completed and sent to the Sponsor or designee to confirm the outcome of the screening process.

Re-screening of a patient will be allowed, if justified and documented by the Investigator.

5.3.3 Treatment

On the day of the first scheduled Pan-HER infusion (C1/D1), and prior to the start of infusion (SOI), the Investigator must assess whether any changes have occurred in the clinical state of the patient, which would exclude the patient from the trial.

Pan-HER will be administered by IV infusion on either a Q1W or a Q2W schedule:

- Q1W: dosing will be every 7 (±2) days. Four (4) doses of Pan-HER administered Q1W constitute 1 cycle.
- Q2W: dosing will be every 14 (±2) days. Two (2) doses of Pan-HER administered Q2W constitute 1 cycle.

Patients in Part 1 will be enrolled to either Q1W or Q2W dose-escalation cohorts until establishment of an MAD, an MTD, and/or a RP2D for each schedule.

During Part 2, all patients will receive the RP2D and regimen of Pan-HER.

For all patients, the dose and schedule to be administered will be documented on the Screening and Allocation Form. Patients will receive the allocated dose and schedule according to their cohort assignment until treatment withdrawal. There will be no intra-patient dose-escalation. Dose-delays of Pan-HER and/or intra-patient dose-reduction(s) may be required upon occurrence of specific toxicities, as described in **Section 7.1.4**.

Treatment will continue until unacceptable toxicity or other conditions preventing further treatment, progressive disease (PD), termination of the trial, or patient's decision to withdraw.

Disease status evaluation will be by computed tomography (CT) or magnetic resonance imaging (MRI) according to Response Evaluation Criteria in Solid Tumors (Version 1.1) (RECIST v1.1) (22).

5.3.4 End of Treatment and Follow-up Visit

An End of Treatment (EOT) Visit will be performed for all patients within 10 days from the decision to discontinue treatment.

The patient will return for a 1-Month Follow-up Visit (1M FUP) 30 (+7) days after the last dose of Pan-HER.

Part 2 ONLY: After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or overall survival (OS) every 2 months. Response assessment follow-up is required in the event of an ongoing stable disease (SD) or objective response (OR, defined as partial response [PR] or complete response [CR]), as per RECIST v1.1 at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, or termination of the trial. This continued follow-up does not require an in-person visit at the trial site but may be obtained by collection of data/documentation.

5.3.5 Schedule of Assessments

Schedule of Assessments are provided in **Table 2** (Q1W dosing) and **Table 3** (Q2W dosing).

Visit windows are included. The projection of visit days within each cycle must be made from Day 1 of the respective cycle. Furthermore, each new cycle must be initiated as soon as possible after completion of the previous cycle to maintain the dosing schedule.

All individual assessments are to be performed on or about the indicated visit day (i.e., ±2 days) unless otherwise stated. All efforts should be made to perform assessments as close as possible to the scheduled time points.

Table 2 Schedule of Assessments: Q1W Dosing

Pre-Treatment Period		**Treatment Period[1]**														**Post-Treatment Period[2]**	
	Screening	**Cycle 1**					**Cycle 2, 4, 6 etc.**					**Cycle 3, 5, 7 etc.**				**EOT**	**1M FUP**
Day within Cycle Visit Window (± days)	D-14 to D-1	D1	D3	D8 (±2)	D15 (±2)	D22 (±2)	D1 (±2)	D8 (±2)	D15 (±2)	D22 (±2)	End of Cycle	D1 (±2)	D8 (±2)	D15 (±2)	D22 (±2)	≤ 10 d from the decision of trial treatment withdrawal	1 month after last dose of trial treatment (30+7d)
Informed Consent[3]	X																
Baseline Characteristics[4]/Eligibility	X	X															
Safety Assessments																	
Medication/Procedure Survey	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
(S)AE Survey and Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLT Evaluation[5] **Part 1 only**		X	X	X	X	X	C2 only										
Vital Signs and Body Measurements	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X
ECOG PS[6]	X	X[6]					X					X				X	X
Physical Examination[6]	X	X[6]					X					X				X	X
ECG[7]	X															X	
ECHO or MUGA scan[8]	X															X	
Safety blood samples[6,9]	X	X[6]	X	X	X	X	X		X			X		X		X	X
Urinalysis[6,9]	X	X[6]			X		X					X				X	X
Pregnancy Test	X															X	
Complement Panel[10] **Part 2 only**		X															
Disease Assessments																	
Disease Status Evaluation by CT/ MRI[11,12]	X										X					X[12]	X[12]
Tumor Marker Evaluation, if applicable[13]	X										X					X	X
Archival Tumor Tissue[14] **Part 1: Submit if available (optional)**	X																
Additional Assessments																	
PK Samples[15]		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
ADA Sample		X					C2 only					X				X	X
Skin Biopsy[16]	X			X	X												
Tumor Biopsy[17] **Part 1: Optional** **Part 2: Required**	X										C2 only						
Biomarker Blood Sample[18]	X										C2 only					X	
Trial Treatment																	
Pan-HER Premedication[19]		X		X	X	X	X	X	X	X		X	X	X	X		
Pan-HER Infusion		X		X	X	X	X	X	X	X		X	X	X	X		
Post-Infusion Monitoring		X		X	X	X	X	X	X	X		X	X	X	X		

Abbreviations (in alphabetical order): ADA, anti-drug antibody; C, Cycle; CT, computed tomography; D/d, day(s); DLT, dose-limiting toxicity; EOT, End of Treatment; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; MRI, magnetic resonance imaging; MUGA, multi-gated acquisition; 1M FUP, 1-Month Follow-up; PK, pharmacokinetic; (S)AE, (serious) adverse event

1) The treatment period continues until the patient is withdrawn from Pan-HER.
2) **Applicable for Part 2 only:** After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS every 2 months. Response assessment follow-up is required in the event of an ongoing SD, PR or CR at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, or termination of the trial. This continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation.
3) Informed consent may be obtained outside the 14-day screening period prior to C1/D1, but is recommended to be obtained no earlier than 4 weeks prior to the planned C1/D1.
4) Screening assessments/baseline characteristics include demographics, medical history, tumor histology, mutation status, extent of disease, prior anti-cancer treatment etc.
5) DLT evaluation, **Applicable for Part 1 only**: DLTs are reported during Cycle 1 with final assessment 7 days after the last dose of Cycle 1 or prior to dosing on C2/D1.
6) Does not need to be performed on C1/D1 if performed during screening ≤ 7 days from C1/D1.
7) In addition to the scheduled timepoints, an ECG should be performed in the event of cardiac symptoms.
8) In addition to the scheduled timepoints, an ECHO/MUGA should be performed in the event of cardiac symptoms.
9) Local laboratory results must be available and assessed prior to each Pan-HER infusion for all infusions during Cycle 1, and for every second infusion from Cycle 2 onwards. Refer to **Section 8.2.9** for further details
10) Complement sampling, **Applicable for Part 2 only**, will be done C1/D1and in the event of an IRR. Refer to **Section 8.2.10** for further details.
11) CT or MRI imaging schedule and conditions, applying to all cohorts:
    - A CT/MRI performed within 28 days prior to C1/D1 can be used for evaluation of eligibility and as baseline scan, provided that the CT/MRI has been performed according to the clinical trial protocol requirements.
    - The first CT/MRI assessment for response is done at the end of Cycle 2 and thereafter repeated at the end of every second cycle (in the week prior to Day 1 of the next cycle).
    - In the event of suspected PD, a CT/MRI is to be performed as soon as possible.
    - In the event of CR/PR, a confirmatory CT/MRI is to be performed 28 (+7) days after the first assessment of CR/PR.
12) A CT/MRI at EOT should only be performed if the previous CT/MRI has been performed >3 weeks before; a CT/MRI scan at 1M FUP should only be performed if no CT/MRI documents disease progression before or at EOT.
13) Tumor marker evaluation to include tumor markers that are part of the trial site standard practices as indicated by tumor type, if applicable.
14) Archival tumor tissue, **applicable for patients in Part 1 only if tissue is available**: To be assessed locally, preferably by immunohistochemistry (IHC). Does not need to be repeated if EGFR and HER2 status have been assessed previously and the pathology report is available to document findings.
15) Extended PK sampling for PK profiling will be done starting C1/D1 and C1/D22. Refer to **Table 11** for further details.
16) Skin biopsy: All patients enrolled will undergo skin biopsies. Sample is to be obtained during screening after patient eligibility has been confirmed. Sampling is to be repeated Cycle 1/Day 8 (prior to dosing) and Cycle 1/Day 15 (prior to dosing).
17) Tumor biopsy, **Optional for patients in Part 1. Required for all patients in Part 2:** To be assessed centrally. Tumor biopsy is to be performed after patient eligibility has been confirmed. Archival tissue may be accepted at screening if suitable for central analysis. Sampling is repeated at the end of Cycle 2 or upon PD, whichever occurs first. Refer to **Section 8.7** for further details.
18) Biomarker blood sample: To be obtained during screening after patient eligibility has been confirmed. Sampling is to be repeated at the end of Cycle 2 or upon PD, whichever occurs first, and at EOT.
19) Premedication: For Part 1, premedication is mandatory prior to each dose of Pan-HER. For Part 2, premedication is mandatory prior to each dose of Pan-HER during Cycle 1. In Part 2, premedication may be withdrawn after Cycle 2 on a patient-by-patient basis, if the patient is without evidence of IRRs. Refer to **Section 7.2.1** for details.

Table 3 Schedule of Assessments: Q2W Dosing

Pre-Treatment Period		Treatment Period[1]										Post-Treatment Period[2]	
	Screening	Cycle 1					Cycle 2, 4, 6 etc.			Cycle 3, 5, 7 etc.		EOT	1M FUP
Day within Cycle Visit Window (± days)	D-14 to D-1	D1	D3	D8 (±2)	D15 (±2)	D22 (±2)	D1 (±2)	D15 (±2)	End of Cycle	D1 (±2)	D15 (±2)	≤ 10 d from the decision of trial treatment withdrawal	1 month after last dose of trial treatment (30+7d)
Informed Consent[3]	X												
Baseline Characteristics[4]/Eligibility	X	X											
Safety Assessments													
Medication/Procedure Survey	X	X	X	X	X	X	X	X	X	X	X	X	X
(S)AE Survey and Reporting	X	X	X	X	X	X	X	X	X	X	X	X	X
DLT Evaluation[5] **Part 1 only**		X	X	X	X	X	C2 only						
Vital Signs and Body Measurements	X	X		X	X	X	X	X		X	X	X	X
ECOG PS[6]	X	X[6]					X			X		X	X
Physical Examination[6]	X	X[6]					X			X		X	X
ECG[7]	X											X	
ECHO or MUGA scan[8]	X											X	
Safety blood samples[6,9]	X	X[6]	X	X	X	X	X	X		X	X	X	X
Urinalysis[6,9]	X	X[6]			X		X			X		X	X
Pregnancy Test	X											X	
Complement Panel[10] **Part 2 only**		X											
Disease Assessments													
Disease Status Evaluation by CT/ MRI[11,12]	X								X			X[12]	X[12]
Tumor Marker Evaluation, if applicable[13]	X								X			X	X
Archival Tumor Tissue[14] **Part 1: Submit if available (optional)**	X												
Additional Assessments													
PK Samples[15]		X	X	X	X	X	X	X		X	X	X	X
ADA Sample		X					C2 only			X		X	X
Skin Biopsy[16]	X			X	X								
Tumor Biopsy[17] **Part 1: Optional / Part 2: Required**	X								C2 only				
Biomarker Blood Sample[18]	X								C2 only			X	
Trial Treatment													
Pan-HER Premedication[19]		X			X		X	X		X	X		
Pan-HER Infusion		X			X		X	X		X	X		
Post-Infusion Monitoring		X			X		X	X		X	X		

Abbreviations (in alphabetical order): ADA, anti-drug antibody; C, Cycle; CT, computed tomography; D/d, day(s); DLT, dose-limiting toxicity; EOT, End of Treatment Visit; ECG, electrocardiogram; ECHO, echocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; MRI, magnetic resonance imaging; MUGA, multi-gated acquisition; 1M FUP, 1-Month Follow-up Visit; PK, pharmacokinetic; (S)AE, (serious) adverse event

1) The treatment period continues until the patient is withdrawn from Pan-HER
2) **Applicable for Part 2 only:** After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS every 2 months. Response assessment follow-up is required in the event of an ongoing SD, PR or CR at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, or termination of the trial. This continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation
3) Informed consent may be obtained outside the 14-day screening period prior to C1/D1, but is recommended to be obtained no earlier than 4 weeks prior to the planned C1/D1
4) Screening assessments/baseline characteristics include demographics, medical history, tumor histology, mutation status, extent of disease, prior anti-cancer treatment etc.
5) DLT evaluation, **Applicable for Part 1 only**: DLTs are reported during Cycle 1 with final assessment 7 days after the last dose of Cycle 1 or prior to dosing on C2/D1
6) Does not need to be performed on C1/D1 if performed during screening ≤ 7 days from C1/D1
7) In addition to the scheduled timepoints, an ECG should be performed in the event of cardiac symptoms
8) In addition to the scheduled timepoints, an ECHO/MUGA should be performed in the event of cardiac symptoms
9) Local laboratory results must be available and assessed prior to each Pan-HER infusion for all infusions during Cycle 1, and for every second infusion from Cycle 2 onwards. Refer to **Section 8.2.9** for further details
10) Complement sampling, **Applicable for Part 2 only,** will be done C1/D1and in the event of an IRR. Refer to **Section 8.2.10** for further details
11) CT or MRI imaging schedule and conditions, applying to all cohorts:
    - A CT/MRI performed within 28 days prior to C1/D1 can be used for evaluation of eligibility and as baseline scan, provided that the CT/MRI has been performed according to the clinical trial protocol requirements
    - The first CT/MRI assessment for response is done at the end of Cycle 2 and thereafter repeated at the end of every second cycle (in the week prior to Day 1 of the next cycle)
    - In the event of suspected PD, a CT/MRI is to be performed as soon as possible
    - In the event of CR/PR, a confirmatory CT/MRI is to be performed 28 (+7) days after the first assessment of CR/PR
12) A CT/MRI at EOT should only be performed if the previous CT/MRI has been performed >3 weeks before; a CT/MRI scan at 1M FUP should only be performed if no CT/MRI documents disease progression before or at EOT
13) Tumor marker evaluation to include tumor markers that are part of the trial site standard practices as indicated by tumor type, if applicable
14) Archival tumor tissue, **applicable for patients in Part 1 only if tissue is available**: To be assessed locally, preferably by immunohistochemistry (IHC). Does not need to be repeated if EGFR and HER2 status have been assessed previously and the pathology report is available to document findings
15) Extended PK sampling for PK profiling will be done starting C1/D1 and C2/D1. Refer to **Table 11** for further details
16) Skin biopsy: All patients enrolled will undergo skin biopsies. Sample is to be obtained during screening after patient eligibility has been confirmed. Sampling is to be repeated Cycle 1/Day 8 and Cycle 1/Day 15 (prior to dosing)
17) Tumor biopsy, **Optional for patients in Part 1. Required for all patients in Part 2:** To be assessed centrally. Tumor biopsy is to be performed after patient eligibility has been confirmed. Archival tissue may be accepted at screening if suitable for central analysis. Sampling is repeated at the end of Cycle 2 or upon PD, whichever occurs first. Refer to **Section 8.7** for further details
18) Biomarker blood sample: To be obtained during screening after patient eligibility has been confirmed. Sampling is to be repeated at the end of Cycle 2 or upon PD, whichever occurs first, and at EOT. For those timepoints where both a blood sample and a tumor biopsy are to be obtained, blood sample to be collected first.
19) Premedication: For Part 1, intensive prophylaxis, as defined herein, on a mandatory basis is required to reduce the risk of IRRs and oropharyngeal mucositis. For Part 2, prophylaxis is mandatory during Cycle 1 and Cycle 2. Thereafter, if the patient is without evidence of IRRs or mucositis, the Investigator may choose to withdraw related medications with subsequent dosing. Refer to **Sections 7.2.1** and **7.2.2** for details

5.4 Recruitment Period

Part 1 of the trial is expected to begin Q4 2016.

Patients will be sequentially enrolled to dose-escalation cohorts on either a Q1W or a Q2W schedule until establishment of a RP2D and regimen, expectedly Q1 2019.

Enrollment to the expansion cohorts in Part 2 of the trial will commence upon approval of a protocol amendment defining the expansion cohorts to be further explored. Enrollment is expected to be from Q1 2019 to Q3 2020.

5.5 Number of Patients

In total, approximately 134 patients will be included in this trial.

It is estimated that approximately 34 patients will be enrolled to receive increasing doses of Pan-HER during Part 1. The exact number of patients will depend upon the observed tolerability of Pan-HER and the potential for adding additional patients to a cohort to ensure a sufficient number of evaluable patients per cohort. For details, refer to **Section 7.1.3.2**.

It is planned to enroll and treat approximately 100 patients during Part 2.

For details regarding the sample size considerations, please refer to **Section 10.1**.

5.6 End of Trial

The end of trial will be reached at the latest 1 month (30 +7 days) after the last patient has discontinued Pan-HER. During Part 2, patients will continue to be followed to assess duration of disease stabilization, response and/or overall survival.

Once all patients have discontinued Pan-HER, or 6 months after the last patient has started treatment with Pan-HER, whichever occurs first, the trial objectives will be considered to have been met. Thereafter, patients still in treatment with Pan-HER, if any, will be given the opportunity to continue their treatment. However, while the Sponsor still needs to collect certain data to meet its regulatory obligations (AEs, SAEs, dosing of Pan-HER, reason for withdrawal, etc.), the Sponsor may elect to reduce the efficacy assessments and other assessments required, as well as scale down data collection, and/or switch patients to an extension/rollover protocol.

6. PATIENT SELECTION AND WITHDRAWAL

Questions regarding patient eligibility must be addressed and resolved by the Investigator in consultation with the Sponsor or designee prior to enrollment. All referenced toxicity grading within this protocol will be according to the Common Terminology Criteria for Adverse Events (Version 4.03) (CTCAE v4.03).

6.1 Inclusion Criteria

For inclusion in the trial, all of the following criteria must be fulfilled:

1. Written informed consent given before any trial-specific procedure is initiated
2. Male or female, at least 18 years of age at the time of informed consent
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1
4. Life expectancy >3 months assessed during Screening
5. Documented (histologically- or cytologically-proven) epithelial tumor malignancy that is locally advanced or metastatic, having received all therapy known to confer clinical benefit
6. If female and of childbearing potential, a negative pregnancy test

   Note: Women are considered of childbearing potential unless they have been hysterectomized, have undergone tubal ligation or have been postmenopausal for at least one year.

7. Not of childbearing potential or agrees to use a medically effective method of contraception as per institutional standards during the trial and for 3 months after the last dose of trial drug

   Note: Women are considered of childbearing potential unless they have been hysterectomized, have undergone tubal ligation or have been postmenopausal for at least one year.

8. <u>Part 2 ONLY:</u>

   a. Epithelial malignancy (HER2+ solid tumor malignancy Basket Cohort, pancreatic carcinoma, and 2 other tumor types to be specified in a protocol amendment), measurable according to RECIST v1.1 that has been confirmed by CT or MRI within 4 weeks prior to C1/D1

      Note: Measurable disease is defined as 1 or more target lesions assessed by CT or MRI. A tumor lesion situated in a previously irradiated area is considered measurable only if subsequent disease progression has been documented in the lesion

   b. Willingness to undergo a pre-and post-dosing biopsy (total of 2 biopsies) from primary or metastatic tumor site(s) considered safe for biopsy

      Note: For patients on anticoagulant therapy at the time of biopsy, it must be deemed safe by the Investigator to have anticoagulant therapy held prior to the procedure

6.2 Exclusion Criteria

Patients meeting any of the following criteria will not be permitted to enter the trial:

1. Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 4 weeks or 5 plasma half-lives, whichever is shortest, prior to C1/D1 except:

    - Nitrosoureas and mitomycin C within 6 weeks prior to C1/D1

2. Part 2 ONLY: Radiotherapy against target lesions within 4 weeks prior to C1/D1, unless there is documented progression of the lesion following the radiotherapy

    Note: Radiotherapy for pain control against non-target lesions is allowed, as long as it does not influence bone marrow function.

3. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) within 2 weeks prior to C1/D1 with the exception of the following allowed therapies:

    a. Hormonal therapy (e.g., Megace) for appetite stimulation

    b. Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations

    c. Hormone replacement therapy at standard doses for end-organ failure

    d. Steroid therapy as prophylaxis for contrast reactions

    e. Intra-articular steroid injections

    f. Hormonal therapy for ovarian suppression*, hormonal contraceptive therapy, post-menopausal hormone replacement therapy (HRT)

    g. Gonadotropin-releasing hormone (GnRH) analogs in patients with prostate cancer*

    h. Low-dose maintenance steroid therapy for other conditions (excluding steroid tapers for brain edema/metastases/radiation)

    i. Higher dose steroid therapy for treatment of an acute intercurrent illness in patients with stable disease or an ongoing response. In such situations, study drug treatment should be interrupted for the duration of immunosuppressive therapy

    *Patients must have been on a stable dose for at least 3 months prior to study start, and if continuing must remain on the stable dose while receiving study treatment (i.e., such treatment will not be considered as systemic hormonal therapy for the purpose of study eligibility).

4. Use of hematopoietic growth factors within 2 weeks prior to C1/D1

5. Active second malignancy or history of another malignancy within the last 3 years, with the exception of:

    a. Treated, non-melanoma skin cancers

b. Treated carcinoma in situ of the breast or cervix

c. Controlled, superficial carcinoma of the urinary bladder

d. T1a or b carcinoma of the prostate treated according to local standard of care, with prostate-specific antigen (PSA) within normal limits for the institution

6. Central nervous system (CNS) malignancies including:

   a. Primary malignancies of the CNS

   b. Known, untreated CNS or leptomeningeal metastases, or spinal cord compression; patients with any of these not controlled by prior surgery or radiotherapy, or symptoms suggesting CNS metastatic involvement for which treatment is required

   Note: Patients with treated CNS metastases will be eligible if they are asymptomatic, do not require corticosteroids, and have confirmation of at least stable brain disease status as assessed by 2 imaging studies performed at least 4 weeks apart with the most recent study performed within 4 weeks prior to first trial drug administration. Prophylactic anticonvulsant medications are allowed.

   Patients with newly identified CNS metastases during study will be considered to have PD and will be discontinued from treatment.

7. Inadequate recovery from an acute toxicity associated with any prior antineoplastic therapy

   Note: With the exception of persistent Grade 2 alopecia, peripheral neuropathy, decreased hemoglobin, and/or end-organ failure being adequately managed by hormone replacement therapy, patients must have recovered from acute toxicity by C1/D1; any Grade 1 residual toxicity may be acceptable.

8. Major surgical procedure within 4 weeks prior to C1/D1 or inadequate recovery from any prior surgical procedure

9. Non-healing wounds on any part of the body

10. Active thrombosis, or a history of deep vein thrombosis or pulmonary embolism, within 1 month prior to C1/D1, unless adequately treated and stable

11. Active uncontrolled bleeding or a known bleeding diathesis

12. Significant gastrointestinal abnormalities, including but not limited to:

    a. History of inflammatory bowel disease (e.g., ulcerative colitis, Crohn’s disease)

    b. Diarrhea ≥ Grade 2 within 2 weeks prior to C1/D1

13. Significant cardiovascular disease or condition, including:

    a. Congestive heart failure currently requiring therapy

    b. Class III or IV cardiovascular disease according to the New York Heart Association's (NYHA) functional criteria (23)

    c. Left ventricular ejection fraction (LVEF) ≤50% by Multi-Gated Acquisition (MUGA) scan or transthoracic echocardiogram (ECHO)

d. Need for antiarrhythmic medical therapy for a ventricular arrhythmia

e. Severe conduction disturbance (e.g., 3rd degree heart block)

f. Unstable angina pectoris (last episode within 6 months prior to C1/D1)

g. Uncontrolled hypertension (per the Investigator's discretion)

h. Myocardial infarction within 6 months prior to C1/D1

14. Abnormal hematologic, renal or hepatic function as defined by the following criteria:

a. Absolute neutrophil count (ANC) $<1.5 \times 10^9$/L ($1500/mm^3$)

b. Hemoglobin ≤8 g/dL

c. Platelet count $<100 \times 10^9$/L ($100,000/mm^3$)

d. Serum creatinine >1.5 × upper limit of normal (ULN) for the institution

e. Aspartate aminotransferase (AST) >3.5 × ULN for the institution or AST >5 × ULN for the institution in case of known liver metastases

f. Alanine aminotransferase (ALT) >3.5 × ULN for the institution or ALT >5 × ULN for the institution in case of known liver metastases

g. Total bilirubin >1.5 × ULN for the institution

h. Prothrombin time (PT) as assessed by International Normalized Ratio (INR) >1.5 × ULN for the institution*

i. Partial thromboplastin time (PTT) >1.5 × ULN for the institution*

*Unless on a stable dose (per the Investigator's discretion) of anticoagulant therapy for a prior thrombotic event

15. Any of the following within 2 weeks prior to C1/D1:

a. Any serious or uncontrolled infection

b. Any infection requiring parenteral antibiotics

c. Unexplained fever >38.0 °C

16. Known or suspected hypersensitivity to any of the excipients of the Pan-HER drug product

17. Any other life-threatening illness, significant organ system dysfunction, or clinically significant laboratory abnormality, which in the opinion of the Investigator, would either compromise the patient's safety or interfere with the evaluation of the safety of the trial drug

18. Any disorder that compromises the ability of the patient to give written informed consent and/or to comply with trial procedures or is unwilling or unable to comply with trial requirements at the discretion of the Investigator

19. Breast feeding, or plans by the patient (or the patient's partner) to become pregnant during treatment or within 3 months after the EOT

6.3 Withdrawal from Treatment and Trial

The visit schedule for the treatment period will apply until Pan-HER has been discontinued. Once this has occurred, an EOT Visit will be performed within 10 days from the decision to discontinue Pan-HER.

After EOT, the patient will continue to be followed until 1 month (30 +7 days) after the last dose of Pan-HER, when the 1M FUP Visit must be completed.

6.3.1 Withdrawal from Treatment

The patient must be withdrawn from treatment with Pan-HER in the event of any of the following:

- A DLT considered by the Investigator to require treatment discontinuation (Part 1 only) (See **Section 9.5**)
- Occurrence of an AE considered by the Investigator to require treatment discontinuation
- Need for more than three dose-reductions of Pan-HER
- Patients with hepatotoxicity that cannot be explained by factors not related to Pan-HER, i.e., Hy's Law criteria (24)

  Note: Patients meeting all three of the following are considered to have met Hy's Law criteria:

  - Hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above ULN of ALT or AST (or > 3 × baseline if elevated at study entry due to hepatic involvement by tumor).
  - Elevation of serum total bilirubin to ≥2×ULN, without findings of cholestasis (elevated serum alkaline phosphatase [ALP] < 2×ULN).
  - No other reason to explain the combination of increased aminotransferase 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.
- PD, verified by CT/MRI according to RECIST v1.1
- Treatment failure not meeting the criteria for PD, but considered by the Investigator to require treatment discontinuation
- Requirement for a significant surgical procedure

  Note: Patients requiring a minor surgical procedure (e.g., port placement, skin abscess drainage) may continue at the Investigator's discretion following discussion with the Sponsor or designee. A brief interruption in therapy may be considered.

- An intercurrent illness which, in the opinion of the Investigator, would prevent completion of trial-related evaluations
- Use of prohibited concomitant medication, as defined in **Section 7.5.2**
- Pregnancy
- Significant deviation from the eligibility criteria may require discontinuation after discussion with the Sponsor
- Noncompliance with trial procedures may require discontinuation after discussion with the Sponsor
- Patient election to discontinue treatment
- Termination of the trial by the Sponsor

6.3.2 Withdrawal from Trial

The patient must be withdrawn from trial in the event of any of the following:

- Patient election to discontinue from trial (patients may leave the trial at any time for any reason if they wish to do so, without any consequences)
- The Investigator judges it necessary due to medical reasons

The EOT and the 1M FUP visits should be performed to the extent possible and the Investigator should ensure any SAE is followed as described in **Section 9.3**.

Part 2 ONLY: After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS every 2 months. Response assessment follow-up is required in the event of an ongoing SD, PR or CR, as per RECIST v1.1 at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, or termination of the trial. This continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation.

6.4 Replacement of Patients

6.4.1 Part 1, Dose-Escalation Cohorts

Patients in Part 1, who do not complete Cycle 1 as defined in **Section 9.5.2**, for reasons other than drug toxicity, will be replaced.

Data from these patients will be included in the safety analysis, but will not contribute to the determination of the MTD.

6.4.2 Part 2, Dose-Expansion

It is not planned to replace any patients in Part 2.

7. TREATMENT

7.1 Investigational Medical Product/Sym013/Pan-HER

The IMP in this trial is Sym013/Pan-HER.

Pan-HER IMP is a clear to opalescent, colorless to slightly yellow liquid, formulated at 12 mg/mL to be administered as an IV infusion through a peripheral line or indwelling venous access device.

The IMP is provided in clear glass vials with a nominal fill volume of 10 mL. The closure system for the IMP vials consists of FluroTec®-coated Bromobutyl rubber stoppers, secured with a flip-off seal cap. The materials used are of pharmacopeial quality and considered suitable for storage of sterile injectable solutions. Please refer to **Table 4** for a full list of excipients.

Table 4 Description of Investigational Medicinal Product/Sym013/Pan-HER

Ingredients	Quantity per mL	Function
Pan-HER drug substance	12.0 mg	Active pharmaceutical ingredient
Acetic acid	0.12 mg	Buffering agent
Sodium acetate trihydrate	2.45 mg	Buffering agent
Sodium chloride	7.01 mg	Tonicity modifier
Trehalose dihydrate	22 mg	Stabilizer
Polysorbate 20 (Tween®20)	0.1 mg	Stabilizer
Water for injection	q.s. 1.0 mL	Diluent

Abbreviations (in alphabetical order): q.s., quantum sufficit (as much as suffices)

7.1.1 Packaging and Labeling of Pan-HER

Pan-HER IMP will be provided as 10 mL clear glass vials, Type 1.

Labeling will be in accordance with all applicable local regulatory requirements.

7.1.2 Handling, Storage and Preparation of Pan-HER

All handling, storage, and preparation of IMP should take place at the trial site pharmacy. The Investigator is responsible for informing the pharmacy of the dose of Pan-HER to be administered to a given patient, taking into account the patient's body weight.

Pan-HER is to be stored in a refrigerator at 2-8ºC (36-46 ºF), protected from direct sunlight, and may not be frozen.

Pan-HER will be diluted in saline to effect a total infusion volume of 250 mL. The infusion must be completed within 24 hours after preparation of the infusion bag.

A detailed pharmacy guide, specifying handling, storage, and preparation of Pan-HER, will be provided to the trial sites.

7.1.3 Administration of Pan-HER

7.1.3.1 Treatment Schedule

All patients will be administered IV infusions of Pan-HER, dosed according to body weight, through a peripheral line or indwelling venous access device, and with the use of an infusion pump and an inline filter. Pan-HER will be administered on either a Q1W or a Q2W schedule:

- Q1W: dosing will be every 7 (±2) days. Four (4) doses of Pan-HER administered Q1W constitute 1 cycle
- Q2W: dosing will be every 14 (±2) days. Two (2) doses of Pan-HER administered Q2W constitute 1 cycle

For all Pan-HER infusions, a complete dosing history will be recorded:

- Total dose and volume administered
- Start and stop time of infusion
- Infusion interruption or termination, including times, and reason for such actions

7.1.3.2 Part 1, Dose-Escalation

Single-Patient Cohorts and Stopping Rule

The starting dose of Pan-HER will be 1 mg/kg Q1W. The following dose levels of Pan-HER are planned to be evaluated:

Q1W

- Dose Level 1: 1 mg/kg Q1W
- Dose Level 2: 2 mg/kg Q1W
- Dose Level 3: 4 mg/kg Q1W
- *Dose Level 4P: 6 mg/kg Q1W + P (lower doses with prophylaxis may be explored, if indicated)
- *Dose Level 5P: 9 mg/kg Q1W + P
- *Dose Level 6P: 12 mg/kg Q1W + P
- *Dose Level 7P: 15 mg/kg Q1W + P
- *Dose Level 8P: 18 mg/kg Q1W + P (highest potential dose allowed per protocol)

Q2W

- Dose Level 4: 6 mg/kg Q2W
- Dose Level 5: 9 mg/kg Q2W
- *Dose Level 5P: 9 mg/kg Q2W + P
- *Dose Level 6P: 12 mg/kg Q2W + P
- *Dose Level 7P: 15 mg/kg Q2W + P
- *Dose Level 8P: 18 mg/kg Q2W + P (highest potential dose allowed per protocol)

*Mandatory intensive IRR and oropharyngeal mucositis prophylaxis; 4-hour infusion (designated "P")

Note: Patients entered to Dose Levels 1, 2 and 3 treated Q1W. As of Amendment 3, the dosing schedule in this trial was changed to Q2W. Patients entered to the trial prior to implementation of this amendment could continue to be treated Q1W.

Note: As of Amendment 5, patients entered to Dose Level 5P and all patients thereafter must receive intensive prophylaxis on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis, and must receive Pan-HER over a fixed (at minimum) 4-hour (+10 min) period unless further prolongation is required for an individual patient due to the occurrence of an IRR. For patients entered to the trial prior to Amendment 5, these changes could be implemented at the Investigator's discretion based on the individual patient's prior experience with Pan-HER dosing.

As of Amendment 6: Q1W dosing is reintroduced under the prophylaxis and infusion duration conditions outlined in Amendment 5. All patients must receive intensive prophylaxis, as defined herein (**Section 7.2.1** and **Section 7.2.2**), on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis and must receive Pan-HER infusions over a fixed (at minimum) 4-hour (+10 min) period (**Section 7.1.3.4**) unless further prolongation is required for an individual patient due to the occurrence of an IRR (**Section 7.1.3.7**). Reevaluation of Q1W dosing will begin at the 6 mg/kg dose; however, lower doses may be explored if indicated based on tolerability.

In the initial portion of dose-escalation, patients will be sequentially enrolled to single-patient cohorts of increasing doses of Pan-HER. One patient will be treated at each dose level until the occurrence of a toxicity* during Cycle 1 that activates the stopping rule of the single-patient cohort titration design. The cohort will expand to 3 patients and the design switch to a classical 3+3 dose-escalation design.

*Grade 2 toxicity, assessed by the Investigator as possibly, probably, or related to Pan-HER with the exception of Grade 2 alopecia, nausea, anemia, lymphopenia, and/or eosinophilia. Toxicity grading will be according to the CTCAE v4.03.

If a toxicity that activates the stopping rule of the single-patient cohort design has not occurred in the first 3 cohorts (i.e., 1 mg/kg, 2 mg/kg, and 4 mg/kg), the next cohort to open will be a 3-patient cohort and the design will switch to the 3+3 design.

Note: The transition from single patient cohorts to 3+3 dose-escalation design occurred beginning with Dose Level 3 (4 mg/kg Q1W). All Dose Levels evaluated thereafter are to be comprised of a minimum of 3 patients.

Each patient enrolled will receive Pan-HER at the allocated dose and schedule, unless dose-reduction is necessary as specified in **Section 7.1.4**. There will be no intra-patient dose-escalation.

The SMC will review safety data and make decisions regarding the advisability of continuing accrual to a particular dose cohort, and dose-escalation and accrual of patients to a higher dose cohort.

Classical 3+3 Dose-Escalation Design

During the 3+3 design portion of dose-escalation, at least 3 patients will be treated per dose level.

Staggered Dosing: Enrollment will be staggered between the first and second patient in each new dose level tested. The first patient must have completed and tolerated the first 2 doses of Pan-HER with Q1W dosing, or the first dose of Pan-HER with Q2W dosing, including follow-up until Day 15 of Cycle 1 (C1/D15) in order to allow for review of clinical and laboratory assessments. Thereafter patients within a cohort may be added concurrently.

Additional Patients: There is the potential for additional patients to be enrolled in the dose-escalation portion of the trial to ensure a sufficient number of evaluable patients per cohort by entering an additional patient to a cohort (e.g., increase a 1 patient cohort to 2 patients, a 3 patient cohort to 4 patients, or a 6 patient cohort to 7 patients).

Note: Should this action be taken, cohort tolerability assessment and subsequent dose-escalation will occur when the minimum number of patients required to evaluate tolerability have completed Cycle 1. However, if any additional patient experiences an event that would, per protocol, result in either cohort expansion or the halting of dose-escalation, protocol rules as outlined herein will be followed.

Escalation Rules: Escalation from a current dose level to the next will only proceed following evaluation of tolerability of the current dose level. Thus, dosing of the first patient at any new dose level will commence only after all patients to be treated at the current dose level have completed Cycle 1, and the current dose level has been found to be tolerable. The dose-escalation decision points are listed below:

- If no DLTs are encountered in any of the first 3 patients completing Cycle 1 within a dose level, dose-escalation may continue to the next level
- If 1 of 3 patients within a dose level experiences a DLT, 3 more patients will be enrolled at the same dose level (to a total of 6 patients). If no DLTs are encountered in the 3 additional

patients, dose-escalation may continue to the next level when all patients have completed and tolerated Cycle 1

- If ≥2 patients within a dose level (of up to 6 patients) experience a DLT, then that dose will be considered to have exceeded the MTD and the dose level just below this MAD will be considered to be the potential MTD
- Once the potential MTD has been declared, the MTD dose level will be completed to a total of 6 patients, if not already accomplished. In order to confirm the MTD, ≤1 of 6 patients within a dose level may have experienced a DLT
- An MTD may or may not be found within the dose levels tested. Dose-escalation may be stopped due toxicity observations other than DLTs and/or results from PK and/or target engagement analyses

Each patient enrolled will receive Pan-HER at the allocated dose and schedule, unless dose-reduction is necessary as specified in **Section 7.1.4**. There will be no intra-patient dose-escalation.

During Part 1, intermediate dose level(s) between 2 planned dose levels may be evaluated to further characterize safety and tolerability of Pan-HER, if indicated based on toxicity observations and/or results from PK and/or target engagement analyses.

The SMC will review safety data and make decisions regarding the advisability of continuing accrual to a particular dose cohort, dose-escalation and accrual of patients to a higher dose cohort, and the RP2D to be used in Part 2.

RP2D: The RP2D may include a dose or a combination of doses equal to or lower than the MTD for the Q1W and/ or Q2W dosing regimens. A dose or doses between tolerated doses investigated in Part 1 may also be selected if data indicate this to be optimal. Furthermore, the RP2D and regimen ultimately identified for use in Part 2 of this trial may be a dose or a combination of doses to be administered on a Q1W schedule, a Q2W schedule, or a combination thereof. The selection will be based on tolerability demonstrated with Q1W and Q2W dosing, as well as available PK and target engagement results, as applicable.

7.1.3.3 Part 2, Dose-Expansion Cohorts

Once the RP2D and regimen have been established during dose-escalation, enrollment into the 4 separate dose-expansion cohorts will commence (Cohort A, Cohort B, Cohort C, or Cohort D). All patients enrolled will be treated with Pan-HER at the established RP2D and regimen.

7.1.3.4 Duration of Infusion for Administration of Pan-HER

Pan-HER will be administered following delivery of premedication as specified in **Section 7.2.1** and **Section 7.2.2**.

Prior to Amendment 5

As the risk of an IRR is highest for the first administration of a mAb and diminishes with subsequent infusions, the minimum duration of the infusion is required to be approximately 2 hours (+10 minutes) for the first infusion of Pan-HER, approximately 1.5 hours (+10 minutes) for the second infusion and approximately 1 hour (+10 minutes) for all subsequent infusions.

For the first infusion, the infusion rate will start at 1 mL/minute. The infusion rate will be increased at reasonable intervals throughout the 2-hour infusion period according to the trial site practices for IV infusion of mAbs. For subsequent infusions, the infusion rate will be adjusted in order to reach an infusion time of 1.5 and 1 hour respectively.

Recommended guidelines for infusion rates are provided in **Table 5**, **Table 6**, and **Table 7**.

Table 5 Infusion Rate for First Infusion of Pan-HER

Infusion Time Interval	Infusion Rate	Approximate Volume Infused during interval
0-30 min	1 mL/min = 60 mL/h	30 mL
31-60 min	1.5 mL/min = 90 mL/h	45 mL
61-90 min	2 mL/min = 120 mL/h	60 mL
91- approx. 120 min	4 mL/min = 240 mL/h	115 mL
		Total = 250 mL

Abbreviations (in alphabetical order): h, hour; min, minutes

Table 6 Infusion Rate for Second Infusion of Pan-HER

Infusion Time Interval	Infusion Rate	Approximate Volume Infused during interval
0-30 min	1 mL/min = 60 mL/h	30 mL
31-60 min	2.5 mL/min = 150 mL/h	75 mL
61- approx. 90 min	5 mL/min = 300 mL/h	145 mL
		Total = 250 mL

Abbreviations (in alphabetical order): h, hour; min, minutes

Table 7 Infusion Rate for Third and Subsequent Infusions of Pan-HER

Infusion Time Interval	Infusion Rate	Approximate Volume Infused during interval
0-30 min	2.5 mL/min = 150 mL/h	75 mL
31- approx. 60 min	5.8 mL/min =350 mL/h	175 mL
		Total = 250 mL

Abbreviations (in alphabetical order): h, hour; min, minutes

The duration of Pan-HER-infusion will be prolonged by 0.5 hours (or longer, if indicated) for all subsequent patients entered to the trial in the following situations:

- In the event of a Grade 2 IRR in ≥ two thirds of the patients entered to a cohort
- In the event of a Grade 3 or greater IRR in any patient within a cohort

These same criteria will be applied in the event IRRs occur on an extended infusion schedule.

Amendment 5 Note: Prolongation of Pan-HER infusions by 0.5 hours was implemented on 2 occasions:

- Beginning with Dose Level 5 (9 mg/kg Q2W), and due to Grade 2 IRRs in ≥ two thirds of patients entered to Dose Level 4 (6 mg/kg Q2W), the minimum duration of infusion was prolonged by 0.5 hours to approximately 2.5 hours (+10 min) for the first infusion of Pan-HER, approximately 2 hours (+10 min) for the second infusion, and approximately 1.5 hours (+10 min) for all subsequent infusions.
- During Dose Level 5 (9 mg/kg Q2W), and due to a Grade 3 IRR in a patient entered to Dose Level 5 (9 mg/kg Q2W), the minimum duration of infusion was prolonged by 0.5 hours to approximately 3 hours (+10 min) for the first infusion of Pan-HER, approximately 2.5 hours (+10 min) for the second infusion, and approximately 2 hours (+10 min) for all subsequent infusions.

Effective with Amendment 5

Beginning with Dose Level 5P (9 mg/kg Q2W with intensive prophylaxis) and all patients thereafter, the duration of the infusion is required to be at minimum 4 hours (+10 min) for all infusions of Pan-HER (unless further prolongation is required for an individual patient due to the occurrence of an IRR). Titrated rate increases during infusions, and infusion duration reductions after C1/D1, will no longer be allowed.

Recommendations for management of an IRR in individual patients can be found in **Section 7.1.3.7**.

7.1.3.5 Patient Monitoring During and After Infusion of Pan-HER

Patients will be treated on an outpatient basis.

Pan-HER infusions must be administered under the close supervision of an experienced physician in an environment where full resuscitation facilities are immediately available.

Patients will be carefully observed for a minimum of 2 hours following completion of the first administration of Pan-HER and a minimum of 1 hour following completion of subsequent administrations. At the end of each infusion, the IV line must remain in place for at least 1 hour to allow administration of IV drugs, if necessary.

7.1.3.6 Infusion-Related Reactions to Pan-HER

An IRR is defined as an AE occurring during the Pan-HER infusion and up to 2 hours after the end of infusion (EOI), which is assessed by the Investigator as possibly, probably, or related to Pan-HER. Signs of IRRs may include but are not limited to facial flushing and swelling, shortness of breath, headache, diaphoresis, tachycardia, hypotension, chills, rigors, chest and throat tightness, as well as chest, back and/or abdominal discomfort.

7.1.3.7 Handling of Infusion-Related Reactions to Pan-HER

Recommended guidelines for management of IRRs are shown in **Table 8**. In all cases, the Investigator should use best clinical judgment in managing such reactions.

Table 8 Infusion-Related Reactions Management Guidelines

CTCAE Grade	Management/Treatment
Grade 1 Mild transient reaction; infusion interruption not indicated; intervention not indicated	• Continue infusion; consider slowing to 50% of the prior rate • Monitor closely • If infusion is extended, administer subsequent infusions during Cycle 1 at the prolonged rate • Thereafter, if vital signs remain stable and symptoms do not recur, at the discretion of the Investigator an attempt may be made to slowly increase the rate of infusion. Final infusion duration should not be briefer than the initial rate attempted in the patient
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h	• Interrupt infusion for a minimum of 30 minutes • Administer symptomatic treatment (e.g., antihistamines, NSAIDs, etc.) and appropriate supportive care (e.g., bronchodilator, oxygen, etc.), as indicated • When symptoms have resolved or decreased to Grade 1, restart infusion at 50% of the prior rate • Monitor closely • If symptoms recur, stop the infusion, institute remedial therapy, monitor closely and evaluate whether the patient can continue the trial • Administer subsequent infusions during Cycle 1 at the prolonged rate • Thereafter, if vital signs remain stable and symptoms do not recur, at the discretion of the Investigator an attempt may be made to slowly increase the rate of infusion. Final infusion duration should not be briefer than the initial rate attempted in the patient
Grade 3 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	• Discontinue the infusion • Administer symptomatic treatment (e.g., antihistamines, NSAIDs, glucocorticoid etc.) and appropriate supportive care (e.g., bronchodilator, oxygen, IV fluid etc.), as indicated • Do not resume infusion • Patient will either be discontinued from further treatment or receive subsequent treatments at a reduced dose (if >6 hours in duration) ; if treatment is continued administer subsequent infusions during Cycle 1 at 50% of the prior rate • Thereafter, if vital signs remain stable and symptoms do not recur, at the discretion of the Investigator an attempt may be made to slowly increase the rate of infusion. Final infusion duration should not be briefer than the initial rate attempted in the patient.
Grade 4 Life-threatening consequences; urgent intervention indicated	• Discontinue infusion • Administer necessary life-support measures, as indicated • Discontinue from further treatment

Abbreviations (in alphabetical order): CTCAE, Common Terminology Criteria for Adverse Events v4.03; h, hours; IV, intravenous; ; NSAID, nonsteroidal anti-inflammatory drug

7.1.4 Dose Adjustment and Delays of Pan-HER

The dose of Pan-HER in mg/kg assigned to the individual patient, will be confirmed by the Sponsor or designee prior to C1/D1.

Based on the body weight of the patient, the trial site will calculate the nominal dose of Pan-HER to be administered in mg.

Weight changes (≥ ±10%) for a patient during trial should be accompanied by recalculation of the dose (**Section 7.1.4.1**).

Furthermore, dose-delays of Pan-HER and intra-patient dose-reduction(s) may also be required upon occurrence of specific toxicities (**Section 7.1.4.2**).

7.1.4.1 Dose-Adjustment for Body Weight

Pan-HER is dosed in mg/kg and the dose to be administered will be calculated based on the actual body weight of the patient. The dose calculated may be used for subsequent infusions, unless body weight changes of ≥ ±10%, in which case the dose should be adjusted according to the change in body weight. Recalculation for lower weight changes is allowed if required by trial site standard practices.

7.1.4.2 Dose-Delays for Pan-HER-Related or Disease-Related Toxicities

Clinical judgment will be used when determining whether it is advisable to continue a patient on to the next dosing. In order to dose a patient, the following retreatment criteria must be met. Evaluations must occur at minimum prior to each Cycle 1 dose and prior to D1 and D15 doses each cycle thereafter:

1. ANC >1.5 $\times 10^9$/L (1500/mm^3)
2. Platelet count >75 $\times 10^9$/L (75,000/mm^3)
3. Any ongoing AEs should NOT meet the criteria for DLT, during the DLT-observation period
4. Any ongoing AEs, assessed as possibly, probably, or related to Pan-HER, should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved with the exception of Grade 2 clinical events that are being adequately controlled with best supportive care (e.g., nausea, vomiting, diarrhea, fatigue) and asymptomatic laboratory abnormalities that are considered clinically insignificant or that are resolving with medical therapy

Should any one of the criteria above not be met, dosing of Pan-HER must be delayed until the patient meets the above criteria. All per protocol assessments must be done.

7.1.4.3 Dose-Reduction for Pan-HER-Related Toxicities

Patients experiencing any of the following toxicities, assessed as possibly, probably, or related to Pan-HER, will have their dose reduced in accordance with the reduction schedule outlined in **Table 9**:

1. Grade 3 non-hematologic toxicity regardless of duration, with the exception of:
    a. Grade 3 nausea, vomiting, diarrhea, or fatigue lasting ≤2 days with best supportive care
    b. Grade 3 asymptomatic electrolyte abnormality that is not considered clinically significant by the Investigator and that is controlled with medical therapy
2. Grade 4 non-hematologic toxicity, with the exception of:
    a. Grade 4 asymptomatic electrolyte abnormalities that is not considered clinically significant by the Investigator and that is controlled with medical therapy
3. Neutropenia that is:
    a. Grade 3-4 febrile neutropenia
    b. Grade 4 and sustained (i.e., ANC $<0.5 \times 10^9$/L [500/mm^3], duration >5 days)
4. Thrombocytopenia that is
    a. Grade 3 with clinically significant hemorrhage
    b. Grade 4 (platelets $<25 \times 10^9$/L [25,000/mm^3])
5. AST/ALT elevation >3×ULN (or >3× baseline if elevated at study entry due to hepatic involvement by tumor) with bilirubin elevation >2×ULN without evidence of cholestasis that cannot be explained by factors not related to Pan-HER
6. Evidence of cardiac toxicity as defined by either:
    a. ≥16% absolute decrease in LVEF from baseline, or
    b. LVEF below the institutional lower limit of normal and ≥10% absolute decrease in LVEF from baseline

Need for more than three dose-reductions of Pan-HER will lead to withdrawal from treatment.

Table 9 Pan-HER Dose-Reduction Schedule

Dose Level	First Reduction	Second Reduction	Third Reduction
Dose level 1 1.0 mg/kg	0.5 mg/kg	0.25 mg/kg	0.125 mg/kg
Dose level 2	1 mg/kg	0.5 mg/kg	0.25 mg/kg
Dose level 3	Dose level 2	1 mg/kg	0.5 mg/kg
Dose level 4	Dose level 3	Dose level 2	1 mg/kg
Continue as above	Next lower tolerated dose	Next lower tolerated dose	Next lower tolerated dose

Dose-reductions will be to the next lower tolerated dose (one level per dose-reduction step). If dose-reduction below a previously tested dose level is warranted, the dose will be reduced by 50% (i.e., to ½ the previous dose) in any subsequent stepwise reduction(s). Need for more than three dose-reductions of Pan-HER will lead to withdrawal from treatment.

7.2 Other Drugs to be Used in the Trial

7.2.1 Pre-Medication for Pan-HER Infusion-Related Reactions

There is an inherent risk for IRRs with the administration of mAbs. A premedication schedule will therefore be implemented for all patients treated.

For Part 1, premedication is mandatory prior to each dose of Pan-HER.

For Part 2, premedication is mandatory prior to each dose of Pan-HER during Cycle 1 and 2.

As of Amendment 5, all patients must be premedicated as described with standard therapies that include each of the following. The recommended premedication doses are as follows:

- Montelukast (selective leukotriene receptor antagonist) 10 mg PO daily × 7 prior to each Pan-HER infusion (schedule may be extended to daily throughout study at the Investigator's discretion); plus approx. 0.5 hours prior to the start of Pan-HER infusion
- Dexamethasone 10 mg PO, approx. 12 and 6 hours prior to the start of Pan-HER infusion
- Glucocorticoid therapy equivalent to 80-100 mg IV methylprednisolone, approx. 0.5 to 2 hours prior to the start of Pan-HER infusion
- Antihistamine (H1 antagonist) equivalent to 25-50 mg IV diphenhydramine, approx. 0.5 hours prior to the start of Pan-HER infusion
- Antihistamine (H2) antagonist such as 50 mg IV ranitidine or 30 mg famotidine, approx. 0.5 hours prior to the start of Pan-HER infusion

- Acetaminophen such as 1000 mg IV or PO (orally), approx. 0.5 hours prior to the start of Pan-HER infusion

In Part 2, if a patient is without evidence of IRRs after Cycle 2, the Investigator may choose to withdraw premedication on a patient-by-patient basis with subsequent dosing in order to determine whether such continued therapy is necessary in that patient. Where practical, it is recommended that withdrawal of premedication be done in a gradual fashion.

For those patients who experienced symptoms suggestive of an IRR after Cycle 1, consideration should be given to continuing premedication for at minimum 1 to 2 additional doses before any future attempt to withdraw.

7.2.2 Treatment of Toxicities (Other Than IRRs)

7.2.2.1 Mandatory Prophylactic Treatment

Oropharyngeal Mucositis

As of Amendment 5, for prophylaxis against Pan-HER-associated oropharyngeal mucositis, the following management is mandatory throughout the Pan-HER treatment period during Part 1, and throughout the Cycle 1 and 2 Pan-HER treatment period during Part 2:

- Use of alcohol-free dexamethasone-containing oral solution; recommended 10 mL containing 0.5 mg/5 mL dexamethasone, 4× per day (swish/gargle for approximately 2 minutes then spit)
- Avoidance of alcohol- or peroxide-containing mouthwashes
- In addition, patients to be provided with instructions by the site on how best to prevent and manage oral symptoms, including but not limited to instruction to rinse mouth frequently with water (may add salt or baking-soda), use saliva substitutes if needed, apply lip moisturizer, maintain good oral hygiene, dietary restrictions, etc.

In Part 2, if a patient is without evidence of mucositis after Cycle 2, the Investigator may choose to withdraw prophylaxis on a patient-by-patient basis with subsequent dosing to determine whether such continued therapy is necessary in that patient. Where practical, it is recommended that withdrawal of prophylactic therapy be done in a gradual fashion.

Other Toxicities

Mandatory prophylactic treatment will be implemented for all patients treated in this trial should an increased incidence begin to occur of other mild-to-moderate Pan-HER-related reactions that

are amenable to prophylaxis with standard agents. Such actions will occur following discussions within the SMC.

7.2.2.2 Therapeutic Treatment

Oropharyngeal Mucositis

As of Amendment 5, in the event of development of Pan-HER-associated oropharyngeal mucositis, appropriate standard supportive care measures are to be implemented and should include:

- Application of topical or local analgesic agents such as oral benzocaine preparations
- Protective barrier-based combination mouthwash (e.g., Magic Mouthwash or similar preparation)
- Hydration, nutritional support, as needed
- Systemic analgesia, as needed
- Antibiotic, antifungal, antiviral support, as needed
- Other methods of support, per institutional standards

Cardiac Toxicity

Recent studies administering anti-HER2 drugs have confirmed the potential for cardiac toxicity, specifically dilated cardiomyopathy. Patients will be scheduled for an ECHO at screening to exclude enrollment of patients with insufficient LVEF; alternatively, a MUGA scan of the heart can be performed. Follow-up cardiac evaluations will also be performed at the EOT visit.

In the event of cardiac symptoms (e.g., shortness of breath, edemas) an electrocardiogram (ECG) and an ECHO or MUGA is to be performed as soon as possible to ensure clinically relevant cardiac AEs are detected, including but not limited to left ventricular systolic dysfunction and LVEF decrease.

Gastrointestinal Toxicity

Recent studies with anti-HER drugs have confirmed the potential for gastrointestinal toxicity, including diarrhea, stomatitis, nausea and vomiting. Appropriate standard supportive care measures are recommended for symptomatic patients.

Integument Toxicity

AEs of skin and subcutaneous tissues are a hallmark of anti-EGFR drugs and, to a lesser degree, of anti-HER2/HER3 drugs. The toxicity studies in cynomolgus monkeys have revealed limited signs of skin toxicity. Therefore, it is considered appropriate to remain reactive to symptoms with standard supportive care measures; however, preemptive skin care measures or treatment (including, topical or oral antibiotics and corticosteroids) remain at the Investigator's discretion.

Fatigue

Recent studies with anti-HER3 drugs have revealed the potential of chronic fatigue following administration. A causal treatment of chronic fatigue is unknown and therefore a treatment program managing the physical and emotional effects of chronic fatigue symptoms should be considered at the Investigator's discretion.

Other Potential Toxicities

Recent studies with anti-HER drugs have revealed further potential toxicities as listed below:

- Hepatotoxicity
    - Regular serum chemistry samples will be analyzed to address potential increase in liver function tests
- Pulmonary tissue toxicity
    - It is considered appropriate to remain reactive, e.g., symptomatic patients should be scheduled for thoracic X-ray or thoracic CT to address potential interstitial lung disease or acute interstitial pneumonitis
- Metabolic deteriorations
    - Regular blood samples will be analyzed to assess hyperglycemia, hypomagnesemia, and hypokalemia
- Musculoskeletal and connective tissue disorders
    - It is considered appropriate to remain reactive, e.g., joint pain requiring supportive care measures

7.3 Blinding

Not applicable.

7.4 Drug Accountability and Compliance Check

The Investigator is responsible for ensuring accountability for the IMP, including maintenance of IMP accountability records.

IMP accountability records will include a full inventory of the IMP including:

- Confirmation of IMP delivery to the trial site
- Record of each dose dispensed
- The return of unused IMP to the Sponsor or designee
- Record of any on-site destruction of unused IMP, as agreed with the Sponsor or designee

Records will specify dates, quantities, batch numbers, use-by dates and patient numbers, as applicable.

The Investigator, or designee, should maintain records that adequately document:

- That the patients were provided the doses specified by the protocol, and
- That all IMP provided by the Sponsor was fully reconciled

7.5 Concomitant Medication/Therapy

7.5.1 Allowed Medication/Therapy and Procedures During the Trial

Patients may receive their current concomitant medication and any medication considered necessary for the welfare of the patient during trial, except if listed in **Section 7.5.2**.

Furthermore, the following are permitted during the trial:

- Premedication with standard therapies prior to Pan-HER administration to reduce the risk of IRRs
- Prophylaxis and treatment of Pan-HER-related toxicities
- Radiotherapy for pain control against non-target lesions, as long as it does not influence bone marrow function

7.5.2 Prohibited Medication/Therapy and Procedures During the Trial

The following medications and procedures are <u>not</u> allowed from C1/D1, or as specified in the inclusion/exclusion criteria, until the EOT Visit:

- Anti-cancer treatment, including cytotoxic or cytostatic agents, hormonal therapy (except as physiologic hormone replacement) and EGFR/HER-targeting therapies

- Radiotherapy against target lesion(s) (Part 2 only)
- Systemic immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) with the exception of the following allowed therapies:
    - Hormonal therapy (e.g., Megace) for appetite stimulation
    - Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations
    - Hormone replacement therapy at standard doses for end-organ failure
    - Steroid therapy as prophylaxis for contrast reactions
    - Intra-articular steroid injections
    - Hormonal therapy for ovarian suppression, hormonal contraceptive therapy, post-menopausal HRT
    - GnRH analogs in patients with prostate cancer
    - Low-dose maintenance steroid therapy for other conditions (excluding steroid tapers for brain edema/metastases/radiation)
    - Higher dose steroid therapy for treatment of an acute intercurrent illness in patients with stable disease or an ongoing response. In such situations, study drug treatment should be interrupted for the duration of immunosuppressive therapy
- Prophylactic use of hematopoietic growth factors during Cycle 1
- Use of alcohol- or peroxide-containing mouthwashes
- Major surgery that would preclude the patient from complying with the requirements of the protocol

If any one of the above listed medications/procedures becomes necessary during the trial, the patient must be withdrawn from Pan-HER and the EOT Visit should be performed. The 1M FUP Visit should then be performed, no less than 1 month (30+7 days) after the last dose of Pan-HER.

7.6 Medical Care of Patients after End of Trial Participation

After completing participation in this trial, patients will be offered standard of care treatment in accordance with generally accepted medical practice and depending on the patient's individual medical need. During Part 2, patients will continue to be followed for survival.

8. TRIAL ASSESSMENTS

All trial assessments are considered mandatory for all patients included in the trial, unless otherwise stated. All assessments are to be performed on or about the indicated visit day (e.g., ±2 days) unless otherwise stated.

8.1 Baseline Characteristics / Eligibility Assessments

8.1.1 Signing of Informed Consent

Prior to any trial-related procedure, unless such testing was performed previously as part of the routine clinical management of the patient.

- Screening

  Note: Informed consent may be obtained outside the 14-day screening period prior to C1/D1, but is recommended to be obtained no earlier than 4 weeks prior to the planned C1/D1.

8.1.2 Demographics

To include date of birth (or year of birth/age in regions where applicable), sex, race and ethnicity.

- Screening

8.1.3 Medical History

To include prior and ongoing medical illnesses and conditions and prior surgical procedures not related to the primary diagnosis.

- Screening

8.1.4 Tumor Characteristics and Extent of Disease

To include diagnosis and date of initial diagnosis, staging at time of initial diagnosis and at screening, tumor histology, mutational status, current location of metastases, and date of most recent disease progression.

- Screening

8.1.5 Prior Cancer Treatments

To include prior surgical procedures for the primary diagnosis, as well as prior radiotherapy, chemotherapy and/or biological targeted therapy, investigational treatments, and/or procedures. Include dates of treatments, numbers of cycles, and best response to such treatments.

- Screening
- C1/D1 (prior to dosing)

8.2 Safety Assessments

To be performed within 14 days of C1/D1 (first dose of Pan-HER), unless otherwise specified. Details on the safety assessments, including assessment timepoints, are presented in the following subsections.

8.2.1 Medication/Procedure Survey

To include all medications taken other than Pan-HER and all procedures performed during trial. For medications: Include generic name or brand name, indication for use, dose and frequency, route of administration, start and stop dates or if ongoing at 1M FUP Visit. For procedures: Include date and reason for procedure.

- Starting from date of screening
- Until the date of the 1M FUP

8.2.2 Adverse Events Survey

For details about (S)AEs and (S)AE reporting, refer to **Section 9**.

- Starting from signing of informed consent for participation in the trial
- Until the date of the 1M FUP

  Note: Patients who sign informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

8.2.3 Dose-Limiting Toxicities Evaluation (Part 1 Only)

For details about AEs meeting DLT criteria, refer to **Section 9.5**.

- Starting from the first dose of Pan-HER (C1/D1)
- Reported during Cycle 1 with final assessment 7 days after the last dose of Cycle 1 for Q1W dosing, 14 days after the last dose of Cycle 1 for Q2W dosing, or prior to dosing on Day 1 of Cycle 2 (C2/D1)

8.2.4 Vital Signs and Body Measurements

To include temperature, heart rate, blood pressure, height (screening only), and body weight.

- Screening
- Prior to each dosing

- EOT
- 1M FUP
- As clinically indicated

8.2.5 ECOG Performance Status

To be assessed by ECOG PS score.

- Screening
- Day 1 of each cycle (prior to dosing)

  Note: Does not need to be assessed prior to C1/D1, if assessed during screening ≤ 7 days from C1/D1.
- EOT
- 1M FUP
- As clinically indicated

8.2.6 Physical Examination

Full physical examination at Screening to include evaluation of the following: general appearance, skin, head, ears, eyes, nose, throat, neck/thyroid, chest, cardiovascular system, abdomen, musculoskeletal system, lymph nodes, neurologic status and mental status. Thereafter, a targeted physical examination may be performed as indicated.

- Screening
- Day 1 of each cycle (prior to dosing)

  Note: Does not need to be assessed prior to C1/D1, if assessed during screening ≤ 7 days from C1/D1.
- EOT
- 1M FUP
- As clinically indicated

8.2.7 Electrocardiogram (ECG)

To include standard 12-lead ECG. The Investigator, or qualified designee, should document the evaluation of the ECG, including specification of any abnormality as clinically significant or not clinically significant.

- Screening
- EOT

- As clinically indicated. In the event of cardiac symptoms (e.g., shortness of breath, edemas) an ECG should be performed as soon as possible

8.2.8 Echocardiogram (ECHO) or Multi-Gated Acquisition (MUGA) Scan

Patients will be scheduled for an ECHO at screening to exclude enrollment of patients with evidence of insufficient cardiac function (LVEF ≤50%); alternatively, a radionuclide angiography, i.e., MUGA scan, of the heart may be performed.

- Screening
- EOT
- As clinically indicated. In the event of cardiac symptoms (e.g., shortness of breath, edemas) an ECHO or MUGA is to be performed as soon as possible

8.2.9 Laboratory Assessments and Pregnancy Test

All routine laboratory analyses will be performed at a laboratory facility local to the trial site.

Sponsor or designee must be provided with trial site laboratory normal ranges for all required parameters prior to screening of the first patient at the site. Likewise, any change in laboratory normal ranges during the trial should be forwarded to the Sponsor or designee promptly during the trial.

Blood samples will be taken at the scheduled visits and analyzed for the following parameters as per **Table 10** and as clinically indicated. Results must be available and assessed prior to dosing of Pan-HER, when sampling is scheduled on days of dosing. All individual assessments are to be performed on or about the indicated visit day (i.e., ±2 days) unless otherwise stated.

Table 10 Schedule of Safety Blood and Urine Samples

Sample Analysis	Screening	Cycle 1				Cycles Thereafter		EOT	1M FUP
Day within Cycle		D1	D3 D8	D15	D22	D1	D15		
Hematology Panel	X	X[1]	X	X	X	X	X	X	X
Biochemistry Panel	X	X[1]	X	X	X	X	X	X	X
Coagulation Panel	X	X[1]		X		X		X	X
Urinalysis	X	X[1]		X		X		X	X
Pregnancy Test	X							X	

Abbreviations (in alphabetical order): D, day; EOT, End of Treatment Visit; 1M FUP, 1-Month Follow-up Visit

1) Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1

8.2.9.1 Hematology Panel

To include complete blood count with differential, ANC, and platelet count.

- Screening
- Cycle 1
  - Weekly (prior to dosing if on dosing days)

    Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1.
  - Day 3
- Each cycle thereafter
  - Day 1 and 15 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

In the event of hematologic toxicity, the evaluation frequency should be increased to include additional evaluations between scheduled assessments, as clinically indicated.

8.2.9.2 Biochemistry Panel

To include sodium, potassium, chloride, bicarbonate or carbon dioxide, blood urea nitrogen (BUN), creatinine, glucose, bilirubin [total and direct], AST, ALT, ALP, calcium, magnesium, phosphorus, albumin, total protein, uric acid, amylase, lipase, and creatine kinase (fasting not required). Clinically significant electrolyte abnormalities should be corrected prior to dosing.

- Screening
- Cycle 1
  - Weekly (prior to dosing if on dosing days)

    Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1.
  - Day 3
- Each cycle thereafter
  - Day 1 and 15 (prior to dosing)
- EOT
- 1M FUP

- As clinically indicated

In the event of significant biochemistry abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated. In the event of creatine kinase abnormalities, isoenzyme analysis should be performed.

8.2.9.3 Coagulation Panel

To include PT, PTT and INR

- Screening
- Cycle 1
  - Day 1 and Day 15 (prior to dosing)

    Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1.
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

8.2.9.4 Urinalysis

Multi-parameter chemical test strips are acceptable and should include assessment of: Specific gravity, pH, protein, glucose, ketones, occult blood, leukocyte esterase, nitrite, bilirubin, and urobilinogen.

- Screening
- Cycle 1
  - Day 1 and Day 15 (prior to dosing)

    Note: Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1.
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

8.2.9.5 Pregnancy Test

Serum human Chorionic Gonadotropin (β-hCG) at screening, urine β-hCG thereafter, in women of childbearing potential

- Screening
- EOT
- As clinically indicated

Women are considered of childbearing potential unless they have been hysterectomized, have undergone tubal ligation or have been postmenopausal for at least one year.

8.2.10 Complement Panel (Part 2 only) (Central Laboratory)

To include total complement hemolytic activity (CH50), C3, C4, C3a, and C4a

- Cycle 1 (timepoints coincide with PK sampling)
  - Day 1
    - Prior to SOI (- 4h)
    - 4 hours after EOI (±30 min)
- In the event of an IRR

Note: A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.

8.3 Disease Assessments

8.3.1 Disease Status Evaluation by CT or MRI

The anti-tumor activity of Pan-HER will be assessed by the Investigator, or qualified designee, according to RECIST v1.1. Refer to **Appendix 1**.

Patients will undergo imaging by CT or MRI of neck, chest, abdomen and pelvis as indicated based on tumor type and clinical judgment in order to follow the underlying malignancy. The use of CT or MRI must be consistent per patient throughout the trial. Use of contrast is preferred but is at the discretion of the Investigator, as medically indicated.

- Screening

  Note: A CT/MRI performed within 28 days prior to Day 1 may be used for evaluation of eligibility and as baseline scan, provided that the CT/MRI has been performed according to the protocol requirements.

- End of Cycle 2 and end of every second cycle thereafter, i.e., Cycle 4, 6, 8 etc.

  Note: End of cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle.

- Suspected PD (as soon as possible)
- Confirmation of response, to be performed 28 (+7) days after the first assessment of CR/PR
- EOT (if >3 weeks since previous CT/MRI)
- At 1M FUP (if PD was not documented before or at EOT)

If PD is documented at any time, no further disease assessments will be required. Patients with documented PD will be discontinued from Pan-HER so that alternative management of their malignancy may be considered.

To be assigned a status of confirmed PR or CR, changes in disease status must be confirmed by repeat imaging studies performed no less than 28 days (4 weeks) after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after trial entry at a minimal interval in general no less than 6-8 weeks from first dose of Pan-HER.

Imaging data (imaging studies and derived assessments) will be stored by the trial sites and will be available upon request for potential review by the Sponsor or an independent radiology reviewer. <u>For Part 2 only</u>: In addition, imaging studies will be sent to an imaging facility for storage to ensure central availability and readiness for read at a future time upon Sponsor or Health Authority (HA) request.

For all imaging time points, the following will be recorded as per RECIST v1.1: Target lesions including size, location, and type (nodal/non-nodal); sum of diameters of target lesions; any new lesions noted during trial, including size, location, and type (nodal/non-nodal); final response assessment at each visit (PD, SD, PR, CR or Not Evaluable [NE]).

8.3.2 Tumor Marker Evaluation (as per standard practice of a trial site)

To include tumor markers that are part of the trial site standard practices, as indicated by tumor type.

It is recommended that tumor markers are evaluated at timepoints coinciding with the CT/MRI imaging studies as listed in **Section 8.3.1**.

8.3.3 Archival Tumor Tissue for EGFR, HER2 Assessment (Part 1 only)

To be assessed locally, preferably by immunohistochemistry (IHC) for EGFR and HER2 expression level, if tissue is available. Only applicable to patients included in Part 1. Does not need to be repeated if previously assessed and the pathology report is available to document findings.

- Screening

8.4 Pharmacokinetic Assessments (Central Laboratory)

PK samples will be taken according to the schedules shown in **Table 11** and **Table 12** and analyzed centrally. Actual time will be recorded for all samples taken.

Note: Comprehensive collection of clinical samples is critical to the conduct of this study. In situations where collection of the EOI + 8h samples is logistically difficult due to clinic staff availability, the observation period may be shortened and an "end of day" sample may be obtained at the latest practical time. Such an option (if to be routinely employed) is available only after previous discussion with and approval by the Sponsor.

Table 11 Schedule of Pharmacokinetic (PK) Assessments: Q1W Dosing

		Cycle 1				Cycle 2 Onward				EOT	1M FUP
Sampling Time	**Window**	**D1-D3**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22**		
Prior to SOI	- 4 h	X	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]		
EOI	+ 10 min	X	X[1]	X[1]	X	X[1]	X[1]	X[1]	X[1]		
EOI + 2 h	±30 min	X			X						
EOI + 4 h	±30 min	X			X						
EOI + 8 h[2]	±90 min	X			X						
EOI + 24 h	±6 h	X			X						
EOI + 48 h	-12 h to + 24 h	X			X						
During Visit	NA									X	X

Abbreviations (in alphabetical order): D, day; EOI, End of Infusion, EOT, End of Treatment Visit; NA, Not Applicable; h, hour; min, minutes; 1M FUP, 1-Month Follow-up Visit; SOI, Start of Infusion

1) If Pan-HER dosing is delayed, only one PK sample should be taken during the visit.
2) Effective with Amendment 6, sampling at this timepoint is optional.

Table 12 Schedule of Pharmacokinetic (PK) Assessments: Q2W Dosing

		Cycle 1				Cycle 2		Cycle 3 Onward		EOT	1M FUP
Sampling Time	**Window**	**D1-D3**	**D8**	**D15**	**D22**	**D1-D3**	**D15**	**D1**	**D15**		
Prior to SOI	- 4 h	X		X[1]		X	X[1]	X[1]	X[1]		
EOI	+ 10 min	X		X[1]		X	X[1]	X[1]	X[1]		
EOI + 2 h	±30 min	X				X					
EOI + 4 h	±30 min	X				X					
EOI + 8 h[2]	±90 min	X				X					
EOI + 24 h	±6 h	X				X					
EOI + 48 h	-12 h to + 24 h	X				X					
During Visit	NA		X		X					X	X

Abbreviations (in alphabetical order): D, day; EOI, End of Infusion, EOT, End of Treatment Visit; NA, Not Applicable; h, hour; min, minutes; 1M FUP, 1-Month Follow-up Visit; SOI, Start of Infusion

1) If Pan-HER dosing is delayed, only one PK sample should be taken during the visit.
2) Effective with Amendment 6, sampling at this timepoint is optional.

A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.

Serum concentrations of each of the 6 mAbs that comprise Pan-HER will support the PK endpoints of the trial. The serum concentrations may also be used in an exploratory population PK analysis which will be reported separately from the clinical trial report.

In the event that a collected serum sample is inadequate or insufficient for PK analysis, the analysis of PK may be performed using an anti-drug antibody (ADA) serum sample from the same time point, if available.

8.5 Anti-Drug Antibody Testing (Central Laboratory)

To assess formation of ADA. All samples must be taken prior to the Pan-HER infusion of that visit. Analysis of ADA and residual serum levels of Pan-HER will be performed at a central laboratory. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites. In the event that a collected serum sample is inadequate or insufficient for ADA analysis, the analysis of ADA can be done using a PK serum sample from the same time point, if available.

- C1/D1

- C2/D1
- Prior to every second cycle thereafter, i.e., Cycle 3, 5, 7 etc.
- EOT
- 1M FUP

8.6 Skin Biopsy (Central Laboratory)

To be performed only after eligibility has been confirmed.

All patients enrolled will undergo 3 skin biopsies for evaluation of target engagement (EGFR and HER3). Analysis of skin biopsy samples will be performed at a central laboratory. Biopsy specimens will be obtained using standard techniques and formalin-fixed, paraffin-embedded according to standard laboratory practice. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to trial sites.

Skin biopsies are requested from a rash-free area.

- Screening, after confirmation of eligibility
- C1/D8 (prior to dosing if on dosing day)
- C1/D15 (prior to dosing)

8.7 Tumor Biopsy (Central Laboratory)

Part 1: Optional (requires separate informed consent) and only applicable for patients where a tumor lesion is considered safe for biopsy. To be performed after eligibility has been confirmed.

Part 2: Required. Patients must have tumor lesion considered safe for biopsy. To be performed after eligibility has been confirmed.

- Screening, after confirmation of eligibility

  Note: Archival tissue may be accepted, if suitable for central analysis as specified in the laboratory manual. It must be ensured that the archived biopsy can be made available to the central laboratory prior to deciding to omit the tumor biopsy procedure at time of screening.

- End of Cycle 2 (prior to dosing Cycle 3) or upon PD, whichever occurs first

  Note: End of cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle. If feasible, it is preferred that the second biopsy is taken from the same tumor site from which the first biopsy was taken.

To include a tumor biopsy performed by a core biopsy of a locally recurrent or metastatic lesion. The procedure at time of screening will take place after eligibility has been confirmed and prior

to first Pan-HER administration. The tumor biopsy must be performed with minimal morbidity to the patient by a percutaneous core needle biopsy either with or without the aid of an imaging modality chosen at the discretion of the physician performing the biopsy.

Biopsy specimens will be obtained using standard sterile surgical techniques and formalin-fixed, paraffin-embedded according to standard laboratory practice. All tumor tissue samples should be reviewed by a pathologist to confirm the presence of tumor cells before the tissue sample (block or slides) is sent to the central laboratory for analysis. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.

Analysis of tumor biopsies will include target engagement (EGFR, HER2 and HER3) and may furthermore include proteins and genes that are unknown or have not been included in the scientific hypotheses at the present time of trial, but that, during the collection of data from this trial, may evolve as new candidate genes and markers related to Pan-HER safety, efficacy, or mechanism of action.

All analyses will be related to and used in connection with the data collected in the present trial and Pan-HER program, and the identity of the patient will remain confidential. The analyses will not have any medical consequences for the patient.

Tumor biopsy samples will be stored for up to 15 years after completion of the trial, where after all samples will be destroyed.

8.8 Biomarker Blood Sample (Central Laboratory)

To be performed only after eligibility has been confirmed.

Peripheral blood samples are taken for subsequent biomarker analysis. Analysis of all samples will be performed at a central laboratory. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.

- Screening, after confirmation of eligibility
- End of Cycle 2 (prior to dosing Cycle 3) or upon PD, whichever occurs first

  Note: End of cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle. For those timepoints where both a blood sample and a tumor biopsy are to be obtained, blood sample to be collected first.
- EOT

The purpose of the pharmacodynamic biomarker analysis is to develop an approach for the identification and validation of genes or proteins that may predict which patients are likely to respond to Pan-HER, and that may change with the possible development of acquired resistance to Pan-HER. Potential biomarkers of interest include genes, gene transcripts, and proteins of the HER family receptors and molecules of the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways involved in HER signaling.

Analysis of biomarker samples may include genes and/or proteins that are unknown or have not been included in the scientific hypotheses of this trial, but that, during the collection of data from this trial, may evolve as new candidate genes and markers related to Pan-HER safety, efficacy, or mechanism of action.

All analyses will be related to and used only in connection with the data collected in the present trial, and the identity of the patient will remain confidential. The analyses will not have any medical consequences for the patient.

Biomarker samples will be stored for up to 15 years after completion of the trial where after all samples will be destroyed.

8.9 Handling of Biological Samples

All biological samples to be analyzed locally will be collected and handled according to institutional practices.

All biological samples to be analyzed centrally will be collected and handled according to a detailed laboratory manual.

Retention time for biologic specimens will be specified in the laboratory manual.

8.10 Follow-up Assessments

Assessments at the 1M FUP Visit include disease status and subsequent cancer therapy.

Part 2 ONLY: After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or OS every 2 months. Response assessment follow-up is required in the event of an ongoing SD, PR or CR, as per RECIST v1.1 at the 1M FUP Visit, until PD or another therapeutic intervention is initiated. Survival follow-up is required until death, withdrawal of consent, or termination of the trial. This continued follow-up does not require an in-person visit at the trial site, but may be obtained by collection of data/documentation.

8.11 Appropriateness of Measurements

Standardized methods for assessments of efficacy and safety variables will be used.

9. ADVERSE EVENTS

9.1 Definitions of Adverse Events

9.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or a clinical investigation subject administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Causality for the above-mentioned AE will be assessed appropriately as: Not Related to IMP, Unlikely Related to IMP, Possibly Related to IMP, Probably Related to IMP, or Related to IMP. In addition, any AE, regardless of causality, that also meets the seriousness criteria, will be reported on an SAE form.

9.1.2 Events Not to be Considered as Adverse Events

A pre-existing condition (i.e., a disorder that is present before the AE recording period starts and is noted on the medical history/physical examination form) should not be recorded as an AE unless the condition worsens, or episodes increase in frequency during the AE recording period. Refer to **Section 9.2.1**.

PD will not be captured as an AE unless the nature of the PD is different than expected (i.e., signs/symptoms that are not typical of PD).

Note: PD may be reported as an AE in the case of patient death, with death being the outcome of the event.

An abnormal laboratory value or an abnormality in physiological testing (such as ECGs) per se need not be reported as an AE unless one of the following applies:

- The Investigator considers the abnormality clinically significant
- The event meets the definition of an SAE
- The event requires an intervention
- The event results in an action taken with Pan-HER (dose-reduction and/or withdrawal)

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be recorded as AEs. A medical condition for which an unscheduled procedure was performed, should however be recorded if it meets the definition of an AE. For example, an acute appendicitis should be recorded as the AE and not the appendectomy.

Procedures to support the treatment regimens, such as insertion of central venous catheters etc. should not be recorded as AEs, unless the procedures result in complications.

9.1.3 Adverse Events of Medical Interest

Not applicable.

9.1.4 Serious Adverse Events

An SAE is an AE that meets one or more of the following regulatory outcomes criteria:

- Results in death

  Note: In the case of deaths, the event(s) leading to the death should be recorded and reported as SAE(s) with the outcome “Fatal”. The death itself will not be reported as an event (SAE), unless the cause of the death is unknown (e.g., in case of unexplained or sudden death).

- Is life-threatening

  Note: The term "life-threatening" in this definition refers to an event in which the patient is at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might cause death if it was more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is medically important

  Note: Medical and scientific judgment must be exercised in deciding whether an AE is believed to be “medically important”. Medically important events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

9.1.5 Events that Do Not Meet the Definition of Serious Adverse Events

PD will not be captured as an SAE unless the nature of the PD is different than expected (i.e., signs/symptoms that are not typical of PD).

Note: PD may be reported as an SAE in the case of patient death, with death being the outcome of the event.

Elective surgery or other scheduled hospitalization periods that were planned before the patient was included in this trial are not to be recorded as SAEs, unless an outcome is considered serious.

Hospitalization for observation or convenience following the Pan-HER infusions without an SAE occurring should not be recorded as an SAE, e.g., if a patient is hospitalized merely for observation, or if a patient finalizes the infusion at a time of day requiring a convenience overnight stay in the hospital.

If procedures to support the treatment regimens require hospitalization, they should not be recorded as SAEs. However, in cases where a procedure results in complications requiring/prolonging hospitalization this must be recorded and reported as an SAE.

9.2 Adverse Event Recording and Reporting Instructions

9.2.1 Adverse Event Recording Period

All AEs will be recorded from signing of informed consent for participation in the trial. The recording period ends at the time of the 1M FUP Visit.

Note: Patients who sign informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

The Investigator must record all directly observed AEs and all AEs spontaneously reported by the patient. A general, open-ended type of question should be used to elicit a response from the patient, such as, “How have you been feeling?” or “Have you had any health problems since your last visit?”.

All AEs that occur in patients during the AE recording period must be recorded/entered on the AE section of the Case Report Form (CRF), whether or not the event is assessed as related to Pan-HER. If the AE is serious, the SAE report forms must also be completed and submitted (see **Section 9.3**).

9.2.2 Diagnosis

A diagnosis should be recorded if possible. If no diagnosis is available, signs and symptoms should be recorded instead.

9.2.3 Intensity

All referenced toxicity grading within this protocol will be according to the CTCAE v4.03. If the severity of an AE is not specifically graded by the CTCAE guidance document, the Investigator should use the general definitions of Grades 1 to 5 as per the following, and use his/her best medical judgment to describe the severity of the AE:

- Grade 1: Mild

- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening or disabling
- Grade 5: Death caused by the event

Changes in severity of AEs will be recorded.

Generally, an AE of Grade 4 or 5 qualifies for SAE reporting to the Sponsor or designee; however, the definition of Grade 4 does not necessarily always meet the regulatory definition of "life-threatening". As an example, a laboratory abnormality of Grade 4 does not need to be reported as an SAE, unless it meets one of the seriousness criteria in **Section 9.1.4**.

9.2.4 Relationship to Investigational Medicinal Product/Pan-HER

The Investigator must assess causal relationship to the IMP, Pan-HER. Relatedness has to be assessed and recorded within the initial report (CRF and SAE report form).

The causal relationship is an assessment of whether or not the event is related to the use of the IMP. It is not an evaluation of whether or not the event could hypothetically occur in the investigational patient population.

The causal relationship of an AE to the IMP, Pan-HER, will be rated as follows:

Not Related: The AE is not related to the IMP, which means the event:

- Does not follow a reasonable temporal sequence from drug administration
- Is readily explained by the patient's clinical state or by other modes of therapy administered to the patient
- The AE is clearly NOT related to the IMP

Unlikely Related: The AE is considered not related to the IMP based on the following:

- Does not follow a reasonable temporal sequence from administration of drug
- Could readily be a result of the patient's clinical state, environmental, or toxic factors, or other modes of therapy
- Does not follow a known response pattern to the suspected drug
- Does not reappear or worsen when the drug is re-administered

Possibly Related: The AE might not be related, but possibility cannot be ruled out with certainty and therefore would be considered related based on:

- Follows a reasonable temporal sequence from administration of drug
- Could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy
- Follows a known response pattern to the suspected drug

Probably Related: It has been determined with a high degree of certainty that the AE is associated with administration of IMP based on:

- Follows a reasonable, temporal sequence
- Cannot be reasonably explained by known characteristics of the patient's clinical state, environmental, or toxic factors, or other modes of administered therapy
- The AE disappears or decreases in severity upon cessation of drug, or reduction in dose.
- Follows a known response pattern to the suspected drug

Related: The AE is related to the IMP, which means the event:

- Follows a reasonable temporal sequence from drug administration
- Abates upon discontinuation of the IMP (de-challenge)
- Is confirmed by reappearance of the reaction on repeat exposure (re-challenge)
- Cannot be reasonably explained by the known characteristics of the patient's clinical state
- Is not likely to have been produced by the patient's clinical state or by other modes of therapy administered to the patient

9.2.5 Outcome

Outcome of the AE must be assessed by the Investigator utilizing one of the following terms:

- Recovered
- Recovered with sequelae (if recovered with sequelae, specify sequelae)
- Not recovered
- Fatal
- Unknown

Instructions for reporting changes in an ongoing AE during a patient's participation in the trial are provided in the instructions that accompany the AE CRF pages.

9.2.6 Follow-up of Adverse Events

All AEs should be followed until resolution or until the 1M FUP Visit, whichever comes first.

Note: Patients who sign informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

9.3 Serious Adverse Event Recording and Reporting

9.3.1 Timeframes for Reporting to the Sponsor

All SAEs occurring at any time from signing of informed consent for participation in the trial and until the 1M FUP Visit must be recorded on the SAE Report Form and recorded as an SAE in the CRF.

Note: Patients who sign informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

In case of an SAE, the Investigator must, within 24 hours of first awareness of the event, report the SAE to the Sponsor or designee by fax or e-mail transmission. Fax number(s) and e-mail address(es) will be stated on the SAE Report Form and the SAE Report Form Completion Instructions. SAE follow-up information must also be reported to the Sponsor or designee within 24 hours of awareness.

SAEs still ongoing after the 1M FUP Visit should be followed on a regular basis according to the Investigator's clinical judgment, until the event has been resolved or until the Investigator assesses it as chronic or stable. The Sponsor or designee will pursue sufficient information and will return to the trial sites for such information as deemed required.

If the Investigator becomes aware of an SAE that occurred after the 1M FUP Visit and finds it to be related to the IMP (possibly-, probably-, or related to Pan-HER) or trial conduct, it must be recorded and reported to the Sponsor or designee as an SAE. These SAEs considered related to the IMP and occurring after the 1M FUP Visit will not be reported in the CRF but only on an SAE Report Form instead for recording in the safety database.

The Investigator should be aware of local reporting regulations to the Institutional Review Board (IRB)/Ethics Committee (EC). The Sponsor or designee will either supply the Investigator with the reports, which should be forwarded to the IRB/EC, or report directly to the IRB/EC depending on local regulations.

9.4 Safety Reporting to Health Authorities, Institutional Review Boards/Ethics Committees, and Investigators

Reportability of an SAE as a "Suspected Unexpected Serious Adverse Reaction" (SUSAR) will be determined solely by the Sponsor, based on seriousness, causality, and expectedness criteria.

In addition to SUSARs, the Sponsor or designee is responsible for reporting all relevant safety information regarding SUSARs, or other safety developments, to appropriate HAs and central IRBs/ECs, as well as participating investigators. Reporting of SUSARs to local IRBs/ECs will be handled by the Investigator.

The timeline for notification of SUSARs is within 7 calendar days for fatal/life-threatening events and within 15 calendar days for all other SUSARs.

Additionally, the annual Development Safety Update Report (DSUR) will be submitted by the Sponsor or designee to all appropriate HAs and central IRBs/ECs as per ICH Guidelines. Submission of the DSUR to local IRBs/ECs will be handled as per local regulations and/or requests.

9.5 Dose-Limiting Toxicities (Part 1 Only)

9.5.1 Definition of Dose-Limiting Toxicities

A DLT is defined as any of the following toxicities that occur during the DLT-observation period, if considered related (causality rating of possibly, probably, or related) to Pan-HER:

1. Grade 3 non-hematologic toxicity regardless of duration, with the exception of:
    a. Grade 3 nausea, vomiting, diarrhea, or fatigue lasting ≤2 days with best supportive care
    b. Grade 3 asymptomatic electrolyte abnormality that is not considered clinically significant by the Investigator and that is controlled with medical therapy
2. Grade 4 non-hematologic toxicity, with the exception of:
    a. Grade 4 asymptomatic electrolyte abnormalities that is not considered clinically significant by the Investigator and that is controlled with medical therapy
3. Neutropenia that is:
    a. Grade 3-4 febrile neutropenia
    b. Grade 4 and sustained (i.e., ANC $<0.5 \times 10^9$/L [500/mm^3], duration >5 days)
4. Thrombocytopenia that is
    a. Grade 3 with clinically significant hemorrhage

b. Grade 4 (platelets <25 $\times 10^9$/L [25,000/mm^3])

5. AST/ALT elevation >3×ULN with bilirubin elevation >2×ULN without evidence of cholestasis that cannot be explained by factors not related to Pan-HER

6. Evidence of cardiac toxicity as defined by either:

   a. ≥16% absolute decrease in LVEF from baseline, or

   b. LVEF below the institutional lower limit of normal and ≥10% absolute decrease in LVEF from baseline

7. Inability to complete Cycle 1 at the assigned dose due to ≥ Grade 3 toxicity

8. Treatment delays >2 weeks from the scheduled next dose due to ≥ Grade 3 toxicity

9.5.2 Observation Period for Dose-Limiting Toxicities

The decision to dose-escalate will be based on close monitoring of safety during the observation period for DLTs, defined as the initial 28-day period (±2 days) from first treatment of Pan-HER (i.e., Cycle 1) and including 7 days of follow-up (Q1W dosing) or 14 days of follow-up (Q2W dosing) from the last dose of Cycle 1.

A minimum of 4 Pan-HER infusions (Q1W dosing) or 2 Pan-HER infusions (Q2W dosing) must have been administered at the assigned dose for a patient to have completed the DLT-observation period.

9.5.3 Reporting of Dose-Limiting Toxicities

All presumed DLTs must be reported to the Sponsor or designee within 24 hours after the Investigator or designee have become aware of the event. In addition, DLTs fulfilling the SAE criteria must be reported according to the procedure for SAEs, as outlined in **Section 9.3**.

9.6 Reporting of Infusion-Related Reactions

The definition of an IRR is included in **Section 7.1.3.6**.

All IRRs must be reported in the CRF as an AE with the term “Infusion-related Reaction” followed by a specification of symptoms (e.g., “Infusion-related Reaction with dyspnea and flushing”).

To facilitate ongoing safety review throughout the course of this trial, the occurrence of ≥ Grade 2 IRRs must be reported to the Sponsor or designee within 24 hours of occurrence. As always, any IRR fulfilling the SAE criteria must be reported as per **Section 9.3**.

9.7 Pregnancy

If any trial patient becomes pregnant during the course of the trial, the patient must be discontinued from Pan-HER immediately and the pregnancy must be reported to the Sponsor or designee according to the same timelines as for an SAE. While pregnancy is not considered an AE, all pregnancies are tracked as SAEs within the safety database in order to follow-up on exposure to the fetus/infant.

Pregnancies reported in female partners of male trial patients must also be included in the safety database; therefore, a female partner of a male patient on the trial who becomes pregnant will be approached for consent to have the pregnancy followed until term and reported upon to the Sponsor or designee.

All pregnancies must be followed up every third month to determine outcome and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs as appropriate. Elective terminations for non-medical reasons should be reported as follow-up, but not as a separate AE/SAE unless complications meet AE/SAE criteria. Spontaneous abortion must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the trial and considered by the Investigator as possibly-, probably-, or related to Pan-HER must be promptly reported to the Sponsor or designee.

All pregnancy information including follow-up information must be reported on a designated pregnancy form provided by the Sponsor or designee.

10. STATISTICS

10.1 Sample Size Considerations

The primary endpoint of Part 1 is occurrence of DLTs during Cycle 1 for each of the Pan-HER dosing regimens. The number of enrolled patients will depend on the extent of observed DLTs independently in each cohort. Please refer to **Section 7.1.3.2** for a description of planned dose levels and decision points for dose-escalation. Based on the dose-escalation design, it is planned to enroll approximately 34 patients during the dose-escalation part of the trial.

In Part 2 of the trial, the primary endpoint is documented OR, defined as documented PR or CR assessed by RECIST v1.1 at any time during trial participation, with radiologic evaluation to be performed locally.

During Part 2, it is planned to enroll and treat approximately 100 patients. The planned number of patients to be enrolled might be adjusted when the 4 dose-expansion cohorts (i.e., based on defined molecular profiles(s) and tumor types) have been selected. The protocol amendment defining the dose-expansion cohorts will contain a detailed sample size calculation covering the four expansion cohorts, including expected range of OR.

10.2 Analysis Population

Two analysis sets will be defined in accordance with the consolidated ICH E9 GCP guidelines.

The Full Analysis Set (FAS) will comprise all enrolled patients who have received at least one dose of Pan-HER. The FAS will be used for evaluation of all endpoints except evaluation of DLTs. The patients in the FAS will contribute to the analyses as allocated to treatment. For the evaluation of PK endpoints, patients, full profiles, or single measurements can be excluded from the analyses. The decision of excluding patients, full profiles, or part of profiles will be described in the clinical trial report (CTR).

The DLT Analysis Set will comprise all patients in the FAS enrolled in Part 1, except patients who did not complete Cycle 1 for reasons other than drug toxicity. The DLT Analysis Set will be used for evaluation of DLTs.

10.3 Primary Endpoint and Analysis

10.3.1 Part 1, Dose-Escalation

The primary objective of the dose-escalation part is to assess the safety and tolerability of Pan-HER. This will be assessed by the primary endpoint for Part 1: occurrence of DLTs during Cycle 1 for each of the Pan-HER dose regimens.

All DLT events will be listed by dose cohort and patient. A summary table of DLTs across dose cohorts by System Organ Class (SOC) and preferred term will be presented, if applicable. The summaries will include number of DLTs, number, and percentages of patients experiencing a DLT. The definition of a DLT is included in **Section 9.5.1**.

The MTD is defined as the highest dose with a maximum of 1 out of 6 patients experiencing a DLT. The MTD may or may not be found within the dose levels tested. Based on an overall evaluation of the dose-escalation part, the RP2D to be used in Part 2 will be selected. The RP2D may be equal to or lower than the MTD.

10.3.2 Part 2, Dose-Expansion

The primary objective of Part 2 is to evaluate the antitumor effect of Pan-HER when administered at the RP2D and regimen to patients with advanced epithelial malignancies without available therapeutic options. Four (4) dose-expansion cohorts will be evaluated. This will be assessed by the primary endpoint for Part 2: documented OR, defined as documented PR or CR assessed by RECIST v1.1 at any time during trial participation, with radiologic evaluation to be performed locally.

Number and percentages of patients with documented OR will be presented including corresponding 95% exact Clopper-Pearson Confidence Intervals (CI) for binomial proportion. The summaries will be presented for each tumor type separately.

10.4 Secondary and Exploratory Endpoint and Analysis

All statistical analyses of the secondary and exploratory endpoints for both phases will be descriptive unless otherwise specified. Details will be specified in a separate statistical analysis plan.

In the following sections, ‘cohort’ refers to dose cohort for Part 1 and tumor type for Part 2. Thus, summaries by trial part and cohort will be presented by dose cohorts within Part 1 and tumor types within Part 2.

10.4.1 Efficacy Endpoints and Analyses

All statistical analysis of the secondary endpoints will be presented using the FAS.

The following anti-tumor response endpoints will be measured in Part 1:

- Documented OR, defined as documented PR or CR, from baseline to end of trial participation (in patients with measurable disease only)

The following anti-tumor response endpoints will be measured in Part 2:

- Changes in sum of diameters of target lesions from baseline to end of trial participation
- SD for >16 weeks from baseline
- Time to documented PD, death, patient withdrawal or end of trial participation, whichever comes first
- Overall survival (OS)

Best overall response by RECIST v1.1 will be summarized by trial part and cohort by means of counts and percentages for the categories CR, PR, SD, PD, and NE.

Number and percentages of patients with documented OR in the dose-escalation part will be presented including corresponding 95% exact Clopper-Pearson CI. All documented ORs (Part 1 and Part 2) will be listed including duration (in days) of OR, measured from time of first PR or CR to PD.

Duration of SD is calculated from baseline until first measurement of PD. The number and percentages of patients with SD for more than 16 weeks will be presented by trial part and tumor type.

Time to documented PD, death, patient withdrawal or end of trial participation, whichever comes first, will be presented in a Kaplan-Meier plot. The median progression free survival time, including 95% CI, will be derived. There will be one plot for Part 1, and plots for each of the 4 tumor types in Part 2.

10.4.2 Other Efficacy Assessments

Tumor markers will be listed and summarized as appropriate.

10.4.3 Safety Endpoints and Analyses

The safety endpoints are presented below and will all be presented for the FAS by trial part and tumor type. Safety data will only be presented descriptively, and no formal statistical analyses will be performed.

In Part 1 and Part 2 of the trial, the following safety endpoints will be assessed:

- Nature, incidence and severity of AEs measured from baseline to end of trial participation
- AEs leading to dose-reductions, dose delays and permanent treatment cessation
- Changes in safety laboratory values from baseline to end of trial participation
- Changes in vital signs and physical examinations from baseline to end of trial participation
- Occurrence of ADA to Pan-HER measured in serum at selected timepoints from baseline to end of trial participation

10.4.3.1 Adverse Events

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) current version. AEs will be regarded as treatment emergent AEs (TEAEs) if they occur after first treatment. Non-treatment emergent AEs (non-TEAEs) are defined as AEs collected before dosing. TEAEs will be presented by SOC and preferred term unless stated otherwise. The frequencies of TEAEs will be presented including number and percentages of patients having experienced an event and the total number of events.

AEs including SAEs are reported from signing of the informed consent for participation in the trial and until the end of trial participation. SAEs reported outside the required reporting window are only entered into the safety database and will be described separately in the report.

Note: Patients who sign informed consent and are subsequently deemed to be screening failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

All AEs will be listed. The AEs will be presented using summary tables by trial phase including:

- AEs, in total and sorted by frequency
- AEs by relationship
- AEs by Grade and maximum Grade
- SAEs, in total, and by relationship

- AEs leading to withdrawal from treatment
- AEs leading to trial drug interruption or dose reduction
- Fatal AEs

10.4.3.2 Clinical Laboratory Values

Biochemistry, hematology, and coagulation parameters will be presented using box plots by visits and by trial part and tumor type. In addition, individual patient biochemistry, hematology, and coagulation parameters during the trial will be presented graphically using longitudinal plots. Urinalysis parameters will be summarized using descriptive statistics.

Laboratory values outside normal range will be flagged, and all laboratory values will be listed including grading of abnormal values.

10.4.3.3 Other Safety Assessments

Change in vital signs from baseline to end of trial participation will be summarized by visit, trial part and tumor type. Normal and abnormal findings in physical examination and ECG measurements will be presented in shift tables by visit, trial part and tumor type.

ECOG PS, body weight and ADA results will be listed.

10.4.4 Pharmacokinetic Endpoints and Analyses

The PK endpoints with Q1W dosing will be derived based on the concentration time curves of Pan-HER after the first and fourth infusion of Pan-HER in both parts of the trial, as applicable.

The PK endpoints with Q2W dosing will be derived based on the concentration time curves of Pan-HER after the first and third infusion of Pan-HER in both parts of the trial, as applicable. Refer to **Table 13**. The serum concentration of total Pan-HER will be derived as the sum of the serum concentration of all six constituting antibodies. Supporting plots and PK parameters for the individual antibodies will also be generated.

Table 13 Pharmacokinetic (PK) Endpoints, Definitions, and Derivations

Symbol	Definition and derivation
C_{trough}	Trough concentration (i.e., concentration of Pan-HER measured pre-infusion)
AUC_{τ}	Area under the concentration-time curve in a dosing interval (i.e., from time zero (end of infusion) up to 168 hours). AUC_{τ} will be calculated using the linear trapezoidal method and interpolated in case of measurements after 168 hours, or extrapolated using terminal rate constant and the last quantifiable concentration
$AUC_{\tau 0}$	Area under the concentration-time curve from start of infusion up to 168 hours. $AUC_{\tau 0}$ will be calculated similar to AUC_{τ}
$AUC_{norm, \tau}$	Dose normalized area under the concentration-time curve in a dosing interval, calculated as AUC_{τ} divided by the dose infused
C_{max}	Maximum concentration
T_{max}	Time to reach maximum concentration
C_{EOI}	Concentration at End of Infusion
λ_z	Terminal rate constant (negative of the slope of an ln-linear regression of the un-weighted data considering the terminal phase of the concentration-time curve ≥ limit of quantification). λ_z is not an endpoint, but is used for derivation of endpoints
$T_{½}$	Terminal elimination half-life, calculated as $\ln(2)/ \lambda_z$
CL_S	Clearance after first dose, calculated as $Dose/AUC_{inf}$ for C1/D1, where AUC_{inf} will be calculated as the sum of the area from time zero to time of last quantifiable concentration, t_z, and the area from t_z to infinity. The second area will be estimated using the observed concentration at t_z and the terminal rate constant
CL_{SS}	Clearance after 4th dose, calculated as $Dose/AUC_{\tau}$
V_S	Volume of distribution during the terminal phase after first dose (CL_S/ λ_z)
V_{SS}	Volume of distribution during the terminal phase after 4th dose (CL_{SS}/ λ_z)

C_{max}, C_{EOI}, C_{trough} and T_{max} will be derived from observed data while AUC_{τ}, $AUC_{\tau 0}$, $AUC_{norm, \tau}$, CL_S, CL_{SS}, V_S, V_{SS}, and $T_{½}$ will be estimated using non-compartmental methods and actual time points.

Individual curves of serum concentration of total Pan-HER versus time after the first and fourth infusion of Pan-HER with Q1W dosing, and after the first and third infusion of Pan-HER with Q2W dosing, will be presented on log- and linear scale for all patients in the FAS. Furthermore, trough serum concentrations for the period from first dose to EOT will be presented on linear scale individual plots. In addition, mean concentration time curves will be presented on linear

scale using nominal time point by cohort and trial part. All PK endpoints will be listed and summarized by trial part and cohort.

10.4.5 Additional Endpoints and Analyses

The following additional endpoints will be assessed in Part 1 and Part 2 of the trial:

- EGFR and HER3 receptor down modulation in skin biopsies, measured by percentage and nominal difference in target expression from baseline to end of Cycle 2
- EGFR, HER2 and HER3 receptor down modulation in tumor biopsies (may not be available in Part 1), measured by percentage and nominal difference in target expression from baseline to end of Cycle 2
- Biomarkers relevant to Pan-HER activity
- Tumor genetics, drug target genes, and other biomarker genes that are known to be involved in the development and progression of epithelial malignancies

The additional endpoints, outlined above may include genes and/or proteins that are unknown or have not been included in the scientific hypotheses at the present time of trial, but that, during the collection of data from this trial, may evolve as new candidate genes and markers related to Pan-HER safety, efficacy, or mechanism of action.

Percentage and nominal change in target expression from baseline to end of Cycle 2 or PD (whichever comes first) in skin and tumor biopsy samples will be presented by trial part and tumor type using descriptive statistics including scatter plots of values at end of Cycle 2 versus baseline.

Potential biomarkers include genes, gene transcripts and proteins of the receptor tyrosine kinases (RTKs) and molecules of the EGFR signaling pathway. All biomarkers will be listed.

Exploratory analysis using the biomarkers might be performed.

10.5 Interim Analysis

No interim analysis is planned for this trial.

All relevant safety, PK and toxicity data will be reviewed on an ongoing basis throughout the trial. Please refer to **Section 12**.

Based on an overall evaluation of Part 1 of the trial, the RP2D will be chosen.

10.6 Deviations from the Statistical Plan

Any deviation(s) from the original analysis plan will be described in a protocol amendment and/or in a statistical analysis plan and/or in the final CTR, as appropriate.

10.7 Modelling of Pharmacokinetics and Pharmacodynamics

PK samples will be analyzed on an on-going basis during the trial. These preliminary data will be evaluated by non-compartmental and/or compartmental methods.

All data collected in this trial may be used for modelling of PK and pharmacodynamics to support the planning and dose setting within the current trial as well as for future trials. Preliminary data generated during the trial may be used for exploratory modelling. The final data, i.e.. after database lock, will be used for the final model and potentially for cross-trial modelling. These modelling activities will be reported separately from the current trial.

11. ETHICS

11.1 Institutional Review Board/Ethics Committee

An IRB/EC will review the protocol and any amendments and advertisements used for recruitment, as well as the informed consent documents, their updates (if any), and any other written materials given to the patients. The CTR will include a list of all IRBs/ECs to which the protocol has been submitted and the name of the committee chair.

11.2 Patient Information and Informed Consent

The Investigator or his/her designee must obtain written informed consent from each patient before any trial related procedures are performed. Each patient must receive full patient information before giving consent. The patient information must contain full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved.

Before signing the informed consent form the patient must be given sufficient time to consider his/her possible participation. Each patient must also be informed about his/her right to withdraw from the trial at any time.

Each patient must sign the informed consent form. The informed consent form must be signed and dated both by the patient and by the Investigator or designee providing the information to the patient. The patient receives a copy of the signed form and the original is retained in the Investigator Site File (ISF).

12. SAFETY SURVEILLANCE SET-UP

12.1 Safety Review

An SMC will be established. This committee will include Investigator(s), Medical Monitor(s), and Sponsor's medical representatives. The SMC will review clinical and laboratory safety data regularly throughout the trial and make decisions regarding the advisability of continuing accrual to a particular dose cohort, and/or escalating the dose and allowing accrual to a higher dose cohort. In order to do so, the Investigator must ensure to report safety data to the Sponsor or designee in a timely manner. This includes, but is not limited to:

- SAEs must be reported within 24 hours of awareness (SAE report form)
- DLTs must be reported within 24 hours of occurrence
- IRRs of ≥ Grade 2 must be reported within 24 hours of occurrence
- All AEs will be reported in the CRF in a timely manner
- Dose-modifications (i.e., dose-reduction, temporary interruptions regardless of cause) will be reported in a timely manner
- Local laboratory data will be reported in the CRF in a timely manner

Availability of these data will enable the Sponsor to act promptly in response to safety signals and to ensure that HAs, as well as Investigators, who may be participating in other Pan-HER clinical trials, are informed of events occurring during this trial.

Regular safety teleconferences will be held between the trial site(s) and the Sponsor and/or designee. Such safety teleconferences may fluctuate in frequency based on accrual and trial activity, as indicated. Patients will be carefully evaluated for evidence of all AEs, including potential cumulative and/or delayed toxicities throughout the duration of their time in the trial.

12.2 Other Safety Surveillance Activities

At least one Medical Monitor is assigned to review and evaluate relevant clinical/safety information concerning the clinical trial. The responsibilities of the Medical Monitor include, but are not limited to:

- Evaluation of coding and trending of AEs in conjunction with the Drug Safety physician
- Performing surveillance on potential safety signals in conjunction with the Drug Safety physician
- Evaluating abnormal laboratory values

- Providing medical support to the Sponsor in answering questions related to the protocol
- Updating the SMC on trial status at scheduled meetings

A Drug Safety physician is assigned to review, assess, and approve all SAE cases and associated reports. This physician will also perform the following:

- Assess for safety signals and trends in conjunction with the Medical Monitor
- Assist with questions regarding medical coding of SAEs
- Discussing with the Sponsor Chief Medical Officer, any cases which may present a concern with regard to a signal or safety issue.

13. MONITORING AND QUALITY ASSURANCE

13.1 Compliance with Good Clinical Practice

The responsibilities of the Sponsor, the Monitor, and the Investigator are defined in ICH E6(R2) GCP, and applicable regulatory requirements in the country where the trial takes place. The Investigator is responsible for adhering to the ICH E6(R2) GCP responsibilities of the Investigators, and for dispensing IMP only in accordance with this protocol or a signed amendment, and for its storage and safe handling throughout the trial.

13.2 Source Documents

The Investigator will maintain adequate and accurate records for each patient treated with study drug. Source documents, including but not limited to, hospital, clinic or office charts; laboratory reports; radiology and pathology reports; pharmacy records; study worksheets; anonymized photographs aimed at documenting study-associated clinical findings; and signed ICFs, must completely reflect the nature and extent of the patient's medical care, must be included in the Investigator's files along with patient study records, and must be available for source document verification against entries in the CRF.

Each trial site will permit authorized representatives of the Sponsor and relevant HAs direct access to (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the trial safety and progress. The Sponsor (or designee) will check CRF entries against source documents according to the guidelines of ICH E6(R2) GCP. Data not requiring a separate written record (i.e., data which may be recorded directly in the CRF) will be determined before trial start.

The ICF will include a statement by which patients allow the Sponsor (or designee), as well as authorized regulatory agencies, to have direct access to source data that support data in the CRF (e.g., patient medical files, appointment books, original laboratory records, etc.). The Sponsor (or designee), bound by confidentiality and privacy regulations, will not disclose patient identities or personal medical information.

13.3 Monitoring

Monitoring visits to the trial sites will be made periodically during the trial to ensure that all aspects of the protocol are followed. The Investigator must give the Sponsor and/or their representatives direct access to all relevant source documents to confirm consistency with the CRF entries. Source Data Verification will be conducted according to Sponsor or designee

Standard Operating Procedures (SOPs) and requirements will be specified in a trial specific monitoring plan.

It is important that the Investigator and their relevant personnel are available during monitoring visits and possible audits and that sufficient time is devoted to the process.

14. HANDLING AND PROCESSING OF DATA

14.1 Data Handling

Study data collection, processing, transfer, and reporting, as well as handling of study personnel information, will be done in compliance with ICH E6(R2) GCP and all applicable data protection regulations, including Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation).

14.2 Recording of Data

Clinical trial data for this study will be captured in an electronic format. Electronic data capture (EDC) services will be provided by a vendor to be determined by the Sponsor. The Investigator agrees to provide all information requested in the CRF in an accurate manner according to instructions provided. CRFs are designed for computer processing and analysis. All data must be carefully entered to permit meaningful interpretation. Corrections to entered data will be identified and tracked by audit trails within the EDC system. Data must be entered into CRFs in a timely fashion.

A CRF is required to be submitted for every patient who receives any amount of study drug. This includes submission of retrievable data on patients who withdraw before completion of the study. Prior to submission, CRFs must be reviewed for completeness and accuracy, and signed and dated where indicated, by either the Principal Investigator or a physician Sub-Investigator whose name is listed on the Form FDA 1572 for this study.

All collected data will be entered into a validated database.

14.3 Data Review During this Study

Data obtained from the study will be reviewed in a timely manner throughout by the Sponsor (or designee) and Sponsor's Medical Representative(s) to assess safety and the progress of the project.

14.4 Data Protection

The Investigator, Sponsor, and Sponsor designee(s) will ensure that the confidentiality of the patients' data is preserved. Each participating site will maintain appropriate medical and research records for this trial in compliance with ICH E6(R2) GCP and regulatory and institutional requirements for the protection of confidentiality of patients.

14.5 Data Transactions and Access

The trial data and any other documents transferred to the Sponsor or designee will not contain patient names or other confidential personal data, but patients will be identified using the assigned trial specific patient numbers.

When data are transferred to the Sponsor or designee, access will be limited to relevant persons.

The Investigator will maintain documents that are not for collection by the Sponsor, e.g., patient identification list and the signed informed consent forms.

14.6 Case Report Form

The Investigator or designee will be responsible for entering trial data in the CRF provided. It is the responsibility of the Investigator to ensure the accuracy of the data entered in the CRF.

All collected data will be entered into a validated database.

14.7 Data Processing

A Data Management Plan (DMP) will be prepared for this trial. The Sponsor (or designee) will be responsible for data processing in accordance with applicable Data Management SOPs and the trial DMP.

Once recorded within the electronic CRF, study data will pass through a set of preprogrammed data validation checks designed to identify inconsistencies and other data errors, and also will undergo an additional study-specific data review process, as stated above in **Section 14.3**. Data issues will be queried via the EDC system and query resolutions will be documented.

Entry and processing of data other than those directly recorded on electronic CRFs by trial sites (e.g., imports of laboratory results) will follow vendor(s) SOPs. Transfer of such data from vendor(s) to Sponsor (or designee) will be handled according to vendor(s) data transfer SOPs and the Sponsor data transfer requirements with full compliance to applicable regulations.

Database Lock will occur upon reaching the predefined data cut-off for primary analysis and completion of Sponsor's (or designee's) quality control and quality assurance procedures.

Portable Document Format (PDF) files of the electronic CRFs will be provided to the Investigator upon removal of access to the electronic CRFs.

14.8 Retention of Trial Documents at Site

The Investigator at each trial site must make arrangements to store the essential trial documents (including the ISF) after the end of trial according to ICH E6(R2) GCP and local requirements.

In addition, the Investigator is responsible for archiving all relevant source documents so that the trial data can be compared against source data after completion of the trial, e.g., in case of inspection from authorities.

The Investigator is required to ensure the continued storage of the documents, even if the Investigator should leave the clinic/practice or retire before the end of the required storage period.

14.9 Compliance with the General Data Protection Regulation

The applicable data protection legislation requires that parties enter into a written contract if one party (data processor) processes personal data on behalf of the other party (data controller). This written contract must regulate the subject-matter and duration of the processing, the nature and purpose of the processing, the types of personal data and categories of data subjects, as well as the obligations and rights of the data controller. Accordingly, the parties must enter into a data processing agreement. To the extent the processing of personal data involves transfers of personal data to third countries (e.g., jurisdictions outside of the European Economic Area [EEA]), the parties will enter into the European Commission's standard contractual clauses between the data controller, the data processor, and all sub-processors, if any. The European Commission's standard contractual clauses ensure an adequate level of protection in relation to transfers of personal data to third countries.

15. REGISTRATION AND COMMUNICATION OF RESULTS

15.1 Use of Information

All unpublished information relating to this trial and the IMP is considered confidential by the Sponsor and shall remain the sole property of the Sponsor. The Investigator must accept that the Sponsor may use information from this trial in connection with the development of the IMP, and therefore, may disclose it as required to Investigators, government-licensing authorities, HAs of other governments, stock exchange market and commercial partners.

15.2 Registration and Publication

The trial will be registered in one or more public trial registries and results will be reported according to current legislation. The trial results will be posted in the same clinical trial registries as the initial registration(s) in accordance with the latest International Committee of Medical Journal Editors (ICMJE) recommendations (URL: www.icmje.org).

The Sponsor acknowledges the Investigators' rights to publish the full results of the trial, regardless of the outcome, in accordance with the latest ICMJE recommendations.

The Coordinating Investigator and the Sponsor will decide on the publication strategy. The Coordinating Investigator has the right to publish and present the results and methods as first or last author of multicenter publications. Co-authorship will be decided by the Sponsor and the Coordinating Investigator and will be limited to a number of persons who have contributed substantially to the trial. The Sponsor will have representation in the list of authors.

Publication is subject to the following conditions:

- No publication before the completion of the trial at all participating trial sites without preceding written approval from the Sponsor
- Publications shall not disclose any Sponsor confidential information and property (not including the trial results)
- The Sponsor reserves the right to review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days. The Sponsor cannot require changes to the communication and cannot extend the embargo

16. INSURANCE AND LIABILITY

The Sponsor will take out Human Clinical Trials Insurance for its legal liability in accordance with laws and regulations, and with limits customary or required by law in the territory in question.

17. CHANGES TO THE FINAL CLINICAL TRIAL PROTOCOL

Changes to the protocol will not be implemented without agreement from the Sponsor and prior review and written approval from the HA and IRB/EC, except where necessary to eliminate an immediate hazard to the patient. No protocol waivers will be allowed.

18. PREMATURE TERMINATION OF THE TRIAL OR A TRIAL SITE

18.1 Premature Termination of the Trial

If the Sponsor, the Coordinating Investigator, or the SMC discovers conditions arising during the trial, which indicates that the trial should be halted, the trial can be terminated after appropriate consultation between the Sponsor, the SMC, and the Coordinating Investigator. The HA and IRB/EC will be notified in writing. The reason will be stated.

Conditions that may warrant termination of the trial include, but are not limited to the following:

- The discovery of an unexpected and significant or unacceptable risk to the patients enrolled in the trial
- The discovery of lack of efficacy
- Failure of the Investigators to enter patients at an acceptable rate in the trial as a whole
- A decision on the part of the Sponsor to suspend or discontinue development of the IMP

18.2 Premature Termination of a Trial Site

The Sponsor can also decide to terminate single trial sites prematurely. Conditions that may warrant termination include, but are not limited to the following:

- Insufficient adherence to protocol requirements
- Failure to enter patients at an acceptable rate

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20. APPENDICES

Appendix 1: Summary of Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

For details, see Eisenhauer EA, Therasse P, Bogaerts J, et al (2009). New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) (22).

Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

Measurable:

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

Non-measurable:

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability:

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are non-measurable.

Cystic lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts
- "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions

Lesions with prior local treatment

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

Methods of Measurement

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study

- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung

- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans)

- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement

- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint

- Tumor markers: Tumor markers alone cannot be used to assess objective tumor response

- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD

Tumor response evaluation

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is

the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. Response criteria are listed in **Table 14** and **Table 15**.

Table 14 Response Criteria for Evaluation of Target Lesions

	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

Table 15 Response Criteria for Evaluation of Non-Target Lesions

	Evaluation of Target Lesions
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression)
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Evaluation of Best Overall Response

It is assumed that at each protocol specified time point, a response assessment occurs. **Table 16** provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 16 Overall Response Status for Patients with Baseline Measurable Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviation: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of CR or PR is NOT required:

Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered NE.

Best response determination in trials where confirmation of CR or PR is required:

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as shown in **Table 17**.

Table 17 Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[1]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Abbreviation: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

1) If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

21. SUMMARY OF CHANGES

21.1 Protocol Amendment 1 dated 03-Oct-2016

- Modified inclusion criteria for Part 1 and 2 to clarify that patients must have received all therapy known to confer clinical benefit in order to be eligible for inclusion
- Modified withdrawal criteria to include that the need for more than three dose-reductions of Pan-HER will lead to treatment withdrawal
- Modified dose-delay criteria
- Modified dose-reduction criteria
- Modified the definition of dose-limiting toxicities (Part 1 only) by removing the exception of Grade 3 IRR that is transient

Refer to **Table 18** for the changes in Protocol Amendment 1.

Table 18 Protocol Amendment 1

SECTION	ORIGINAL TEXT	NEW TEXT
1. Synopsis Main Inclusion and Exclusion Criteria	Documented (histologically- or cytologically-proven) epithelial malignancy that is locally advanced or metastatic and that is refractory to standard therapy or for which no standard therapy is available	Documented (histologically- or cytologically-proven) epithelial malignancy that is locally advanced or metastatic, having received all therapy known to confer clinical benefit
6.1 Inclusion Criteria	Documented (histologically- or cytologically-proven) epithelial malignancy that is locally advanced or metastatic and that is refractory to standard therapy or for which no standard therapy is available	Documented (histologically- or cytologically-proven) epithelial malignancy that is locally advanced or metastatic, having received all therapy known to confer clinical benefit
6.3.1 Withdrawal from Treatment	*Not applicable*	*Added withdrawal criteria:* Need for more than three dose-reductions of Pan-HER
7.1.4.2 Dose-Delays for Pan-HER-Related or Disease-Related Toxicities	1. ANC >1.0 ×10^9/L (1000/mm^3) 2. Platelet count >60 ×109/L (60,000/mm3)	1. ANC >1.5 ×10^9/L (1500/mm^3) 2. Platelet count >75 ×10^9/L (75,000/mm^3)
7.1.4.3 Dose-Reduction for Pan-HER-Related Toxicities	c. Grade 3 IRR that is transient (resolving ≤6 hours from onset)	*Removed* *New text added:* Need for more than three dose-reductions of Pan-HER will lead to withdrawal from treatment. *Table 8 and footnote updated*

SECTION	ORIGINAL TEXT	NEW TEXT
9.5.1 Definition of Dose-Limiting Toxicities	c. Grade 3 IRR that is transient (resolving ≤6 hours from onset)	*Removed*

21.2 Protocol Amendment 2 dated 14-Nov-2016

- Clarified exclusion criteria #2 by allowing radiotherapy against target lesions within 4 weeks prior to C1/D1, provided there is documented progression of the lesion following the radiotherapy
- Clarified exclusion criteria #12a by providing specific examples of inflammatory bowel disease that would exclude the patient
- Clarified exclusion criteria #14i that the Investigator will decide whether the patient can be considered to be on a stable dose of anticoagulant therapy
- Deleted exclusion criteria related to HIV and hepatitis B or C
- For Part 2 ONLY: included continued follow-up for response and/or overall survival after the 1M FUP Visit and added related secondary endpoint of overall survival
- Clarified that the retreatment criteria must be evaluated at minimum prior to each Cycle 1 dose and prior to D1 and D15 doses each cycle thereafter.
- Modified retreatment criteria #4 by allowing Grade 2 clinical events that are being adequately controlled with best supportive care and asymptomatic laboratory abnormalities that are considered clinically insignificant or that are resolving with medical therapy
- Recommended that informed consent be obtained no earlier than 4 weeks prior to the planned C1/D1
- Clarified that the local assessment of archival tumor tissue for EGFR and HER2 is preferred done by immunohistochemistry (IHC)
- Updated events not to be considered as AEs to include PD, unless the nature of the PD is different than expected
- Updated timelines for reporting of SAE Follow-up information
- Included other minor updates and clarifications

Refer to **Table 19** for the changes in Protocol Amendment 2.

Table 19 Protocol Amendment 2

SECTION	ORIGINAL TEXT	NEW TEXT
1. Synopsis: Trial Periods 5.3.4 End of Treatment and Follow-up Visit 6.3.2 Withdrawal from Trial 8.10 Follow-up Assessments	*Not applicable*	**Part 2 ONLY, continued follow-up for response and/or overall survival:** After the 1M FUP Visit, the Investigator will make every effort to obtain follow-up information on response assessment and/or overall survival (OS) every 2 months. Response assessment follow-up is required in the event of an ongoing stable disease (SD) or objective response (OR, defined as PR or CR), as per RECIST v1.1 at the 1M FUP Visit, until progressive disease (PD) or another therapeutic intervention is initiated. Survival follow-up is required…
1. Synopsis: Number of Patients 5.5 Number of Patients	The exact number of patients will depend upon the observed tolerability of Pan-HER and occurrence of discontinuation of patients during the DLT-observation period for reasons other than toxicity.	The exact number of patients will depend upon the observed tolerability of Pan-HER and the potential for adding additional patients to a cohort to assure a sufficient number of evaluable patients per cohort.
1. Synopsis: Main Inclusion and Exclusion Criteria 6.2 Exclusion Criteria	Main exclusion criteria: • Part 2 ONLY: Radiotherapy against target lesions within 4 weeks prior to C1/D1 • History of inflammatory bowel disease • Abnormal hematologic, renal or hepatic function as defined by the following criteria: i. Partial thromboplastin time (PTT) >1.5 ULN for the institution* *Unless on a stable dose of anticoagulant therapy for a prior thrombotic event • Known history of human immunodeficiency virus (HIV) infection • Known active hepatitis B or C virus infection	Main exclusion criteria: • Part 2 ONLY: Radiotherapy against target lesions within 4 weeks prior to C1/D1, unless there is documented progression of the lesion following the radiotherapy • History of inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease) • Abnormal hematologic, renal or hepatic function as defined by the following criteria: i. Partial thromboplastin time (PTT) >1.5 ULN for the institution* *Unless on a stable dose (per the investigator's discretion) of anticoagulant therapy for a prior thrombotic event *Removed known history of HIV infection* *Removed known active hepatitis B or C virus infection*
5.6 End of Trial	*Not applicable*	During Part 2, patients will continue to be followed to assess duration of disease stabilization, response and/or overall survival.

SECTION	ORIGINAL TEXT	NEW TEXT
7.1.3.2 Part 1, Dose-Escalation: Classical 3+3 Dose-Escalation Design	*Not applicable*	There is the potential for additional patients to be enrolled in the dose-escalation portion of the trial to ensure a sufficient number of evaluable patients per cohort by entering an additional patient to a cohort (e.g. increase a 1 patient cohort to 2 patients, a 3 patient cohort to 4 patients, or a 6 patient cohort to 7 patients)…
7.1.4.2 Dose-Delays for Pan-HER-Related or Disease-Related Toxicities	In order to dose a patient, the following criteria must be met:… 4. Any ongoing AEs, assessed as possibly, probably, or related to Pan-HER, should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved with the exception of laboratory abnormalities that are considered clinically insignificant	In order to dose a patient, the following retreatment criteria must be met. Evaluations must occur at minimum prior to each Cycle 1 dose and prior to D1 and D15 doses each cycle thereafter:… 4. Any ongoing AEs, assessed as possibly, probably, or related to Pan-HER, should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved with the exception of Grade 2 clinical events that are being adequately controlled with best supportive care (e.g. nausea, vomiting, diarrhea, fatigue) and asymptomatic laboratory abnormalities that are considered clinically insignificant or that are resolving with medical therapy
7.6 Medical Care of Patients after End of Trial Participation	*Not applicable*	During Part 2, patients will continue to be followed for survival.
8.1.1 Signing of Informed Consent	Note: Informed consent may be obtained outside the 14-day screening period prior to C1/D1	Note: Informed consent may be obtained outside the 14-day screening period prior to C1/D1, but is recommended to be obtained no earlier than 4 weeks prior to the planned C1/D1
8.2.1 Medication/ Procedure Survey	To include all medications and/or treatments taken other than Pan-HER. Include generic name or brand name, indication for use, dose and frequency, route of administration, start and stop dates or if ongoing at 1M FUP Visit.	To include all medications taken other than Pan-HER and all procedures performed during trial. For medications: Include generic name or brand name, indication for use, dose and frequency, route of administration, start and stop dates or if ongoing at 1M FUP Visit. For procedures: Include date and reason for procedure.
8.2.6 Physical Examination	Full physical examination at Screening to include…	*Removed breasts, lungs, pulses*
8.3.3 Archival Tumor Tissue for EGFR, HER2 Assessment (Part 1 only)	To be assessed locally for EGFR and HER2 expression level, if tissue is available.	To be assessed locally, preferably by immunohistochemistry (IHC) for EGFR and HER2 expression level, if tissue is available.

SECTION	ORIGINAL TEXT	NEW TEXT
9.1.1 Adverse Event	PD will be captured as an AE. Events associated with the actual PD will also be captured, as determined by the Investigator. Additionally, AEs occurring simultaneously with PD, but which may not be related to the actual PD, will also be captured.	*Removed*
9.1.2 Events Not to be Considered as Adverse Events 9.1.5 Events that Do Not Meet the Definition of Serious Adverse Events	*Not applicable*	PD will not be captured as an AE/SAE unless the nature of the PD is different than expected (i.e. other diagnosis and/or signs/symptoms that are not typical of PD). PD may be reported as an AE/SAE in the case of patient death, with death being the outcome of the event. An abnormal laboratory value or an abnormality in physiological testing (such as ECGs) per se need not be reported as an AE unless one of the following applies: • The Investigator considers the abnormality clinically significant • The event meets the definition of an SAE • The event requires an intervention • The event results in an action taken with Pan-HER (dose-reduction and/or withdrawal)
10.4.1 Efficacy Endpoints and Analyses	The following anti-tumor response endpoints will be measured in Part 2:…	The following anti-tumor response endpoints will be measured in Part 2:… • Overall survival (OS)

21.3 Protocol Amendment 3 dated 26-Apr-2017

- Changed the dosing schedule from Q1W to Q2W due to AEs seen on the 4 mg/kg and to further explore the safety and tolerability of Pan-HER when given Q2W
- Clarified that patients entered to the study prior to implementation of Amendment 3 will continue to be treated on the Q1W schedule
- Revised the PK collection timepoints for the Q2W dosing schedule
- Changed dose-escalation from a modified Fibonacci scheme to fixed dose levels
- Included a PET expansion cohort to evaluate the effects on tumor metabolism of Pan-HER when administered at the RP2D
- Modified inclusion criteria to include the criteria for patients participating in the PET expansion cohort
- Extended the number of cohorts in the dose-expansion part of the trial and increased the overall number of patients and number of participating sites accordingly
- Added the option for investigators to include an H2 antagonist and/or acetaminophen premedication, where indicated

Refer to **Table 20** for the changes in Protocol Amendment 3.

Table 20 Protocol Amendment 3

SECTION	ORIGINAL TEXT	NEW TEXT
1. Synopsis: Overall Trial Design 5.1 Overall Design and Plan 7.1.3.2 Part 1, Dose-Escalation 7.1.3.3 Part 2, Dose-Expansion Cohorts	*Not applicable*	As of Amendment 3: A total of 6 patients entered Part 1 of this trial: 1 patient each at Dose Level 1 and 2, and 4 patients at dose Level 3 (1, 2, and 4 mg/kg, respectively) were treated on a weekly schedule (Q1W; 4 doses equaling 1 cycle)…
	This is an open-label, multicenter trial… on a weekly schedule… Four (4) doses of Pan-HER administered weekly constitute 1 cycle.	This is an open-label, multicenter trial… on a Q2W (previously Q1W) schedule… With the change in dosing schedule, 2 doses of Pan-HER administered Q2W constitute 1 cycle.
	Not applicable	Once the RP2D is selected, an expansion cohort of patients with fluorodeoxyglucose (FDG)-avid tumors will undergo pre- and post-dosing fluorine-18 radiolabeled FDG (^{18}F-FDG) positron emission tomography (PET) imaging…
	Two tumor types to be evaluated in this part of the trial will be selected based upon findings from Part 1… Patients will be entered, depending upon their underlying malignancy, to one of 2 corresponding expansion cohorts: Cohort A or Cohort B.	Four tumor types to be evaluated in this part of the trial will be selected based upon findings from Part 1… Patients will be entered, depending upon their underlying malignancy, to 1 of 4 corresponding expansion cohorts: Cohort A, Cohort B, Cohort C, or Cohort D.
	From starting dose n_0, dose-escalation of Pan-HER will adhere to the following: Doses are initially escalated by 100% at each step n_1, n_2 etc. until a G2T occurs or completion…	*Text removed.* *Figure updated.*
	Part 1/Dose-escalation: The starting dose of Pan-HER will be 1.0 mg/kg. Initially, patients will be sequentially enrolled to single-patient cohorts of increasing doses of Pan-HER with 100% increase in dose from the previous dose level tested. One patient will be treated at each dose level until the occurrence of a toxicity* during Cycle 1... If such a toxicity has not occurred in the first 3 cohorts… the next cohort to open will be a 3-patient cohort at 8 mg/kg and the design will switch to the 3+3 design. The increase in dose between dose levels will follow a modified Fibonacci scheme. At the first dose-escalation step, approximately 67% will be added to the previous dose…	**Part 1/Dose-escalation:** The starting dose of Pan-HER will be 1.0 mg/kg. The following dose levels of Pan-HER potentially will be evaluated… Initially, one patient will be treated at each dose level until the occurrence of a toxicity* during Cycle 1… If such a toxicity has not occurred in the first 3 cohorts… the next cohort to open will be a 3-patient cohort and the design will switch to the 3+3 design. *Removed modified Fibonacci scheme text.*

SECTION	ORIGINAL TEXT	NEW TEXT
	Enrollment will be staggered between the first and second patient in each new higher 3+3 dose level tested. The first patient must have completed and tolerated the first 2 doses of Pan-HER…	Enrollment will be staggered between the first and second patient in each new dose level tested. The first patient must have completed and tolerated the first dose (previously the first 2 doses with Q1W dosing) of Pan-HER…
	Not applicable	Once the RP2D is selected, enrollment to the PET Expansion Cohort may begin.
	Part 2/Dose-expansion: …enrollment into the 2 separate dose-expansion cohorts will commence (Cohort A and Cohort B). All patients enrolled will be treated with weekly doses…	**Part 2/Dose-expansion:** …enrollment into the 4 separate dose-expansion cohorts will commence (Cohort A, Cohort B, Cohort C, or Cohort D). All patients enrolled will be treated with Q2W doses…
1. Synopsis: Trial Sites 5.1 Overall Design and Plan	**Part 2/Dose-expansion:** Approximately 10 trial sites	**Part 2/Dose-expansion:** Approximately 20 trial sites
1. Synopsis: Planned Trial Period 5.4 Recruitment Period	…establishment of a RP2D, expectedly Q3-Q4 2017. Enrollment to Part 2 is expected to be from Q1 2018 to Q2 2019.	…establishment of a RP2D, expectedly beginning of 2018. Enrollment to the PET Expansion Cohort may follow. Enrollment to Part 2 is expected to be from second half of 2018 to second half of 2019.
1. Synopsis: Primary and Secondary Objectives 4.1.1 Primary Objective 4.1.3 Exploratory Objective 4.2.1 Primary Objective	**Primary objective of Part 1/Dose-escalation:** To assess the safety and tolerability of Pan-HER when administered weekly…	**Primary objective of Part 1/Dose-escalation:** To assess the safety and tolerability of Pan-HER when administered weekly and Q2W…
	Not applicable	**Exploratory objective of Part 1/Dose-escalation:** To evaluate by ^{18}F-FDG PET the effects on tumor metabolism of Pan-HER when administered Q2W at the RP2D in an expansion cohort of patients with FDG-avid tumors
	Primary objective of Part 2/Dose-expansion: To evaluate the antitumor effect of Pan-HER when administered weekly at the RP2D to patients with advanced epithelial malignancies (2 tumor types to be selected).	**Primary objective of Part 2/Dose-expansion:** To evaluate the antitumor effect of Pan-HER when administered Q2W at the RP2D to patients with advanced epithelial malignancies (4 tumor types to be selected).
1. Synopsis: Trial Periods	**Treatment period:** Patients in the trial will receive weekly…	**Treatment period:** Patients in the trial will receive Q2W (previously Q1W)…

SECTION	ORIGINAL TEXT	NEW TEXT
1. Synopsis: Number of Patients	In total, approximately 75 patients will be included in this trial.	In total, approximately 131 patients will be included in this trial.
	Not applicable	It is estimated that approximately 6 patients will be enrolled to the PET Expansion Cohort. The exact number of patients will depend…
5.5 Number of Patients	It is planned to enroll and treat approximately 50 patients during Part 2 with 25 patients in each dose-expansion cohort.	It is planned to enroll and treat approximately 100 patients during Part 2 with 25 patients in each dose-expansion cohort.
1. Synopsis: Main Inclusion and Exclusion Criteria 6.1 Inclusion Criteria	*Not applicable*	**Main inclusion criteria all patients, Part 1 and Part 2:** • PET Expansion Cohort: Epithelial malignancy, measurable according to RECIST v1.1 that has been confirmed by ^{18}F-FDG-PET imaging to be FDG-avid within 28 days prior to C1/D1
1. Synopsis: Investigational Medicinal Product: Dose(s) and Treatment Schedule	Pan-HER will be initiated on C1/D1 and will be administered weekly by IV infusion in cycles of treatment: • Dosing on Day 1, 8, 15 and 22 of each 28-day cycle (±2 days)	Pan-HER will be initiated on C1/D1 and will be administered Q2W (previously Q1W) by IV infusion in cycles of treatment: • Dosing on Day 1 and 15 of each 28-day cycle (±2 days) As of Amendment 3: Doses previously administered on Days 8 and 22 are omitted.
1. Synopsis: Dose-Limiting Toxicities (Part 1 only) 9.5.2 Observation Period for Dose-Limiting Toxicities	A minimum of 4 infusions of Pan-HER must have been administered at the assigned dose for a patient to have completed the DLT-observation period.	A minimum of 2 infusions (previously 4 infusions with Q1W dosing) of Pan-HER must have been administered at the assigned dose for a patient to have completed the DLT-observation period.
1. Synopsis: Trial Assessments	*Not applicable*	**Disease Assessments:** • Evaluation of tumor metabolic activity by ^{18}F-FDG PET
1. Synopsis: Statistical	It is planned to enroll and treat approximately 50 patients during Part 2: 25 patients in each dose-expansion cohort, selected by underlying malignancy.	It is estimated that approximately 6 patients will be enrolled to the PET Expansion Cohort…

SECTION	ORIGINAL TEXT	NEW TEXT
Methods and Sample Size Considerations 10.1 Sample Size Considerations	The planned number of patients to be enrolled may be adjusted when the two…	It is planned to enroll and treat approximately 100 patients during Part 2: 25 patients in each dose-expansion cohort, selected by underlying malignancy. The planned number of patients to be enrolled may be adjusted when the four…
3.2.4.1 Protocol Sym013-01	*Text previously under 3.2.4 Summary of Clinical Findings* This is the first clinical trial to study Pan-HER.	*Added subheading 3.2.4.1* This is the first clinical trial to study Pan-HER. <u>As of Amendment 3</u>, a total of 6 patients have been entered to Part 1 of this trial…
3.2.4.2 Other Anticipated Clinical Findings	*Not applicable*	*Added subheading 3.2.4.2*
3.5 Overall Benefits/Risk	Enrollment will be staggered by 2 weeks between the first and second patient in each new higher dose level tested…	Enrollment will be staggered by 2 weeks between the first and second patient in each new dose level tested…
5.2.1 Rationale for Trial Design	The trial is designed to select a safe and well-tolerated dose of Pan-HER during Part 1 and to investigate the selected dose in 2 groups…	The trial is designed to select a safe and well-tolerated dose of Pan-HER during Part 1 and to investigate the selected dose in 4 groups…
5.2.2 Rationale for Trial Population	In Part 2, the RP2D will be investigated in patients with epithelial malignancies (2 tumor types to be selected; patients to be entered to Cohort A or Cohort B, collectively called “dose-expansion cohorts”)... A rationale for the 2 tumor types…	In Part 2, the RP2D will be investigated in patients with epithelial malignancies (4 tumor types to be selected; patients to be entered to Cohort A, Cohort B, Cohort C, or Cohort D, collectively called “dose-expansion cohorts”)… A rationale for the 4 tumor types…
5.3.3 Treatment 7.1.3.1 Treatment Schedule	Pan-HER will be administered by IV infusion on a weekly schedule, i.e. dosing will be every 7 (±2) days. Four (4) doses of Pan-HER administered weekly constitute 1 cycle.	Pan-HER will be administered by IV infusion on a Q2W (previously Q1W) schedule, i.e. dosing will be every 14 (±2) days. Two (2) doses of Pan-HER administered Q2W constitute 1 cycle. <u>As of Amendment 3</u>: With the previous Q1W schedule, dosing was every 7 (±2) days. Four (4) doses of Pan-HER administered Q1W constituted 1 cycle. Enrollment to the PET Expansion Cohort may follow.
5.3.5 Schedule of Assessments	A schedule of assessments for Part 1 and Part 2 is provided in Table 2.	Schedule of assessments for Part 1 and Part 2 are provided in Table 2 (Q1W dosing) and Table 3 (Q2W dosing).
6.2 Exclusion Criteria	*Exclusion Criteria #7:* NOTE: With the exception of alopecia, patients must have recovered…	*Exclusion Criteria #7:* NOTE: With the exception of persistent Grade 2 alopecia and/or peripheral neuropathy, patients must have recovered…
7.1.3.2 Part 1, Does-Escalation	The increase in dose between dose levels will follow a modified Fibonacci scheme…	*Removed text.*

SECTION	ORIGINAL TEXT	NEW TEXT
	When calculating the doses for each new dose level, the following approach will be applied…	
7.2.1 Pre-Medication for Pan-HER Infusions	*Not applicable*	All patients must be premedicated as described with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to including an H2 antagonist and/or acetaminophen…
8.2.3 Dose-Limiting Toxicities Evaluation (Part 1 Only) 9.5.2 Observation Period for Dose-Limiting Toxicities	• Reported during Cycle 1 with final assessment 7 days after the last dose of Cycle 1 or prior to dosing on Day 1 of Cycle 2 (C2/D1)	• Reported during Cycle 1 with final assessment 14 days (previously 7 days with Q1W dosing) after the last dose of Cycle 1 or prior to dosing on Day 1 of Cycle 2 (C2/D1)
8.3.4 ^{18}F-FDG PET Imaging (PET Expansion Cohort Only)	*Not applicable*	*Added section.*
8.4 Pharmacokinetic Assessments	Serum concentrations of total Pan-HER will support the PK endpoints of the trial. A subset of the PK samples will be analyzed for the serum levels of each of the six mAbs constituting Pan-HER. These results will be reported separately from the clinical trial report.	*Table 11 is for PK samples for Q1W dosing and Table 12 is for PK samples for Q2W dosing.* Note: Comprehensive collection of clinical samples is critical to the conduct of this study… Serum concentrations of each of the 6 mAbs that comprise Pan-HER will support the PK endpoints of the trial. The serum concentrations may also be used in an exploratory population PK analysis which will be reported separately from the clinical trial report.
10.4 Secondary and Exploratory Endpoint and Analysis	All statistical analyses of the secondary endpoints for both phases will be performed after completion of Part 2 of the trial.	All statistical analyses of the secondary and exploratory endpoints for both phases will be descriptive unless otherwise specified. Details will be specified in a separate statistical analysis plan.
10.4.4 Pharmacokinetic	The PK endpoints will be derived based on the concentration time curves of Pan-HER, after the first and fourth infusion…	The PK endpoints with Q2W dosing will be derived based on the concentration time curves of Pan-HER, after the first and third infusion…

SECTION	ORIGINAL TEXT	NEW TEXT
Endpoints and Analyses		As of Amendment 3: For patients entered to Dose Level 1, 2 and 3 (1, 2, and 4 mg/kg, respectively) treated on a Q1W schedule…
10.4.5 Additional Endpoints and Analyses	*Not applicable*	• Changes in tumor metabolism as evaluated by ^{18}F-FDG PET

21.4 Protocol Amendment 4 dated 04-May-2017

- Modified the biomarker blood sample section to clarify that the collected biomarker sample is not plasma only
- Clarified that the pre-medication dose for acetaminophen is recommended
- Minor typographical error has been corrected

Refer to **Table 21** for the changes in Protocol Amendment 4.

Table 21 Protocol Amendment 4

SECTION	ORIGINAL TEXT	NEW TEXT
3.5 Overall Benefits/Risk	As Pan-HER has not been investigated in humans, the benefits and the safety profile of Pan-HER cannot be established.	As limited clinical information is available for patients treated with Pan-HER (see Section 3.2.4.1), the benefits and the safety profile of Pan-HER have not been fully established.
7.2.1 Pre-Medication for Pan-HER Infusions	Acetaminophen (optional) 1000 mg IV or PO (orally), approx. 0.5 hours prior to the start of Pan-HER infusion	Acetaminophen (optional) such as 1000 mg IV or PO (orally), approx. 0.5 hours prior to the start of Pan-HER infusion
8.8 Biomarker Blood Sample	Peripheral blood samples are taken for preparation of plasma and subsequent biomarker analysis. Analysis of all plasma samples will be performed at a central laboratory… Analysis of biomarker plasma samples may include genes… Aliquots of plasma samples will be stored…	Peripheral blood samples are taken for subsequent biomarker analysis. Analysis of all samples will be performed at a central laboratory… Analysis of biomarker samples may include genes… Biomarker samples will be stored…

21.5 Protocol Amendment 5 dated 23-Jan-2018

- Prophylaxis for both IRR and mucositis made mandatory in Part 1 (dose-escalation) to facilitate a more accurate evaluation of the safety and tolerability of Pan-HER at dose levels likely to be therapeutically active.
- Added mandatory prophylactic treatment for both IRR and mucositis as well as supportive care measures in the event of Pan-HER associated mucositis.
- Prolonged the infusion of Pan-HER with delivery over a fixed infusion period of 4 hours to reduce the risk of IRRs.
- Specified that increased infusion rate and reduced infusion duration after C1/D1 will no longer be allowed.
- Modified exclusion criteria and prohibited medication to specify when the use of steroid therapy is allowed.
- Added collection of blood samples for complement hemolytic activity analysis.
- Specified the process for data recording, validation, review, and query resolution.
- Included other minor updates, clarifications, and structural reformatting.

Refer to **Table 22** for the changes in Protocol Amendment 5.

Table 22 Protocol Amendment 5

SECTION	ORIGINAL TEXT	NEW TEXT
1 Synopsis: Overall Trial Design 5.1 Overall Design and Plan 7.1.3.2 Part 1, Dose-Escalation	• Dose Level 1: 1 mg/kg • Dose Level 2: 2 mg/kg • Dose Level 3: 4 mg/kg • Dose Level 4: 6 mg/kg • Dose Level 5: 9 mg/kg • Dose Level 6: 12 mg/kg • Dose Level 7: 15 mg/kg • Dose Level 8: 18 mg/kg (highest potential dose allowed per protocol)	Q1W • Dose Level 1: 1 mg/kg • Dose Level 2: 2 mg/kg • Dose Level 3: 4 mg/kg Q2W • Dose Level 4: 6 mg/kg • Dose Level 5: 9 mg/kg Q2W with mandatory intensive IRR and mucositis prophylaxis; 4h infusion (designated “P”) • Dose Level 5P: 9 mg/kg • Dose Level 6P: 12 mg/kg • Dose Level 7P: 15 mg/kg • Dose Level 8P: 18 mg/kg (highest potential dose allowed per protocol) As of Amendment 5, patients entered to Dose Level 5P and all patients thereafter must receive intensive prophylaxis…
1 Synopsis:	For Part 1 of the trial, Pan-HER will be administered following delivery of	For Part 1 of the trial, Pan-HER will be administered following delivery of

SECTION	ORIGINAL TEXT	NEW TEXT
Investigational Medicinal Product: Dose(s) and Treatment Schedule	mandatory premedication prior to each infusion. For Part 2, premedication is mandatory prior to each dose of Pan-HER during Cycle 1. If the patient is without evidence of infusion-related reactions (IRRs) after Cycle 1, the Investigator may choose to withdraw premedication with subsequent dosing. Gradual withdrawal of premedication is recommended. The duration of infusion will be: • Approximately 2 hours (+10 min) for the 1st infusion • Approximately 1.5 hours (+10 min) for the 2nd infusion • Approximately 1 hour (+10 min) for subsequent infusions	intensive prophylaxis, as defined herein, on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis. For Part 2, IRR and mucositis prophylaxis is mandatory during Cycle 1 and Cycle 2. If the patient is without evidence of IRRs or mucositis after Cycle 2, the Investigator may choose to withdraw related medications with subsequent dosing. Gradual withdrawal of medications is recommended. The duration of infusion will be (prior to Amendment 5): • Approximately 2 hours (+10 min) for the 1st infusion • Approximately 1.5 hours (+10 min) for the 2nd infusion • Approximately 1 hour (+10 min) for subsequent infusions The duration of infusion will be (effective with Amendment 5): • Minimum of 4 hours (+10 min) for all infusions. Titrated rate increases during infusions, and infusion duration reductions after C1/D1, will no longer be allowed.
3.2.4.1 Protocol Sym013-01	This is the first clinical trial to study Pan-HER. As of Amendment 3, a total of 6 patients have been entered to Part 1 of this trial… As of Amendment 3: Due to the occurrence of Grade 1-2 oral mucositis, rash, and diarrhea at the 4 mg/kg dose, the dosing interval in this trial has been changed from Q1W to every second week (Q2W; 2 doses equaling 1 cycle)...	This is the first clinical trial to study Pan-HER. As of Amendment 5, a total of 16 patients have been entered to Part 1 of this trial… Regarding IRRs, despite required premedication with a glucocorticoid and an antihistamine, 2 of 4 patients at 4 mg/kg experienced Grade 1-2 events… Regarding mucositis, Grade 1 to 2 events were observed in 4 of 4 patients at 4 mg/kg on the Q1W schedule, and on the Q2W schedule following recommended prophylaxis… Regarding rash and diarrhea, Grade 1-2 acneiform/maculopapular rash has been reported in 11 patients at 2 mg/kg and above; and Grade 1-2 diarrhea has been reported in 4 patients at 4 mg/kg and above. While data in this ongoing clinical trial have not been fully verified, other study drug-related AEs have included… As of Amendment 5: As described, 2 events meeting the protocol DLT criteria have occurred in the 9 mg/kg cohort, IRR and mucositis, and while increased prophylaxis for each was recommended, it was not fully implemented in advance of these events...

SECTION	ORIGINAL TEXT	NEW TEXT
6.2 Exclusion Criteria	3. Immunosuppressive or systemic hormonal therapy within 2 weeks prior to C1/D1 with the exception of the following allowed therapies: a. Hormonal therapy (e.g., Megace) for appetite stimulation b. Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations c. Oral replacement glucocorticoid therapy for adrenal insufficiency d. Low-dose maintenance steroid therapy for other conditions (excluding steroid tapers for brain edema/metastases/radiation) e. Steroid therapy as prophylaxis for contrast reactions f. Hormonal contraceptive therapy g. Gonadotropin-releasing hormone (GnRH) analogs in patients with prostate cancer	3. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) within 2 weeks prior to C1/D1 with the exception of the following allowed therapies: a. Hormonal therapy (e.g. Megace) for appetite stimulation b. Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations c. Hormone replacement therapy at standard doses for end-organ failure d. Steroid therapy as prophylaxis for contrast reactions e. Intra-articular steroid injections f. Hormonal therapy for ovarian suppression*, hormonal contraceptive therapy, post-menopausal hormone replacement therapy (HRT) g. Gonadotropin-releasing hormone (GnRH) analogs in patients with prostate cancer* h. Low-dose maintenance steroid therapy for other conditions (excluding steroid tapers for brain edema/metastases/radiation) i. Higher dose steroid therapy for treatment of an acute intercurrent illness in patients with stable disease or an ongoing response. In such situations, study drug treatment should be interrupted for the duration of immunosuppressive therapy *Patients must have been on a stable dose for at least 3 months prior to study start, and if continuing must remain on the stable dose while receiving study treatment (i.e. such treatment will not be considered as systemic hormonal therapy for the purpose of study eligibility).
	6. Known central nervous system (CNS) or leptomeningeal metastases not controlled by prior surgery or radiotherapy, or symptoms suggesting CNS involvement for which treatment is required	6. Central nervous system (CNS) malignancies; known, untreated CNS or leptomeningeal metastases, or spinal cord compression, any of the above not controlled by prior surgery or radiotherapy, or symptoms suggesting CNS involvement for which treatment is required
	7. Inadequate recovery from an acute toxicity associated with any prior antineoplastic therapy NOTE: With the exception of persistent Grade 2 alopecia and/or peripheral neuropathy, patients must have recovered from acute toxicity by C1/D1; any Grade 1 residual toxicity may be acceptable	7. Inadequate recovery from an acute toxicity associated with any prior antineoplastic therapy NOTE: With the exception of persistent Grade 2 alopecia, peripheral neuropathy, decreased hemoglobin, and/or end-organ failure being adequately managed by hormone replacement therapy, patients must have recovered from acute toxicity by C1/D1; any Grade 1 residual toxicity may be acceptable
6.3.1 Withdrawal	NOTE: Patients meeting all three of the following are considered to have	NOTE: Patients meeting all three of the following are considered to have

SECTION	ORIGINAL TEXT	NEW TEXT
from Treatment	met Hy's Law criteria: • Hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above ULN of ALT or AST • Elevation of serum total bilirubin to ≥2×ULN, without findings of cholestasis (elevated serum alkaline phosphatase [ALP])…	met Hy's Law criteria: • Hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above ULN of ALT or AST (or > 3 × baseline if elevated at study entry due to hepatic involvement by tumor) • Elevation of serum total bilirubin to ≥2×ULN, without findings of cholestasis (elevated serum alkaline phosphatase [ALP] < 2×ULN)…
7.1.3.4 Duration of Infusion for Administration of Pan-HER	*Not applicable*	Amendment 5 Note: Prolongation of Pan-HER infusions by 0.5 hours was implemented on 2 occasions: • Beginning with Dose Level 5 (9 mg/kg), and due to Grade 2 IRRs in ≥ two thirds of patients entered to Dose Level 4 (6 mg/kg)… • During Dose Level 5 (9 mg/kg), and due to a Grade 3 IRR in a patient entered to Dose Level 5 (9 mg/kg)… **Effective with Amendment 5** Beginning with Dose Level 5P (9 mg/kg with intensive prophylaxis) and all patients thereafter, the duration of the infusion is required to be...
7.1.4 Dose Adjustment and Delays of Pan-HER	Weight changes (≥ ±10%) for a patient during trial will require recalculation of the dose.	Weight changes (≥ ±10%) for a patient during trial should be accompanied by recalculation of the dose.
7.1.4.1 Dose-Adjustment for Body Weight	The dose calculated may be used for subsequent infusions, unless body weight changes of ≥ ±10%, in which case the dose must be adjusted according to the change in body weight.	The dose calculated may be used for subsequent infusions, unless body weight changes of ≥ ±10%, in which case the dose should be adjusted according to the change in body weight.
7.1.4.3 Dose-Reduction for Pan-HER-Related Toxicities	5. AST/ALT elevation >3×ULN with bilirubin elevation >2×ULN without evidence of cholestasis that cannot be explained by factors not related to Pan-HER	5. AST/ALT elevation >3×ULN (or >3× baseline if elevated at study entry due to hepatic involvement by tumor) with bilirubin elevation >2×ULN without evidence of cholestasis that cannot be explained by factors not related to Pan-HER
7.2.1 Pre-Medication for Pan-HER Infusion-Related Reactions	For Part 2, premedication is mandatory prior to each dose of Pan-HER during Cycle 1. All patients must be premedicated as described with standard therapies that include a glucocorticoid and an H1 antagonist. Where indicated, consideration may be given to including an H2 antagonist and/or acetaminophen. The recommended premedication doses are as follows: • Glucocorticoid therapy equivalent to 80-100 mg IV methylprednisolone, approx. 0.5 to 2 hours prior to the start of Pan-HER infusion • Antihistamine (H1 antagonist) equivalent to 25-50 mg IV	For Part 2, premedication is mandatory prior to each dose of Pan-HER during Cycle 1 and 2. As of Amendment 5, all patients must be premedicated as described with standard therapies that include each of the following. The recommended premedication doses are as follows: • Montelukast (selective leukotriene receptor antagonist) 10 mg PO daily × 7 prior to each Pan-HER infusion… • Dexamethasone 10 mg PO, approx. 12 and 6 hours prior to the start of Pan-HER infusion

SECTION	ORIGINAL TEXT	NEW TEXT
	diphenhydramine, approx. 0.5 hours prior to the start of Pan-HER infusion • Antihistamine (H2) antagonist (optional) such as 50 mg IV ranitidine or 30 mg famotidine, approx. 0.5 hours prior to the start of Pan-HER infusion • Acetaminophen (optional) such as 1000 mg IV or PO (orally), approx. 0.5 hours prior to the start of Pan-HER infusion In Part 2, if a patient is without evidence of IRRs after Cycle 1…	• Glucocorticoid therapy equivalent to 80-100 mg IV methylprednisolone, approx. 0.5 to 2 hours prior to the start of Pan-HER infusion • Antihistamine (H1 antagonist) equivalent to 25-50 mg IV diphenhydramine, approx. 0.5 hours prior to the start of Pan-HER infusion • Antihistamine (H2) antagonist such as 50 mg IV ranitidine or 30 mg famotidine, approx. 0.5 hours prior to the start of Pan-HER infusion • Acetaminophen such as 1000 mg IV or PO (orally), approx. 0.5 hours prior to the start of Pan-HER infusion In Part 2, if a patient is without evidence of IRRs after Cycle 2…
7.2.2.1 Mandatory Prophylactic Treatment	Mandatory prophylactic treatment will be implemented for all patients treated in this trial should an increased incidence begin to occur…	**Oropharyngeal Mucositis** As of Amendment 5, for prophylaxis against Pan-HER-associated oropharyngeal mucositis, the following management is mandatory throughout the Pan-HER treatment period… In Part 2, if a patient is without evidence of mucositis after Cycle 2, the Investigator may choose to withdraw prophylaxis… **Other Toxicities** Mandatory prophylactic treatment will be implemented for all patients treated in this trial should an increased incidence begin to occur…
7.2.2.2 Therapeutic Treatment	*Not applicable*	**Oropharyngeal Mucositis** As of Amendment 5, in the event of development of Pan-HER-associated oropharyngeal mucositis, appropriate standard supportive care measures are to be implemented and should include…
7.5.2 Prohibited Medication/Therapy and Procedures During the Trial	• Systemic immunosuppressive or systemic hormonal therapy with the exception of the following allowed therapies: o Hormonal therapy (e.g., Megace) for appetite stimulation o Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations o Oral replacement glucocorticoid therapy for adrenal insufficiency o Low-dose maintenance steroid therapy for other conditions (excluding steroid tapers for brain edema/metastases/radiation) o Steroid therapy as prophylaxis for contrast reactions o Hormonal contraceptive therapy o GnRH analogs in patients with prostate cancer o Low-dose maintenance steroid therapy for other conditions	• Systemic immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) with the exception of the following allowed therapies: o Hormonal therapy (e.g. Megace) for appetite stimulation o Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations o Hormone replacement therapy at standard doses for end-organ failure o Steroid therapy as prophylaxis for contrast reactions o Intra-articular steroid injections o Hormonal therapy for ovarian suppression, hormonal

SECTION	ORIGINAL TEXT	NEW TEXT
	(excluding steroid tapers for brain edema/metastases/radiation) • Prophylactic use of hematopoietic growth factors during Cycle 1 • Major surgery that would preclude the patient from complying with the requirements of the CTP	contraceptive therapy, post-menopausal HRT ○ GnRH analogs in patients with prostate cancer ○ Low-dose maintenance steroid therapy for other conditions (excluding steroid tapers for brain edema/metastases/radiation) ○ Higher dose steroid therapy for treatment of an acute intercurrent illness in patients with stable disease or an ongoing response. In such situations, study drug treatment should be interrupted for the duration of immunosuppressive therapy • Prophylactic use of hematopoietic growth factors during Cycle 1 • Use of alcohol- or peroxide-containing mouthwashes • Major surgery that would preclude the patient from complying with the requirements of the CTP
8.2.10 Complement Panel	*Not applicable*	To include total complement hemolytic activity (CH50), C3, C4, C3a, and C4a… Note: Comprehensive collection of clinical samples is critical to the conduct of this study... A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites in Part 2.
8.7 Tumor Biopsy	All analyses will be related to and used only in connection with the data collected in the present trial, and the identity of the patient will remain confidential.	All analyses will be related to and used in connection with the data collected in the present trial and Pan-HER program, and the identity of the patient will remain confidential.
8.8 Biomarker Blood Sample	Note: End of cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle.	Note: End of cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle. For those timepoints where both a blood sample and a tumor biopsy are to be obtained, blood sample to be collected first.
14.2 Recording of Data	*Not applicable*	Clinical trial data for this study will be captured in an electronic format… A CRF is required to be submitted for every patient who receives any amount of study drug… All collected data will be entered into a validated database.
14.3 Data Review During this Study	*Not applicable*	Data obtained from the study will be reviewed in a timely manner throughout by the Sponsor (or designee) and Sponsor's Medical Representative(s) to assess safety and the progress of the project.
14.7 Data Processing	The process of entering or uploading of data from trial sites will assure the accuracy of data entry into the database and include a validation at data entry time (real time validation). Entry or electronic transfer of other data	The Sponsor or designee will be responsible for data processing in accordance with the applicable Data Management SOPs. A Data Management Plan will be generated for this trial.

SECTION	ORIGINAL TEXT	NEW TEXT
	than those directly from trial sites (e.g. imports of laboratory results) will follow the Sponsor requirements for data flow and transfer. The Sponsor or designee will be responsible for data processing in accordance with the applicable data management SOPs. A Data Management Plan will be generated for this trial. Database lock will occur once quality control procedure, and quality assurance procedures (if applicable) have been completed. The Portable Document Format (PDF) files of the CRFs will be provided to the Investigator before access to the CRF is revoked.	Once recorded within the electronic CRF, study data will pass through a set of pre-programmed data validation checks designed to identify inconsistencies and other data errors… Entry and processing of data other than those directly recorded on electronic CRFs by trial sites (e.g. imports of laboratory results) will follow vendor(s) SOPs… Database lock will occur once quality control and quality assurance procedures (if applicable) have been completed upon reaching the data cut-off for primary analysis. Portable Document Format (PDF) files of the CRFs will be provided to the Investigator before access to the CRF system is revoked.

21.6 Protocol Amendment 6 dated 14-Jun-2018

- Reintroduced Q1W dosing in Part 1 dose-escalation (previously halted with Amendment 3); all current and future patients to be treated under the prophylaxis and infusion duration conditions outlined in Amendment 5.
- With reintroduction of Q1W dosing in Part 1, separate dose-escalation cohorts will be entered to assess the safety and tolerability of Pan-HER when administered either Q1W or Q2W; potential doses for evaluation are as previously listed.
- Stated that the RP2D and regimen ultimately identified for use in Part 2 of this trial may be comprised of a fixed dose and schedule, a combination of doses to be administered on either a Q1W schedule or a Q2W schedule, or a combination dose and regimen.
- Omitted expansion cohort of patients with fluorodeoxyglucose (FDG)-avid tumors planned to undergo pre- and post-dosing fluorine-18 radiolabeled FDG (^{18}F-FDG) positron emission tomography (PET) for evaluation of effects of Pan-HER on tumor metabolism.
- Identified populations to be evaluated in 2 of the 4 planned Part 2 dose-expansion cohorts; Cohort A will be a HER2+ solid tumor malignancies Basket Cohort and Cohort B will be pancreatic carcinoma. The composition of Cohort C and Cohort D remains TBD. A protocol amendment detailing all expansion cohorts will follow.
- Increased the number of trial sites and number of patients planned for this trial.
- Modified the washout period between the end of prior therapy and dosing in this trial.
- Specified that patients with primary CNS malignancies are not eligible for participation.

- Increased the total number of skin biopsies per patient from 2 to 3; the schedule for these procedures has been updated.
- Limited Complement sampling to Part 2 only.
- Clarified timeframes for reporting initial SAEs and follow-up SAE information to the Sponsor or designee are within 24 hours of awareness.
- Modified the information to be collected with respect to pregnancies.
- Updated the protocol background to include more recent scientific and clinical experience data.
- Guidelines pertaining to the General Data Protection Regulation have been added.
- Tables and Figure have been updated based on changes described.
- Formatting adjustments, outline modifications, cross-reference link corrections, and other minor typographical corrections and slight wording changes are included.

Refer to **Table 23** for the changes in Protocol Amendment 6.

Table 23 Protocol Amendment 6

SECTION	ORIGINAL TEXT	NEW TEXT
1 Synopsis: Overall Trial Design	As of Amendment 3: A total of 6 patients entered Part 1 of this trial: 1 patient each at Dose Level 1 and 2, and 4 patients at dose Level 3 (1, 2, and 4 mg/kg, respectively) were treated on a weekly schedule (Q1W; 4 doses equaling 1 cycle)… Due to the occurrence of Grade 1-2 oral mucositis, rash, and diarrhea at the 4 mg/kg dose, the dosing interval in this trial has been changed from Q1W to every second week (Q2W; 2 doses equaling 1 cycle)…	*Deleted; this text has been removed.*
	This is an open-label, multicenter trial composed of 2 parts in which Pan-HER will be evaluated when administered by the intravenous (IV) route on a Q2W (previously Q1W) schedule in patients with advanced epithelial malignancies without available therapeutic options. With the change in dosing schedule, 2 doses of Pan-HER administered Q2W constitute 1 cycle. Part 1 is a Phase 1a dose-escalation designed to determine the recommended phase 2 dose (RP2D). Part 2 is a Phase 2a dose-expansion at the RP2D. Four tumor types to be evaluated in this part of the trial will be selected based upon findings from Part 1, additional preclinical data, and additional clinical data available at that time from other agents inhibiting these targets…	This is an open-label, multicenter trial composed of 2 parts in which Pan-HER will be evaluated when administered by the intravenous (IV) route to patients with advanced epithelial malignancies without available therapeutic options. • Part 1 is a Phase 1a dose-escalation evaluating weekly (Q1W) and every second week (Q2W) schedules of administration in separate dose-escalation cohorts to determine the recommended phase 2 dose (RP2D) and regimen of Pan-HER. • Part 2 is a Phase 2a dose-expansion at the RP2D and regimen. Four (4) dose-expansion cohorts will be evaluated in this part of the trial… The RP2D and regimen ultimately identified for use in Part 2 may be comprised of a fixed dose and schedule, a combination of doses to be administered on either a Q1W or Q2W schedule, or a combination dose and regimen…

SECTION	ORIGINAL TEXT	NEW TEXT
	Once the RP2D is selected, an expansion cohort of patients with fluorodeoxyglucose (FDG)-avid tumors will undergo pre- and post-dosing fluorine-18 radiolabeled FDG (^{18}F-FDG) positron emission tomography (PET) imaging to evaluate the effects on tumor metabolism of Pan-HER when administered at this dose…	*Deleted; the PET Expansion Cohort has been removed.*
	Patients entered to Dose Level 1, 2, and 3 (1, 2, and 4 mg/kg, respectively) were treated Q1W. As of Amendment 3, the dosing schedule in this trial has been changed to Q2W. Patients entered to the trial prior to implementation of this amendment will continue to be treated Q1W. As of Amendment 5, patients entered to Dose Level 5P and all patients thereafter must receive intensive prophylaxis…	**As of Amendment 6** At the time of Amendment 3 to this protocol, a total of 6 patients had been entered to Part 1; 1 patient each at Dose Levels 1 and 2 (1 mg/kg and 2 mg/kg, respectively), and 4 patients at Dose Level 3 (4 mg/kg) had been treated weekly (Q1W; 4 doses equaling 1 cycle)... Per Amendment 5, all patients must receive intensive prophylaxis, as defined herein, on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis… With Amendment 6, Q1W dosing is reintroduced under the prophylaxis and infusion duration conditions outlined in Amendment 5…
1 Synopsis: Overall Trial Design (continued)	**Part 1/Dose-escalation**: The starting dose of Pan-HER will be 1.0 mg/kg. The following dose levels of Pan-HER potentially will be evaluated: Q1W • Dose Level 1: 1 mg/kg • Dose Level 2: 2 mg/kg • Dose Level 3: 4 mg/kg Q2W • Dose Level 4: 6 mg/kg • Dose Level 5: 9 mg/kg Q2W with mandatory intensive IRR and mucositis prophylaxis; 4h infusion (designated "P") • Dose Level 5P: 9 mg/kg • Dose Level 6P: 12 mg/kg • Dose Level 7P: 15 mg/kg • Dose Level 8P: 18 mg/kg (highest potential dose allowed per protocol)	**Part 1/Dose-escalation** The starting dose of Pan-HER will be 1 mg/kg Q1W. The following dose levels of Pan-HER are planned to be evaluated: Q1W • Dose Level 1: 1 mg/kg Q1W • Dose Level 2: 2 mg/kg Q1W • Dose Level 3: 4 mg/kg Q1W • *Dose Level 4P: 6 mg/kg Q1W + P (lower doses with prophylaxis may be explored, if indicated) • *Dose Level 5P: 9 mg/kg Q1W + P • *Dose Level 6P: 12 mg/kg Q1W + P • *Dose Level 7P: 15 mg/kg Q1W + P • *Dose Level 8P: 18 mg/kg Q1W + P (highest potential dose allowed per protocol) Q2W • Dose Level 4: 6 mg/kg Q2W • Dose Level 5: 9 mg/kg Q2W • *Dose Level 5P: 9 mg/kg Q2W + P • *Dose Level 6P: 12 mg/kg Q2W + P • *Dose Level 7P: 15 mg/kg Q2W + P • *Dose Level 8P: 18 mg/kg Q2W + P (highest potential dose allowed per protocol) *Mandatory intensive IRR and oropharyngeal mucositis prophylaxis; 4-hour

SECTION	ORIGINAL TEXT	NEW TEXT
		infusion (designated "P")
	The RP2D may be equal to or lower than the MTD. The RP2D will be selected based on safety data, as well as available PK and target engagement results, as applicable.	**RP2D**: The RP2D may include a dose or a combination of doses (e.g., initial loading dose followed by a lower maintenance dose) equal to or lower than the MTD for the Q1W and/or Q2W dosing regimens. A dose or doses between tolerated doses investigated in Part 1 may also be selected if data indicate this to be optimal…
	Once the RP2D is selected, enrollment to the PET Expansion Cohort may begin.	*Deleted; the PET Expansion Cohort has been removed.*
	Part 2/Dose-expansion: Once the RP2D has been established during dose-escalation, enrollment into the 4 separate dose-expansion cohorts will commence (Cohort A, Cohort B, Cohort C, or Cohort D). All patients enrolled will be treated with Q2W doses of Pan-HER at the established RP2D.	**Part 2/Dose-expansion** Once the RP2D and regimen have been established during dose-escalation, enrollment into the 4 separate dose-expansion cohorts will commence (Cohort A, Cohort B, Cohort C, or Cohort D). All patients enrolled will be treated with Pan-HER at the established RP2D and regimen.
1 Synopsis: Trial Sites	**Part 1/Dose-escalation**: 2 to 3 investigational trial sites… **Part 2/Dose-expansion**: Approximately 20 trial sites	**Part 1/Dose-escalation**: Approximately 3 investigational trial sites… **Part 2/Dose-expansion**: Approximately 25 trial sites
1 Synopsis: Planned Trial Period	Part 1 of the trial is expected to begin Q4 2016. Patients will be sequentially enrolled to dose-escalation cohorts until establishment of a RP2D, expectedly beginning of 2018. Enrollment to the PET Expansion Cohort may follow. Enrollment to the expansion cohorts in Part 2 of the trial will commence upon approval of a clinical trial protocol (CTP) amendment defining the expansion cohorts as well as the RP2D to be further explored. Enrollment to Part 2 is expected to be from second half of 2018 to second half of 2019.	Part 1 of the trial is expected to begin Q4 2016. Patients will be sequentially enrolled to dose-escalation cohorts on either a Q1W or a Q2W schedule until establishment of a RP2D and regimen, expectedly Q1 2019. Enrollment to the expansion cohorts in Part 2 of the trial will commence upon approval of a protocol amendment defining the expansion cohorts to be further explored. Enrollment to Part 2 is expected to be from Q1 2019 to Q3 2020.
1 Synopsis: Primary and Secondary Objectives	**Primary objective of Part 1/Dose-escalation**: To assess the safety and tolerability of Pan-HER when administered Q1W and Q2W by IV infusion to patients with advanced epithelial malignancies without available therapeutic options. **Secondary objectives of Part 1/Dose-escalation**: 1. To determine a RP2D of Pan-HER	**Primary objective of Part 1/Dose-escalation**: To assess the safety and tolerability of Pan-HER when administered either Q1W or Q2W by IV infusion to separate dose-escalation cohorts of patients with advanced epithelial malignancies without available therapeutic options. **Secondary objectives of Part 1/Dose-escalation**: 1. To determine a RP2D and regimen of Pan-HER
	Exploratory objective of Part 1/Dose-escalation: To evaluate by 18F-FDG PET the effects on tumor metabolism of Pan-HER when administered Q2W at the RP2D in an expansion cohort of patients with FDG-avid tumors	*Deleted; the PET Expansion Cohort has been removed.*
	Primary objective of Part 2/Dose-expansion: To evaluate the antitumor effect of Pan-HER when administered Q2W at the RP2D to patients with advanced epithelial malignancies (4 tumor types to be selected).	**Primary objective of Part 2/Dose-expansion**: To evaluate the antitumor effect of Pan-HER when administered at the RP2D and regimen to patients with advanced epithelial malignancies without available therapeutic options. Four (4) dose-expansion cohorts will be evaluated.
1 Synopsis: Trial Periods	**Treatment period**: Patients in the trial will receive Q2W (previously Q1W) IV infusions of Pan-HER until occurrence of any of the following:	**Treatment period**: Patients in the trial will receive either Q1W or Q2W IV infusions of Pan-HER, depending upon cohort assignment, until occurrence

SECTION	ORIGINAL TEXT	NEW TEXT
	unacceptable toxicity or other conditions preventing further treatment, disease progression, termination of the trial, or patient's decision to withdraw.	of any of the following: unacceptable toxicity or other conditions preventing further treatment, disease progression, termination of the trial, or patient's decision to withdraw.
1 Synopsis: Number of Patients	In total, approximately 131 patients will be included in this trial. It is estimated that approximately 25 patients will be enrolled to receive increasing doses of Pan-HER during Part 1...	In total, approximately 134 patients will be included in this trial. It is estimated that approximately 34 patients will be enrolled to receive increasing doses of Pan-HER during Part 1…
	It is estimated that approximately 6 patients will be enrolled to the PET Expansion Cohort. The exact number of patients will depend upon identification of patients with FDG-avid tumors.	*Deleted; the PET Expansion Cohort has been removed.*
	It is planned to enroll and treat approximately 100 patients during Part 2 with 25 patients in each dose-expansion cohort.	It is planned to enroll and treat approximately 100 patients during Part 2.
1 Synopsis: Main Inclusion and Exclusion Criteria	**Main inclusion criteria all patients, Part 1 and Part 2**: • PET Expansion Cohort: Epithelial malignancy, measurable according to RECIST v1.1 that has been confirmed by 18F-FDG-PET imaging to be FDG-avid within 28 days prior to C1/D1	*Deleted; the PET Expansion Cohort has been removed.*
	Additional inclusion criteria applicable to Part 2 ONLY: • Epithelial malignancy (types to be specified in a CTP amendment), measurable according to RECIST v1.1 that has been confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) within 4 weeks prior to C1/D1	**Additional inclusion criteria applicable to Part 2 ONLY**: • Epithelial malignancy (HER2+ solid tumor malignancies, pancreatic carcinoma, and 2 other tumor types to be specified in a protocol amendment), measurable according to RECIST v1.1 that has been confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) within 4 weeks prior to C1/D1
	Main exclusion criteria: • Any antineoplastic agent (standard or investigational) within 4 weeks prior to C1/D1	**Main exclusion criteria**: • Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 4 weeks or 5 plasma half-lives, whichever is shortest, prior to C1/D1except: a. Nitrosoureas and mitomycin C within 6 weeks prior to C1/D1
	Main exclusion criteria: • Known central nervous system (CNS) or leptomeningeal metastases not controlled by prior surgery or radiotherapy, or symptoms suggesting CNS involvement for which treatment is required	**Main exclusion criteria**: • Central nervous system (CNS) malignancies including: a. Primary malignancies of the CNS b. Known, untreated CNS or leptomeningeal metastases, or spinal cord compression; patients with any of these not controlled by prior surgery or radiotherapy, or symptoms suggesting CNS metastatic involvement for which treatment is required
1 Synopsis: Investigational Medicinal Product: Dose(s) and Treatment	Pan-HER will be initiated on C1/D1 and will be administered Q2W (previously Q1W) by IV infusion in cycles of treatment: • Dosing on Day 1 and 15 of each 28-day cycle (±2 days) As of Amendment 3: Doses previously administered on Days 8 and 22 are omitted. All patients will receive the allocated dose of Pan-HER until treatment	Pan-HER will be initiated on C1/D1 and, based on cohort assignment, will be administered either Q1W or Q2W to separate dose-escalation cohorts of patients by IV infusion in cycles of treatment: • Q1W: Dosing on Day 1, 8, 15, and 22 of each 28-day cycle (±2 days) • Q2W: Dosing on Day 1 and 15 of each 28-day cycle (±2 days) All patients will receive the allocated dose and schedule of Pan-HER until

SECTION	ORIGINAL TEXT	NEW TEXT
Schedule	withdrawal…	treatment withdrawal…
	The duration of infusion will be (prior to Amendment 5): • Approximately 2 hours (+10 min) for the 1st infusion • Approximately 1.5 hours (+10 min) for the 2nd infusion • Approximately 1 hour (+10 min) for subsequent infusions	*Deleted; infusion duration information prior to Amendment 5 has been removed.*
1 Synopsis: Dose-Limiting Toxicities (Part 1 only)	A minimum of 2 infusions (previously 4 infusions with Q1W dosing) of Pan-HER must have been administered at the assigned dose for a patient to have completed the DLT-observation period.	A minimum of 4 infusions with Q1W dosing, and 2 infusions with Q2W dosing must have been administered at the assigned dose for a patient to have completed the DLT-observation period.
1 Synopsis: Trial Assessments	**Safety Assessments**: *Not applicable* **Disease Assessments**: • Evaluation of tumor metabolic activity by ^{18}F-FDG PET **Additional Assessments**: • PK sampling with extended PK-profiling after the first and fourth infusion of Pan-HER (C1/D1 and C1/D22, respectively)	**Safety Assessments**: • Complement Panel, applicable for Part 2 **Disease Assessments**: *Deleted; the PET Expansion Cohort has been removed.* **Additional Assessments**: • PK sampling with extended PK-profiling after the first and fourth infusion of Pan-HER (C1/D1 and C1/D22, respectively) for Q1W dosing, and after the first and third infusion of Pan-HER (C1/D1 and C2/D1, respectively) for Q2W dosing
1 Synopsis: Statistical Methods and Sample Size Considerations	…Based on the dose-escalation design, it is planned to enroll approximately 25 patients during the first part of the trial.	…Based on the dose-escalation design, it is planned to enroll approximately 34 patients during the first part of the trial.
	It is estimated that approximately 6 patients will be enrolled to the PET Expansion Cohort. The exact number of patients will depend upon identification of patients with FDG-avid tumors. Observations regarding changes in tumor metabolism will be described.	*Deleted; the PET Expansion Cohort has been removed.*
	It is planned to enroll and treat approximately 100 patients during Part 2: 25 patients in each dose-expansion cohort, selected by underlying malignancy. The planned number of patients to be enrolled may be adjusted when the four tumor types have been selected...	It is planned to enroll and treat approximately 100 patients during Part 2. The planned number of patients to be enrolled may be adjusted when the 4 expansion cohorts (i.e., based on defined molecular profile(s) and tumor types) have been selected…
3.1.2 and 3.1.3	*Not applicable*	*Sections 3.1.2 and 3.1.3 have been updated to include more recent scientific and clinical experience data, including new citations from new references 25-29.*
3.2.4.1 Protocol Sym013-01	This is the first clinical trial to study Pan-HER. As of Amendment 5, a total of 16 patients have been entered to Part 1 of this trial: 1 patient each at Dose Level 1 and 2, and 4 patients at Dose Level 3 (1, 2, and 4 mg/kg, respectively) dosed on a weekly (Q1W) schedule, followed by 3 patients at Dose Level 4 and 7 patients at Dose Level 5 (6 and 9 mg/kg, respectively) dosed on an every second week (Q2W) schedule.	This is the first clinical trial to study Pan-HER. As of Amendment 6, a total of 19 patients have been entered to Part 1 of this trial: 1 patient each at 1 mg/kg and 2 mg/kg weekly (Q1W), 4 patients at 4 mg/kg Q1W, 3 patients at 6 mg/kg every second week (Q2W), 7 patients at 9 mg/kg Q2W, and with Amendment 5, 3 patients at the recently initiated cohort of 9 mg/kg Q2W + mandatory intensive prophylaxis for infusion-related reactions (IRRs) and oropharyngeal mucositis…

SECTION	ORIGINAL TEXT	NEW TEXT
		Additional text has been revised throughout this entire section. As of Amendment 6: With Amendment 3, Q1W dosing was halted; with Amendment 6, Q1W dosing is reintroduced under the prophylaxis and infusion duration conditions outlined in Amendment 5…
4.1.1 Primary Objective (Part 1)	To assess the safety and tolerability of Pan-HER when administered Q1W and Q2W by IV infusion to patients with advanced epithelial malignancies without available therapeutic options. As of Amendment 3: The dosing interval in this trial has been changed from Q1W to Q2W (2 doses equaling 1 cycle)…	To assess the safety and tolerability of Pan-HER when administered either Q1W or Q2W by IV infusion to separate dose-escalation cohorts of patients with advanced epithelial malignancies without available therapeutic options.
4.1.2 Secondary Objectives	1. To determine a RP2D of Pan-HER	1. To determine a RP2D and regimen of Pan-HER
4.1.3 Exploratory Objective	To evaluate by fluorine-18 radiolabeled fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) the effects on tumor metabolism of Pan-HER when administered Q2W at the RP2D in an expansion cohort of patients with FDG-avid tumors.	*Deleted; the PET Expansion Cohort has been removed.*
4.2.1 Primary Objective (Part 2)	To evaluate the antitumor effect of Pan-HER when administered Q2W at the RP2D to patients with advanced epithelial malignancies without available therapeutic options (4 tumor types to be selected).	To evaluate the antitumor effect of Pan-HER when administered at the RP2D and regimen to patients with advanced epithelial malignancies without available therapeutic options. Four (4) dose-expansion cohorts will be evaluated: Cohort A (HER2+ solid tumor malignancy Basket Cohort*), Cohort B (pancreatic carcinoma), Cohort C (to be determined [TBD]), or Cohort D (TBD)…
5.1 Overall Design and Plan	This is an open-label, multicenter trial composed of 2 parts in which Pan-HER will be evaluated when administered by the IV route on a Q2W (previously Q1W) schedule in patients with advanced epithelial malignancies without available therapeutic options: • Part 1 is a Phase 1a dose-escalation designed to determine the RP2D • Part 2 is a Phase 2a dose-expansion at the RP2D. Four tumor types to be evaluated in this part of the trial will be selected based upon findings from Part 1, additional preclinical data, and additional clinical data available at that time from other agents inhibiting these targets. Patients will be entered, depending upon their underlying malignancy, to one of 4 corresponding expansion cohorts, Cohort A, Cohort B, Cohort C, or Cohort D.	This is an open-label, multicenter trial composed of 2 parts in which Pan-HER will be evaluated when administered by IV to patients with advanced epithelial malignancies without available therapeutic options: • Part 1 is a Phase 1a dose-escalation evaluating Q1W and Q2W schedules of administration in separate dose-escalation cohorts to determine the recommended phase 2 dose (RP2D) and regimen of Pan-HER • Part 2 is a Phase 2a dose-expansion at the RP2D and regimen. Four (4) dose-expansion cohorts will be evaluated in this part of the trial and will be selected based upon findings from Part 1, additional preclinical data, and additional clinical data available at that time from other agents inhibiting these targets. Patients will be entered, depending upon either a defined molecular profile or profiles, or their underlying malignancy, to 1 of 4 corresponding expansion cohorts: Cohort A (HER2+ solid tumor malignancy Basket Cohort), Cohort B (pancreatic carcinoma), Cohort C (TBD), or Cohort D (TBD).
	During Part 1, cohorts of patients will receive increasing doses of Pan-HER until establishment of: • A maximum administered dose (MAD); a dose, which is evaluated during dose-escalation but demonstrates toxicity above the target toxicity level of	During Part 1, cohorts of patients will receive increasing doses of Pan-HER on either a Q1W or a Q2W schedule until establishment of the following for each schedule: • A maximum administered dose (MAD), the highest dose level

SECTION	ORIGINAL TEXT	NEW TEXT
	33% • An MTD; a dose level below the MAD, which is evaluated to have a toxicity level of 33% or less (An MTD may or may not be found within the dose levels tested. Dose-escalation may be stopped due to toxicity observations other than DLTs and/or results from PK and/or target engagement analyses) • A RP2D to be used in Part 2 (The RP2D may be equal to or lower than the MTD. The RP2D will be selected based on safety data, as well as available PK and target engagement results, as applicable)	administered (in mg/kg). • An MTD; a dose level below the MAD, which is evaluated to have a toxicity level of <33%. An MTD may or may not be found… • A RP2D; the RP2D may be equal to or lower than the MTD for the Q1W and/or Q2W dosing regimens. During Part 2, expansion cohorts of patients will receive the RP2D and regimen... The RP2D and regimen will be selected based on tolerability demonstrated with Q1W and Q2W dosing during Part 1…
	The starting dose of Pan-HER will be 1.0 mg/kg. The following dose levels of Pan-HER potentially will be evaluated: Q1W • Dose Level 1: 1 mg/kg • Dose Level 2: 2 mg/kg • Dose Level 3: 4 mg/kg Q2W • Dose Level 4: 6 mg/kg • Dose Level 5: 9 mg/kg Q2W with mandatory intensive IRR and mucositis prophylaxis; 4h infusion (designated "P") • Dose Level 5P: 9 mg/kg • Dose Level 6P: 12 mg/kg • Dose Level 7P: 15 mg/kg • Dose Level 8P: 18 mg/kg (highest potential dose allowed per protocol) Patients entered to Dose Level 1, 2 and 3 (1, 2, and 4 mg/kg, respectively) were treated Q1W. As of Amendment 3, the dosing schedule in this trial has been changed to Q2W. Patients entered to the trial prior to implementation of this amendment will continue to be treated Q1W. As of Amendment 5, patients entered to Dose Level 5P and all patients thereafter must receive intensive prophylaxis, as defined herein…	The Part 1 starting dose of Pan-HER will be 1 mg/kg Q1W. The following dose levels of Pan-HER are planned to be evaluated: Q1W • Dose Level 1: 1 mg/kg Q1W • Dose Level 2: 2 mg/kg Q1W • Dose Level 3: 4 mg/kg Q1W • *Dose Level 4P: 6 mg/kg Q1W + P (lower doses with prophylaxis may be explored, if indicated) • *Dose Level 5P: 9 mg/kg Q1W + P • *Dose Level 6P: 12 mg/kg Q1W + P • *Dose Level 7P: 15 mg/kg Q1W + P • *Dose Level 8P: 18 mg/kg Q1W + P (highest potential dose allowed per protocol) Q2W • Dose Level 4: 6 mg/kg Q2W • Dose Level 5: 9 mg/kg Q2W • *Dose Level 5P: 9 mg/kg Q2W+ P • *Dose Level 6P: 12 mg/kg Q2W+ P • *Dose Level 7P: 15 mg/kg Q2W + P • *Dose Level 8P: 18 mg/kg Q2W + P (highest potential dose allowed per protocol) *Mandatory intensive IRR and oropharyngeal mucositis prophylaxis; 4-hour infusion (designated "P") Note: Patients entered to Dose Levels 1, 2 and 3 were treated Q1W. As of Amendment 3, the dosing schedule in this trial was changed to Q2W. Patients entered to the trial prior to implementation of this amendment could continue to be treated Q1W. Note: As of Amendment 5, patients entered to Dose Level 5P and all patients thereafter must receive intensive prophylaxis on a mandatory basis

SECTION	ORIGINAL TEXT	NEW TEXT
		to reduce the risk of IRRs and oropharyngeal mucositis, and must receive Pan-HER over a fixed (at minimum) 4-hour (+10 min) period… Note: As of Amendment 6, Q1W dosing is reintroduced under the prophylaxis and infusion duration conditions outlined in Amendment 5…
5.1 Overall Design and Plan (continued)	Once the RP2D is selected, an expansion cohort of patients with FDG-avid tumors will undergo pre- and post-dosing ^{18}F-FDG PET imaging to evaluate the effects on tumor metabolism of Pan-HER when administered at this dose. Imaging to be paired with computed tomography (CT)/ magnetic resonance imaging (MRI) conducted for Disease Status Evaluation. Accrual to this cohort may occur concurrent with accrual to Part 2 of the study.	*Deleted; the PET Expansion Cohort has been removed.*
	During Part 2, the RP2D will be evaluated in 4 dose-expansion cohorts of patients with distinct types of epithelial malignancies. The 4 types of malignancies will be defined based upon findings from Part 1, additional preclinical data, and additional clinical data available at that time from other agents inhibiting these targets… Patients enrolled to dose-expansion cohorts will be treated with Q2W (previously Q1W) IV doses of Pan-HER at the RP2D to investigate the antitumor activity of Pan-HER and to further evaluate safety and tolerability…	During Part 2, the RP2D and regimen will be evaluated in 4 dose-expansion cohorts of patients (Cohort A, Cohort B, Cohort C, or Cohort D). A protocol amendment will be submitted specifying the inclusion and exclusion criteria related to each dose-expansion cohort. Patients enrolled to dose-expansion cohorts will be treated with IV doses of Pan-HER at the RP2D and regimen to investigate the antitumor activity of Pan-HER and to further evaluate safety and tolerability…
	The number of investigational trial sites, hereafter called "trial sites", expected to participate will be approximately 2 to 3 in Part 1 and 20 in Part 2.	The number of investigational trial sites, hereafter called "trial sites", expected to participate will be approximately 3 in Part 1 and 25 in Part 2.
5.2.1 Rationale for Trial Design	Four (4) tumor types to be evaluated in Part 2 will be selected based upon findings from Part 1, additional preclinical data, and additional clinical data from other agents inhibiting these targets available at that time. A CTP amendment will be submitted, detailing the MTD (if found within the dose levels tested), the RP2D, and further specifying the inclusion and exclusion criteria related to each dose-expansion cohort.	Four (4) dose-expansion cohorts to be evaluated in Part 2 will be selected based upon findings from Part 1, additional preclinical data, and additional clinical data from other agents inhibiting these targets available at that time. A protocol amendment will be submitted specifying the inclusion and exclusion criteria related to each dose-expansion cohort.
5.2.2 Rationale for Trial Population	In Part 2, the RP2D will be investigated in patients with epithelial malignancies (4 tumor types to be selected; patients to be entered to Cohort A, Cohort B, Cohort C, or Cohort D, collectively called "dose-expansion cohorts") without available therapeutic options. The selection of tumor types in Part 2 will be based upon findings from Part 1, additional preclinical data, and additional clinical data from other agents inhibiting these targets available at that time. A rationale for the 4 tumor types selected will be provided prior to opening Part 2 of the trial.	In Part 2, the RP2D and regimen will be investigated in patients with epithelial malignancies without available therapeutic options (4 cohorts; patients to be entered to Cohort A [HER2+ solid tumor malignancy Basket Cohort], Cohort B [pancreatic carcinoma], Cohort C [TBD], or Cohort D [TBD], collectively called "dose-expansion cohorts"). The selection of expansion cohorts in Part 2 will be based upon findings from Part 1, additional preclinical data, and additional clinical data from other agents inhibiting these targets available at that time. A rationale for the 4 tumor types selected will be provided prior to opening Part 2 of the trial.
5.3.1 Screening	A copy of the fully executed Screening and Allocation Form will be returned to the trial site for archiving. This form documents the allocated dose of Pan-HER.	A copy of the fully executed Screening and Allocation Form will be returned to the trial site for archiving. This form documents the allocated dose and schedule of Pan-HER.

SECTION	ORIGINAL TEXT	NEW TEXT
5.3.3 Treatment	Pan-HER will be administered by IV infusion on a Q2W (previously Q1W) schedule, i.e. dosing will be every 14 (±2) days. Two (2) doses of Pan-HER administered Q2W constitute 1 cycle. As of Amendment 3: With the previous Q1W schedule, dosing was every 7 (±2) days. Four (4) doses of Pan-HER administered Q1W constituted 1 cycle. Patients in Part 1 will be enrolled to dose-escalation cohorts until establishment of an MAD, an MTD and/or a RP2D. Enrollment to the PET Expansion Cohort may follow. During Part 2, all patients will receive the RP2D of Pan-HER. For all patients, the dose to be administered will be documented on the Screening and Allocation Form. Patients will receive the allocated dose according to the assigned dose level until treatment withdrawal.	Pan-HER will be administered by IV infusion on either a Q1W or a Q2W schedule: • Q1W: dosing will be every 7 (±2) days. Four (4) doses of Pan-HER administered Q1W constitute 1 cycle. • Q2W: dosing will be every 14 (±2) days. Two (2) doses of Pan-HER administered Q2W constitute 1 cycle. Patients in Part 1 will be enrolled to either Q1W or Q2W dose-escalation cohorts until establishment of an MAD, an MTD, and/or a RP2D for each schedule. During Part 2, all patients will receive the RP2D and regimen of Pan-HER. For all patients, the dose and schedule to be administered will be documented on the Screening and Allocation Form. Patients will receive the allocated dose and schedule according to their cohort assignment until treatment withdrawal.
5.4 Recruitment Period	Patients will be sequentially enrolled to dose-escalation cohorts until establishment of a RP2D, expectedly beginning of 2018. Enrollment to the PET Expansion Cohort may follow. Enrollment to the expansion cohorts in Part 2 of the trial will commence upon approval of a CTP amendment, defining the expansion cohorts as well as the RP2D to be further explored. Enrollment is expected to be from second half of 2018 to second half of 2019.	Patients will be sequentially enrolled to dose-escalation cohorts on either a Q1W or a Q2W schedule until establishment of a RP2D and regimen, expectedly Q1 2019. Enrollment to the expansion cohorts in Part 2 of the trial will commence upon approval of a protocol amendment defining the expansion cohorts to be further explored. Enrollment is expected to be from Q1 2019 to Q3 2020.
5.5 Number of Patients	In total, approximately 131 patients will be included in this trial. It is estimated that approximately 25 patients will be enrolled to receive increasing doses of Pan-HER during Part 1.	In total, approximately 134 patients will be included in this trial. It is estimated that approximately 34 patients will be enrolled to receive increasing doses of Pan-HER during Part 1.
	It is estimated that approximately 6 patients will be enrolled to the PET Expansion Cohort. The exact number of patients will depend upon identification of patients with FDG-avid tumors.	*Deleted; the PET Expansion Cohort has been removed.*
	It is planned to enroll and treat approximately 100 patients during Part 2: 25 patients in each dose-expansion cohort.	It is planned to enroll and treat approximately 100 patients during Part 2.
6.1 Inclusion Criteria	8. PET Expansion Cohort: Epithelial malignancy, measurable according to RECIST v1.1 that has been confirmed by 18F-FDG-PET imaging to be FDG-avid within 28 days prior to C1/D1 NOTE: Measurable disease is defined as 1 or more target lesions assessed by CT or MRI. A tumor lesion situated in a previously irradiated area is considered measurable only if subsequent disease progression has been documented in the lesion	*Deleted; the PET Expansion Cohort has been removed.*
	Part 2 ONLY: a. Epithelial malignancy (types to be specified in a CTP amendment), measurable according to RECIST v1.1 that has been confirmed by computed	Part 2 ONLY: a. Epithelial malignancy (HER2+ solid tumor malignancy Basket Cohort, pancreatic carcinoma, and 2 other tumor types to be specified in a protocol

SECTION	ORIGINAL TEXT	NEW TEXT
	tomography (CT) or magnetic resonance imaging (MRI) within 4 weeks prior to C1/D1	amendment), measurable according to RECIST v1.1 that has been confirmed by CT or MRI within 4 weeks prior to C1/D1
6.2 Exclusion Criteria	1. Any antineoplastic agent (standard or investigational) within 4 weeks prior to C1/D1	1. Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 4 weeks or 5 plasma half-lives, whichever is shortest, prior to C1/D1 except: • Nitrosoureas and mitomycin C within 6 weeks prior to C1/D1
	6. Central nervous system (CNS) malignancies; known, untreated CNS or leptomeningeal metastases, or spinal cord compression, any of the above not controlled by prior surgery or radiotherapy, or symptoms suggesting CNS involvement for which treatment is required NOTE: Patients with treated CNS metastases will be eligible if they are asymptomatic, do not require corticosteroids or anticonvulsants, and have confirmation of at least stable brain disease status as assessed by 2 imaging studies performed at least 4 weeks apart with the most recent study performed within 4 weeks prior to first trial drug administration	6. Central nervous system (CNS) malignancies including: a. Primary malignancies of the CNS b. Known, untreated CNS or leptomeningeal metastases, or spinal cord compression; patients with any of these not controlled by prior surgery or radiotherapy, or symptoms suggesting CNS metastatic involvement for which treatment is required Note: Patients with treated CNS metastases will be eligible if they are asymptomatic, do not require corticosteroids, and have confirmation of at least stable brain disease status as assessed by 2 imaging studies performed at least 4 weeks apart with the most recent study performed within 4 weeks prior to first trial drug administration. Prophylactic anticonvulsant medications are allowed. Patients with newly identified CNS metastases during study will be considered to have PD and will be discontinued from treatment.
7.1.3.1 Treatment Schedule	All patients will be administered IV infusions of Pan-HER, dosed according to body weight, through a peripheral line or indwelling venous access device, and with the use of an infusion pump and an inline filter. Pan-HER will be administered on a Q2W (previously Q1W) schedule, i.e. dosing will be every 14 (±2) days. Two (2) doses of Pan-HER administered Q2W constitute 1 cycle. As of Amendment 3: With the previous Q1W schedule, dosing was every 7 (±2) days. Four (4) doses of Pan-HER administered Q1W constituted 1 cycle.	All patients will be administered IV infusions of Pan-HER, dosed according to body weight, through a peripheral line or indwelling venous access device, and with the use of an infusion pump and an inline filter. Pan-HER will be administered on either a Q1W or a Q2W schedule: • Q1W: dosing will be every 7 (±2) days. Four (4) doses of Pan-HER administered Q1W constitute 1 cycle • Q2W: dosing will be every 14 (±2) days. Two (2) doses of Pan-HER administered Q2W constitute 1 cycle
7.1.3.2 Part 1, Dose-Escalation	The starting dose of Pan-HER will be 1.0 mg/kg. The following dose levels of Pan-HER will be potentially evaluated: Q1W • Dose Level 1: 1 mg/kg • Dose Level 2: 2 mg/kg • Dose Level 3: 4 mg/kg Q2W • Dose Level 4: 6 mg/kg • Dose Level 5: 9 mg/kg Q2W with mandatory intensive IRR and mucositis prophylaxis; 4h infusion	The starting dose of Pan-HER will be 1 mg/kg Q1W. The following dose levels of Pan-HER are planned to be evaluated: Q1W • Dose Level 1: 1 mg/kg Q1W • Dose Level 2: 2 mg/kg Q1W • Dose Level 3: 4 mg/kg Q1W • *Dose Level 4P: 6 mg/kg Q1W + P (lower doses with prophylaxis may be explored, if indicated) • *Dose Level 5P: 9 mg/kg Q1W + P • *Dose Level 6P: 12 mg/kg Q1W + P

SECTION	ORIGINAL TEXT	NEW TEXT
	(designated "P") • Dose Level 5P: 9 mg/kg • Dose Level 6P: 12 mg/kg • Dose Level 7P: 15 mg/kg • Dose Level 8P: 18 mg/kg (highest potential dose allowed per protocol) Patients entered to Dose Level 1, 2 and 3 (1, 2, and 4 mg/kg, respectively) were treated Q1W. As of Amendment 3, the dosing schedule in this trial has been changed to Q2W. Patients entered to the trial prior to implementation of this amendment will continue to be treated Q1W. As of Amendment 5, patients entered to Dose Level 5P and all patients thereafter must receive intensive prophylaxis…	• *Dose Level 7P: 15 mg/kg Q1W + P • *Dose Level 8P: 18 mg/kg Q1W + P (highest potential dose allowed per protocol) Q2W • Dose Level 4: 6 mg/kg Q2W • Dose Level 5: 9 mg/kg Q2W • *Dose Level 5P: 9 mg/kg Q2W + P • *Dose Level 6P: 12 mg/kg Q2W + P • *Dose Level 7P: 15 mg/kg Q2W + P • *Dose Level 8P: 18 mg/kg Q2W + P (highest potential dose allowed per protocol) *Mandatory intensive IRR and oropharyngeal mucositis prophylaxis; 4-hour infusion (designated "P") Note: Patients entered to Dose Levels 1, 2 and 3 treated Q1W. As of Amendment 3, the dosing schedule in this trial was changed to Q2W. Patients entered to the trial prior to implementation of this amendment could continue to be treated Q1W. Note: As of Amendment 5, patients entered to Dose Level 5P and all patients thereafter must receive intensive prophylaxis on a mandatory basis to reduce the risk of IRRs and oropharyngeal mucositis, and must receive Pan-HER over a fixed (at minimum) 4-hour (+10 min) period… As of Amendment 6: Q1W dosing is reintroduced under the prophylaxis and infusion duration conditions outlined in Amendment 5…
7.1.3.2 Part 1, Dose-Escalation (continued)	Enrollment will be staggered between the first and second patient in each new dose level tested. The first patient must have completed and tolerated the first dose of Pan-HER including follow-up until Day 15 of Cycle 1 (C1/D15)…	Staggered Dosing: Enrollment will be staggered between the first and second patient in each new dose level tested. The first patient must have completed and tolerated the first 2 doses of Pan-HER with Q1W dosing, or the first dose of Pan-HER with Q2W dosing, including follow-up until Day 15 of Cycle 1 (C1/D15)…
	The RP2D may be equal to or lower than the MTD. The RP2D will be selected based on safety data, as well as available PK and target engagement results, as applicable.	RP2D: The RP2D may include a dose or a combination of doses equal to or lower than the MTD for the Q1W and/ or Q2W dosing regimens. A dose or doses between tolerated doses investigated in Part 1 may also be selected if data indicate this to be optimal…
	Once the RP2D is selected, enrollment to the PET Expansion Cohort may begin.	*Deleted; the PET Expansion Cohort has been removed.*
8.2.3 Dose-Limiting Toxicities Evaluation (Part 1 Only)	• Reported during Cycle 1 with final assessment 14 days (previously 7 days with Q1W dosing) after the last dose of Cycle 1 or prior to dosing on Day 1 of Cycle 2 (C2/D1)	• Reported during Cycle 1 with final assessment 7 days after the last dose of Cycle 1 for Q1W dosing, 14 days after the last dose of Cycle 1 for Q2W dosing, or prior to dosing on Day 1 of Cycle 2 (C2/D1)

SECTION	ORIGINAL TEXT	NEW TEXT
8.2.9 Laboratory Assessments and Pregnancy Test	*Not applicable*	All individual assessments are to be performed on or about the indicated visit day (i.e., ±2 days) unless otherwise stated.
8.2.10 Complement Panel (Part 2 only) (Central Laboratory)	8.2.10 Complement Panel To include total complement hemolytic activity (CH50), C3, C4, C3a, and C4a • Cycle 1 Day 1 (timepoints coincide with PK sampling) Day 1 -Prior to SOI (- 4h) -EOI (+ 10 min) -4 hours after EOI (±30 min) -8 hours after EOI (±90 min) Day 2 -24 hours after EOI (±6 h) •In the event of an IRR Note: Comprehensive collection of clinical samples is critical to the conduct of this study. In situations where collection of the EOI + 8h samples is logistically difficult due to clinic staff availability… A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites in Part 2.	8.2.10 Complement Panel (Part 2 only) (Central Laboratory) To include total complement hemolytic activity (CH50), C3, C4, C3a, and C4a • Cycle 1 (timepoints coincide with PK sampling) Day 1 -Prior to SOI (- 4h) -4 hours after EOI (±30 min) • In the event of an IRR Note: A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.
8.3.4 ^{18}F-FDG PET Imaging (PET Expansion Cohort Only)	8.3.4 ^{18}F-FDG PET Imaging (PET Expansion Cohort Only) An expansion cohort of patients with FDG-avid tumors will undergo 18F-FDG PET imaging to evaluate the effects on tumor metabolism of Pan-HER when administered Q2W at the RP2D…	*Entire section deleted; the PET Expansion Cohort has been removed.*
8.6 Skin Biopsy	All patients enrolled will undergo skin biopsies for evaluation of target-engagement (EGFR and HER3)... Skin biopsies are requested from a rash-free area. • Screening, after confirmation of eligibility • End of Cycle 2 (prior to dosing Cycle 3) or upon PD, whichever occurs first Note: End of cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle	All patients enrolled will undergo 3 skin biopsies for evaluation of target engagement (EGFR and HER3)… Skin biopsies are requested from a rash-free area. • Screening, after confirmation of eligibility • C1/D8 (prior to dosing if on dosing day) • C1/D15 (prior to dosing)
9.3.1 Timeframes for Reporting to the Sponsor	In case of an SAE, the Investigator must, within 24 hours of first awareness of the event, report the SAE to the Sponsor or designee by fax or e-mail. Fax number(s) and e-mail address will be stated in the SAE report form and the SAE report form instructions. Timelines for reporting of SAEs and SAE follow-up information are shown in Table 13.	In case of an SAE, the Investigator must, within 24 hours of first awareness of the event, report the SAE to the Sponsor or designee by fax or e-mail transmission. Fax number(s) and e-mail address(es) will be stated on the SAE Report Form and the SAE Report Form Completion Instructions. SAE follow-up information must also be reported to the Sponsor or designee within 24 hours of awareness.

SECTION	ORIGINAL TEXT	NEW TEXT
		Removed Table: Timelines for Reporting Serious Adverse Events and Follow-up
9.5.2 Observation Period for Dose-Limiting Toxicities	The decision to dose-escalate will be based on close monitoring of safety during the observation period for DLTs, defined as the initial 28-day period (±2 days) from first treatment of Pan-HER (i.e. Cycle 1) and including 14 days (previously 7 days with Q1W dosing) of follow-up from the last dose of Cycle 1. A minimum of 2 infusions (previously 4 infusions with Q1W dosing) of Pan-HER must have been administered at the assigned dose for a patient to have completed the DLT-observation period.	The decision to dose-escalate will be based on close monitoring of safety during the observation period for DLTs, defined as the initial 28-day period (±2 days) from first treatment of Pan-HER (i.e., Cycle 1) and including 7 days of follow-up (Q1W dosing) or 14 days of follow-up (Q2W dosing) from the last dose of Cycle 1. A minimum of 4 Pan-HER infusions (Q1W dosing) or 2 Pan-HER infusions (Q2W dosing) must have been administered at the assigned dose for a patient to have completed the DLT-observation period.
9.7 Pregnancy	Pregnancies reported in female partners of male trial patients must also be included in the database; therefore, a pregnant partner of a trial participant must provide informed consent before information can be collected. All pregnancies must be followed up every third month to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs as appropriate (trial patients only). Elective terminations for non-medical reasons should not be reported as AEs. Spontaneous abortion must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the trial and considered by the Investigator as possibly related to the IMP (possibly, probably, or related to Pan-HER), must be promptly reported to the Sponsor or designee.	Pregnancies reported in female partners of male trial patients must also be included in the safety database; therefore, a female partner of a male patient on the trial who becomes pregnant will be approached for consent to have the pregnancy followed until term and reported upon to the Sponsor or designee. All pregnancies must be followed up every third month to determine outcome and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs as appropriate. Elective terminations for non-medical reasons should be reported as follow-up, but not as a separate AE/SAE unless complications meet AE/SAE criteria. Spontaneous abortion must be reported as an SAE. Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the trial and considered by the Investigator as possibly-, probably-, or related to Pan-HER must be promptly reported to the Sponsor or designee.
10.1 Sample Size Considerations	Based on the dose-escalation design, it is planned to enroll approximately 25 patients during the dose-escalation part of the trial.	Based on the dose-escalation design, it is planned to enroll approximately 34 patients during the dose-escalation part of the trial.
	It is estimated that approximately 6 patients will be enrolled to the PET Expansion Cohort. The exact number of patients will depend upon identification of patients with FDG-avid tumors.	*Deleted; the PET Expansion Cohort has been removed.*
	During Part 2, it is planned to enroll and treat approximately 25 patients in each dose-expansion cohort, selected by underlying malignancy. The planned number of patients to be enrolled might be adjusted when the four tumor types have been selected…	During Part 2, it is planned to enroll and treat approximately 100 patients. The planned number of patients to be enrolled might be adjusted when the 4 dose-expansion cohorts (i.e., based on defined molecular profiles(s) and tumor types) have been selected…
10.3.2 Part 2, Dose-Expansion	The primary objective of Part 2 is to evaluate the antitumor effect of Pan-HER when administered Q2W (previously Q1W) at the RP2D to patients with advanced epithelial malignancies (4 tumor types to be selected).	The primary objective of Part 2 is to evaluate the antitumor effect of Pan-HER when administered at the RP2D and regimen to patients with advanced epithelial malignancies without available therapeutic options. Four (4) dose-expansion cohorts will be evaluated.
10.4.4 Pharmacokinetic	The PK endpoints with Q2W dosing will be derived based on the concentration time curves of Pan-HER, after the first and third infusion of Pan-HER in both parts of the trial.	The PK endpoints with Q1W dosing will be derived based on the concentration time curves of Pan-HER after the first and fourth infusion of Pan-HER in both parts of the trial, as applicable.

SECTION	ORIGINAL TEXT	NEW TEXT
Endpoints and Analyses	As of Amendment 3: For patients entered to Dose Level 1, 2 and 3 (1, 2, and 4 mg/kg, respectively) treated on a Q1W schedule, PK endpoints will be derived based on the concentration time curves of Pan-HER after the first and fourth infusion of Pan-HER.	The PK endpoints with Q2W dosing will be derived based on the concentration time curves of Pan-HER after the first and third infusion of Pan-HER in both parts of the trial, as applicable. The serum concentration of total Pan-HER will be derived as the sum of the serum concentration of all six constituting antibodies. Supporting plots and PK parameters for the individual antibodies will also be generated.
	Individual curves of serum concentration of total Pan-Her versus time after the first and fourth infusion of Pan-HER will be presented on log- and linear scale for all patients in the FAS.	Individual curves of serum concentration of total Pan-HER versus time after the first and fourth infusion of Pan-HER with Q1W dosing, and after the first and third infusion of Pan-HER with Q2W dosing, will be presented on log- and linear scale for all patients in the FAS.
10.4.5 Additional Endpoints and Analyses	• Changes in tumor metabolism as evaluated by ^{18}F-FDG PET	*Deleted; the PET Expansion Cohort has been removed.*
13.2 Source Documents	Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to: Hospital records, clinical and office charts, laboratory notes, memoranda… The Investigator must maintain source documentations for each patient in the trial and all information in the CRF must be traceable to these source documents in the patient's file. Data not requiring a separate written record, i.e. data, which may be recorded directly in the CRF, will be defined before trial start.	The Investigator will maintain adequate and accurate records for each patient treated with study drug. Source documents, including but not limited to, hospital, clinic or office charts; laboratory reports; radiology and pathology reports; pharmacy records; study worksheets; anonymized photographs aimed at documenting study-associated clinical findings; and signed ICFs, must completely reflect the nature and extent of the patient's medical care, must be included in the Investigator's files along with patient study records, and must be available for source document verification against entries in the CRF. The Sponsor (or designee) will check CRF entries against source documents according to the guidelines of ICH E6(R2) GCP. Data not requiring a separate written record (i.e., data which may be recorded directly in the CRF) will be determined before trial start. The ICF will include a statement by which patients allow the Sponsor (or designee), as well as authorized regulatory agencies, to have direct access to source data that support data in the CRF (e.g., patient medical files, appointment books, original laboratory records, etc.). The Sponsor (or designee), bound by confidentiality and privacy regulations, will not disclose patient identities or personal medical information.
14.1 Data Handling	Data will be handled according to good data management practices, all applicable data protection regulations, and will comply with ICH GCP E6(R2).	Study data collection, processing, transfer, and reporting, as well as handling of study personnel information, will be done in compliance with ICH E6(R2) GCP and all applicable data protection regulations…
14.2 Recording of Data	Corrections to entered data will be tracked within the EDC system.	Corrections to entered data will be identified and tracked by audit trails within the EDC system.
14.7 Data Processing	The Sponsor or designee will be responsible for data processing in accordance with the applicable Data Management SOPs. A Data Management Plan will be generated for this trial.	A Data Management Plan (DMP) will be prepared for this trial. The Sponsor (or designee) will be responsible for data processing in accordance with applicable Data Management SOPs and the trial DMP.

SECTION	ORIGINAL TEXT	NEW TEXT
	Database lock will occur once quality control and quality assurance procedures (if applicable) have been completed upon reaching the data cut-off for primary analysis. Portable Document Format (PDF) files of the CRFs will be provided to the Investigator before access to the CRF system is revoked.	Database Lock will occur upon reaching the predefined data cut-off for primary analysis and completion of Sponsor's (or designee's) quality control and quality assurance procedures. Portable Document Format (PDF) files of the electronic CRFs will be provided to the Investigator upon removal of access to the electronic CRFs.
14.9 Compliance with the General Data Protection Regulation	*Not applicable (this is a new section)*	The applicable data protection legislation requires that parties enter into a written contract if one party (data processor) processes personal data on behalf of the other party (data controller). This written contract must regulate the subject-matter and duration of the processing, the nature and purpose of the processing, the types of personal data and categories of data subjects, as well as the obligations and rights of the data controller...