

Official Title: **PHASE II, EXPLORATORY, MULTICENTER, NON RANDOMIZED, SINGLE AGENT COHORT STUDY TO DETERMINE BEST TUMOR RESPONSE WITH TRASTUZUMAB EMTANSINE IN HER2 OVEREXPRESSING SOLID TUMORS**

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PROTOCOL

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PROTOCOL AMENDMENT APPROVAL

Approver's Name	Title	Date and Time (UTC)
[REDACTED]	Company Signatory	09-Feb-2017 09:50:30

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PROTOCOL AMENDMENT, VERSION 2

RATIONALE

Changes to the protocol have been made to address the following:

- Modifications in study screening and assessments, and to include separate 'Schedule of Activities' for the weekly (Regimen A) and 3-weekly (Regimen B) dosing of trastuzumab emtansine treatment.
- The addition of pharmacokinetic objective and endpoints.
- The medical monitor for the study has been replaced.
- Clarification and correction to some minor errors/inconsistencies in the text have been made.

Deleted text appears in ~~black strikethrough~~. New text is marked *in italics*. This amendment represents changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 2

SUMMARY OF CHANGES

GLOBAL CHANGES

The Medical Monitor has been changed to [REDACTED].

The protocol title has been amended throughout the protocol, for consistency, to:
'PHASE II, EXPLORATORY, MULTICENTER, NON RANDOMIZED, SINGLE AGENT COHORT STUDY TO DETERMINE BEST TUMOR RESPONSE WITH TRASTUZUMAB EMTANSINE IN HER2 OVEREXPRESSING SOLID TUMORS'

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

1.1 BACKGROUND ON HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR HER2

{...}

HER2 aberrations (gene amplification, gene mutations and protein overexpression) are reported in diverse other malignancies for instance esophagus, colorectal, pancreatic, bladder and prostate cancer (Yan et al 2014, Yoon et al 2014, Sato-Kuwabara et al 2009, Seo et al 2014, Stoecklein et al 2004, Minner et al 2010, Carneiro et al 2015, Hansel et al 2008). Urothelial bladder cancer (UBC) and *pancreatic cancers/cholangiocarcinoma* are areas of high unmet medical need, and a more efficacious and less toxic therapy is desired. For UBC, it is currently estimated that the incidence of HER2 overexpression (immunohistochemistry [IHC]3+ and IHC2+/in situ hybridization [ISH]+) in UBC ranges from 22-37% (Internal Data, Dendreon DN24-02, Hayashi et al 2014). In *pancreatic ductal adenocarcinoma (PDAC)*, the HER2 gene locus was frequently (24%) amplified and the rate of overexpression (2+ and 3+) was 10%, but no prognostic significance was found (Stoecklein et al 2004). In addition, Safran et al (2004) have reported 30 patients (88%) with IHC2+ and 4 patients (12%) with IHC3+ HER2 status in a Phase II study of trastuzumab in HER2-positive metastatic pancreatic adenocarcinoma. In another Phase II study it has been shown that in contrary to breast and gastric cancer, where HER2 protein and HER2 gene amplification normally match, only 7 out of 11 (64%) patients with IHC3+ and 1 out of 22 (5%) with IHC2+ HER2 expression showed gene amplification (Harder et al 2012). Maybe HER2 overexpression in pancreatic cancer is regulated by other mechanisms on the transcriptional or translational level rather than gene amplification as postulated by Ukita et al (2002) for intrahepatic biliary tract cancer. The role of HER2 targeting therapy in this and potentially other indications is still unclear and needs to be further explored.

1.2.2.5 Nonclinical Development of Trastuzumab Emtansine in Pancreatic Cancers/Cholangiocarcinoma-Cancer

In a study by Buechler et al (2005) the effect of a combination therapy consisting of Herceptin, gemcitabine and docetaxel on anchorage-independent growth of different human pancreatic cancer cell lines was tested. Monotherapy with Herceptin had shown

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some tumor suppressive activity particularly in those cell lines, which overexpress the HER2 receptor (Buechler et al 2001) and gemcitabine is the current standard chemotherapeutic agent for therapy of pancreatic cancer (Slamon 2000). Because of the promising results in BC where the combination therapy of Herceptin plus taxanes has been clinically effective, the combination of Herceptin with docetaxel and gemcitabine was tested (Slamon et al 2001; Pegram et al 2004, Kimura et al 2006). In order to test whether this therapeutic regimen was also effective *in vivo*, a murine model for pancreatic cancer in which tumor xenografts were grown in an orthotopic location within the pancreatic parenchyma was used. Two different human pancreatic cancer cell lines with different characteristics of HER2 expression were *tested induced*. According to the clinical *scoring scheme grading* of HER2 expression, the MIA PaCa-2 cell line would be *scored graded* as HER2 3+ whereas the HPAF-II cell line would be *scored graded* as HER2 (+/-). Monotherapy with individual substances improved the survival benefit moderately. In contrast, there was a dramatic survival improvement upon combination therapy of gemcitabine and docetaxel or both substances plus Herceptin compared to monotherapy alone. More importantly, the metastatic score was reduced when Herceptin was added to gemcitabine and docetaxel in the high HER2-expressing cell line, MIA PaCa-2.

1.2.2.10 Pharmacokinetic Properties of Trastuzumab Emtansine in Pancreatic Cancers/Cholangiocarcinoma Cancer

Currently, there are no PK data available for trastuzumab emtansine in *pancreatic cancers/cholangiocarcinoma cancer*.

1.3 STUDY RATIONALE AND BENEFIT RISK RATIO

A number of anti-HER2 therapies have proven efficacy, are approved and part of the SOC for HER2-positive BC and GC (see Sections 1.1 and 1.2). However, this is not yet the case for trastuzumab emtansine which currently is only available for BC. HER2 overexpression has been identified in some other tumors as described in Section 1.1. These findings pose the intriguing question if trastuzumab emtansine could improve patient outcomes in those tumor types and beyond BC and GC. There is currently no clinical data on the potential therapeutic effect of trastuzumab emtansine treatment in HER2-positive tumors such as esophageal-, colorectal-, *pancreatic*s/cholangio-, prostate and bladder carcinoma.

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1.3.1 Rationale for Patient Selection

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Pancreatic cancers/cholangiocarcinoma cancer: Pancreatic adenocarcinoma is the 5th most frequent cause of cancer related deaths (Hartwig et al 2013). Survival rates remain disappointing (median OS with palliative chemotherapy 11.1 months) and many patients will develop distant metastases (Conroy et al 2011). The HER2 overexpression rate is as high as 11% (and varies widely between patients). Interestingly, overexpression of the HER2 protein does not correlate well to amplification of the HER2

locus; especially it was shown, that HER2 IHC3+ protein expression did not correlate with gene amplification (Harder et al 2012). HER2 overexpression in pancreatic cancer may be due to gene deregulation rather than gene amplification as postulated by Ukita et al (2002) for intrahepatic biliary tract cancer (Harder et al 2012). Nevertheless an approach with an ADC such as trastuzumab emtansine may be considered a potential treatment option.

Cholangiocarcinomas may be considered related tumors and these patients can be included in later stages of this study. The incidence and mortality rates of cholangiocarcinoma, especially those of *intrahepatic cholangiocarcinoma IHC*, are increasing worldwide (Khan et al 2005). Complete resection is the only way to cure the disease at present. However, because cholangiocarcinoma are difficult to diagnose at an early stage and extend diffusely, most patients have unresectable disease at clinical presentation, and prognosis is very poor (5-year survival is 0–40% even in resected cases) (Yoshikawa et al 2008). Approximately 8% of patients have HER2 overexpression (Yan et al 2015 2014) and may therefore benefit from a HER2-targeted therapeutic approach.

Patients diagnosed with *locally advanced (unresectable and not treatable with curative intent)* or metastatic UBC (MUBC) or *locally advanced (unresectable and not treatable with curative intent)* or metastatic pancreatic *cancer/cholangiocarcinoma cancer* have very limited treatment options to date, especially if they present in an advanced stage of their cancer, with a high mortality and low long-time survival rates. New therapeutic approaches are therefore needed for these patients with a high unmet medical need and limited other treatment options, especially in late stage.

1.3.2 Rationale for Study Design

KAMELEON is a Phase II, proof of concept, single arm study, designed to estimate the efficacy of trastuzumab emtansine in HER2 overexpressing *locally advanced (unresectable and not treatable with curative intent)* or metastatic MUBC, *locally advanced (unresectable and not treatable with curative intent)* or metastatic and *metastatic pancreatic cancers/cholangiocarcinoma-cancer* in patients with advanced disease where cure is no longer possible and where no other treatment options are available anymore. This The trial might be opened up to a diverse range of other HER2 overexpressing tumors as described further above. Trastuzumab emtansine has proven efficacious in HER2-positive BC and has a tolerable safety profile (see Section 1.2.2.10). Therefore, the risk benefit in this study is deemed positive.

The study design will allow for the examination of *locally advanced (unresectable and not treatable with curative intent)* or metastatic MUBC and *metastatic pancreatic cancers/cholangiocarcinoma-cancer* with enough statistical power to determine whether further examination may be warranted in these indications or potential additional indications. To investigate a potential difference in treatment efficacy for MUBC and *metastatic pancreatic cancers/cholangiocarcinoma-cancer* with homogeneous HER2 expression and the carcinoma with a more focal HER2 expression, patients will be stratified according to the HER2 IHC pattern in their baseline tissue biopsy (e.g., 30-70%

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vs 71-100% of tumor cells expressing HER2). Patients with very focal HER2 IHC pattern (e.g., < 30%) will be excluded from this study. The open-label, uncontrolled design is appropriate since the trial will only enroll patients with HER2-positive cancers and who in the opinion of the investigator have trastuzumab emtansine as their best treatment option. The study is intended as a proof of concept.

{...}

1.3.4 Rationale for Translational Research Program

This study will generate a unique data set of patients with HER2 expressing *locally advanced (unresectable and not treatable with curative intent) or metastatic MIBC or locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancers/cholangiocarcinoma* cancer treated with trastuzumab emtansine. It will create a comprehensive data set of markers that will be informative about differences and similarities between tissues, treatment outcome in these patients. Therefore, the mandatory archival tumor biopsies from all patients included in this study and the optional biopsy collected at disease progression may be used for exploratory protein, deoxyribonucleic acid (DNA)-based analyses and ribonucleic acid (RNA)-based expression analyses. In addition, mandatory plasma samples at baseline and at various timepoints during treatment will be collected (see Schedule of Activities, Appendix 1). These plasma samples will be used for exploratory biomarker assays which may include but are not limited to analysis of circulating protein and circulating tumor DNA. All exploratory biomarker analyses will be performed retrospectively and are clearly defined in the patient's informed consent.

1.3.5 Benefit Risk Assessment

{...}

HER2 overexpression has been shown in a number of other tumor types. The tumor types investigated in this study have poor prognosis in the advanced setting. Despite some recent progresses in the treatment of these cancers, the current standard of care still results in modest prolongation of survival in the advanced setting. Therefore the prognosis for this advanced-staged cancer types is still poor. Targeted therapies for *locally advanced (unresectable and not treatable with curative intent) or metastatic MIBC* or *locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancers/cholangiocarcinoma-cancer* must not only demonstrate anti-tumor activity but should also minimize the toxicities commonly associated with currently available treatment options. Based on the clinical experience in MBC to date, trastuzumab emtansine has the potential to fulfill this need as therapy for advanced HER2 IHC-positive urothelial and/or *pancreatic cancers/cholangiocarcinoma*, with the option to subsequently include other tumor types as well. A safety plan for this study, including appropriate eligibility criteria, dose modification and/or discontinuation guidelines for each identified and potential risk (see Section 5.1), monitoring of patients at risk as well as regular monitoring of patient safety data by an iDMC, has been put into place to minimize any potential risk in the study patient population.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of trastuzumab emtansine in patients with *locally advanced (unresectable and not treatable with curative intent) or metastatic MIBC* or *locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancers/cholangiocarcinomancer*. Specific objectives and corresponding endpoints for the study are outlined in Table 1 below.

Table 1 Objectives and Corresponding Endpoints

{...}

Pharmacokinetic Objective:	
• To characterize the pharmacokinetics of trastuzumab emtansine	• Concentrations of trastuzumab emtansine in plasma/serum to determine exposure.
(Exploratory) Immunogenicity Objective:	
• To evaluate the immune response to trastuzumab emtansine	• Incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline. • Exploratory assessment of immune checkpoints e.g. inhibitors infiltrating lymphocytes in the tumor before and after treatment by the assessment of immune-related biomarkers such as PDL1 and CD8.
Exploratory Biomarker Objective:	
• To identify biomarkers that are predictive of response, can provide	• To evaluate the HER2 status by IHC and ISH of all

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<p>evidence of trastuzumab emtansine activity, or can increase the knowledge and understanding of disease biology</p>	<p>consenting screened patients.</p> <ul style="list-style-type: none"> • To further evaluate the HER2 status by other exploratory testing methods such as a novel gene-protein assay (GPA), e.g. IHC and ISH combined in one assay, on samples of all consenting screened patients. • Correlate levels of HER2 protein expression, HER2 gene amplification and circulating HER2 extracellular domain (HER2 ECD) to trastuzumab emtansine efficacy. • To evaluate biomarkers that may be associated with response and/or safety on the protein, RNA and DNA level (e.g. by molecular subtyping and gene mutation analysis).
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3.1 DESCRIPTION OF THE STUDY

This is an exploratory, multicenter, non-randomized, Phase II, single agent *cohort* study designed to evaluate the efficacy of trastuzumab emtansine in patients with *locally advanced (unresectable and not treatable with curative intent) or metastatic MIBC or locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancers/cholangiocarcinoma cancer*, with other tumor types being potentially explored at a later point in time.

{...}

Figure 1 Schematic illustration of the KAMELEON study with trastuzumab emtansine treatment in HER2 IHC3+ locally advanced (unresectable and not treatable with curative intent) or metastatic urothelial bladder cancer and pancreatic cancers/cholangiocarcinoma cancer

Figure 1 has been updated to include the pharmacokinetic assessments

{...}

The percentage of HER2 positive UBC differs in the literature and ranges between 22 and 37%, (see Section 1.1). For HER2 IHC3+ with expression equal to 30% and above, the prevalence is between 7 and 18%, for pancreas cancer it is 11% and 8% for cholangiocarcinoma cancer (see Section 1.3.1), depending on the tumor sample, pre-study biopsy or archived tissue. Best tumor response on trastuzumab emtansine treatment will be evaluated; also PFS and OS will be studied as secondary endpoints.

{...}

Figure 2 Schematic illustration of the KAMELEON study with trastuzumab emtansine treatment in HER2 IHC3+ locally advanced (unresectable and not treatable with curative intent) or metastatic urothelial bladder cancer and pancreatic cancers/cholangiocarcinoma cancer

Figure 2 has been updated to amend the target population to include IHC3+, non-focal ($\geq 30\%$ stained cells) from ($> 30\%$ stained cells).

Figure 4 Study scheme of 2.4 mg/kg weekly trastuzumab emtansine administration (Regimen A)

Figure 4 has been updated to include 'Regimen A' in the title. The blood sample has been corrected to 'blood sample for HER2 ECD). An extra footnote has been added to confirm that the figure refers to Cycles 1 to 5 and for Cycle 6 onwards to refer to the Schedule of Assessments (Appendix 1.1).

Figure 5 Study scheme of 3.6 mg/kg 3-weekly trastuzumab emtansine administration (Regimen B)

Figure 5 has been updated to include 'Regimen B' in the title. The blood sample has been corrected to 'blood sample for HER2 ECD). An extra footnote has been added to confirm that the figure refers to Cycles 1 to 5 and for Cycle 6 onwards to refer to the Schedule of Assessments (Appendix 1.2).

3.2 END OF STUDY AND LENGTH OF STUDY

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Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurs first. After completion of treatment, patients will be followed up in a 3 monthly schedule until study close (18 months after last patient in in each cohort). *The treatment period is expected to be 6 months.*

The data cutoff for the primary analysis of BOR will take place 12-10 weeks after the last patient of an individual cohort has been recruited (following a tumor assessment after 6 weeks [2 cycles] with a confirmation of BOR performed no less than 4 weeks after the criteria for response are first met). ~~of BOR within 4 weeks).~~

{...}

3.3 RATIONALE FOR STUDY DESIGN

{...}

3.3.2 Rationale for Patient Population

{...}

There is currently no clinical data on the potential therapeutic effect of trastuzumab emtansine treatment in other HER2 positive tumors such as *locally advanced (unresectable and not treatable with curative intent) or metastatic MIBC or locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancers/cholangiocarcinoma-cancer*. Further information on this disease is presented in Section 1.3.1.

4 **MATERIALS AND METHODS**

4.1 **PATIENTS**

Up to 38 patients per cancer type, i.e. locally advanced (*unresectable and not treatable with curative intent*) or metastatic MIBC and *locally advanced (unresectable and not treatable with curative intent)* or metastatic pancreatic cancers/cholangiocarcinoma cancer, will be enrolled in this study.

4.1.1 **Inclusion Criteria**

1. Histologically centrally confirmed HER2-positive (IHC3+ in $\geq 30\%$ of tumor cells): *locally advanced (unresectable and not treatable with curative intent)* or metastatic ~~or unresectable (not treatable with curative intent)~~ UBC or *locally advanced (unresectable and not treatable with curative intent)* or metastatic pancreatic cancers/cholangiocarcinoma cancer.

HER2 status may be pre-screened at the participating site. However, HER2 determination at the referral center is not accepted to determine study eligibility. HER2 positivity needs to be prospectively confirmed with central laboratory HER2 testing before patient enrollment.

2. There must be no standard treatment options available for patients with the above HER2 overexpressing tumors and they must have undergone at least one prior platinum-based treatment for *locally advanced (unresectable and not treatable with curative intent)* ~~inoperable, locally advanced~~ or metastatic tumor. (Note: for pancreatic cancers/cholangiocarcinoma cancer, prior treatments are NOT required to be platinum-based.)

{...}

6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-24.

{...}

4.1.2 **Exclusion Criteria**

{...}

~~3. Patients with bone metastases are not eligible.~~

- 3 4. Patients with brain metastasis as the sole site of metastatic disease and/or are symptomatic or require therapy to control symptoms.

NB: Brain metastases are allowed provided they are asymptomatic and controlled by previous radiotherapy.

- 4 5. Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg).

- 5 6. Current unstable angina pectoris.

- 6 7. History of symptomatic CHF of any New York Heart Association (NYHA) criteria or ventricular arrhythmia that requires treatment.

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7 8. History of myocardial infarction within the last 6 months.

8 9. Peripheral neuropathy, Grade \geq 3.

9 10. Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy.

10 14. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures).

11 12. History of other malignancy within the last 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, stage I uterine cancer, or other cancers with a similar outcome as those previously mentioned.

12 13. For female patients, current pregnancy and lactation.

13 14. Concurrent, serious, uncontrolled infections or current known infection with human immunodeficiency virus (HIV), active hepatitis B and/or hepatitis C.

14 15. Known prior severe hypersensitivity to trastuzumab and trastuzumab emtansine or the excipients of the investigational medicinal product (IMP).

15 16. Clinically significant bleeding within 30 days before enrollment

16 17. Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment

17 18. Concurrent participation in any other therapeutic clinical trial.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Trastuzumab Emtansine

Trastuzumab emtansine treatment only starts after a successfully completed screening period. There are two treatment regimens:

- Regimen A: trastuzumab emtansine 2.4 mg/kg weekly, IV or
- Regimen B: trastuzumab emtansine 3.6 mg/kg every 3 weeks, IV.

{...}

Regimen A: Trastuzumab emtansine 2.4 mg/kg, weekly dosing in a 3-weekly cycle

{...}

The only available route of administration for trastuzumab emtansine is IV infusion. Trastuzumab emtansine infusion time may be decreased, depending on the patient's tolerability of the infusion. For the first cycle, trastuzumab emtansine should be administered as a 90 (+/- 10) minutes IV infusion. Following the initial dose, patients will be observed for at least 90-60 minutes for fever, chills, or other infusion-associated symptoms. If the 90 minutes infusion is well tolerated, subsequent infusions may be delivered over 30 (+/- 10) minutes with a minimum 30 minute observation period after

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the infusion. The volume contained in the administration tubing should be completely flushed with saline after administration of trastuzumab emtansine. The line should not be used for any other drug administration, but it can be used to administer IV fluids. A filter should be used in conjunction with the infusion set when using 0.9% sodium chloride for dilution.

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Regimen B: Trastuzumab emtansine 3.6 mg/kg, 3-weekly cycle of dosing

{...}

The only available route of administration for trastuzumab emtansine is IV infusion. Trastuzumab emtansine infusion time may be decreased, depending on the patient's tolerability of the infusion. For the first cycle, trastuzumab emtansine should be administered as a 90 (+/- 10) minutes IV infusion. Following the initial dose, patients will be observed for at least 90 60 minutes for fever, chills, or other infusion-associated symptoms. If the 90 minutes infusion is well tolerated, subsequent infusions may be delivered over 30 (+/- 10) minutes with a minimum 30 minute observation period after the infusion. The volume contained in the administration tubing should be completely flushed with saline after administration of trastuzumab emtansine. The line should not be used for any other drug administration, but it can be used to administer IV fluids. A filter should be used in conjunction with the infusion set when using 0.9% sodium chloride for dilution.

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4.3.4 Post-Trial Access to Trastuzumab Emtansine

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A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for *locally advanced (unresectable and not treatable with curative intent) or metastatic MIBC or metastatic pancreatic cancers/cholangiocarcinoma cancer*
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for *locally advanced (unresectable and not treatable with curative intent) or metastatic MIBC or metastatic pancreatic cancers/cholangiocarcinoma cancer*
- Provision of study drug is not permitted under the laws and regulations of the patient's country

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The study will be concluded *18 months after the last patient has been enrolled in the last cohort after the last patient has been followed up for 18 months after last patient has been enrolled*. Patients who have not progressed at the end of the trial and who are still on treatment will be offered the possibility to continue treatment in an extension study.

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4.5.1 Informed Consent Forms and Screening Log

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~~Screening is to be and HER2 testing should ideally be completed within 28 days prior to baseline, however HER2 testing can be performed up to a maximum of 2 years prior to baseline (see Appendices 1.1 and 1.2 for Regimen A and B, respectively). 28 days is accepted unless otherwise stated (see Appendix 1).~~

~~A separate ICF can be used for HER2 testing. The HER2 screening test (determined by the central laboratory) may be performed as soon as a potential patient is identified, at any time prior to enrollment, as long as provided that the HER2 Screening Informed Consent is signed.~~

4.5.6 LVEF Evaluation

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~~ECHO/MUGA will be performed at screening and between Days 15 and 21 in Cycles 1 and 3, and at every third cycle thereafter (Cycles 6, 9 etc), and at the study drug completion visit. and at survival follow up visits, i.e., patients are followed for 18 months after last patient in; during the treatment they will be followed as per treatment schedule and at treatment discontinuation, every 3 months. The same method used at screening should be used throughout the study.~~

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4.5.8 Laboratory, Biomarker, and Other Biological Samples

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4.5.8.2 Blood Samples for Pharmacokinetic Assessments

Samples for evaluation of trastuzumab emtansine, DM1, and total trastuzumab will be collected as shown in Figure 4 (*Regimen A*) and Figure 5 (*Regimen B*).

Limited PK assessments *will be made*:

- *Regimen A: with six sampling timepoints in Cycle 1 (Day 1, Day 8, and Day 15, each predose and 15-30 minutes postdose), one sampling timepoint in Cycle 2 (Day 1, predose), and two sampling timepoints in Cycle 4 (Day 1, predose and 15-30 minutes postdose),*

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- *Regimen B: with two sampling timepoints in Cycle 1 (Day 1 predose and 15-30 minutes postdose), one sampling timepoint in Cycle 2 (Day 1, predose), and two sampling timepoints in Cycle 4 (Day 1, predose and 15-30 minutes postdose).*

~~with six sampling timepoints in Cycle 1 (Day 1, Day 8, and Day 15, each predose and 15-30 minutes postdose), and one sampling timepoint in Cycle 2 (Day 1, predose), and two sampling timepoints in Cycle 4 (Day 1, predose and 15-30 minutes postdose), as shown in Figure 4 and Figure 5, will be made.~~

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of *locally advanced (unresectable and not treatable with curative intent) or metastatic MIBC or pancreatic cancers/cholangiocarcinoma cancer* should be recorded on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. ~~The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

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5.3.5.11 Hospitalization or Prolonged HospitalizATION

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~~The following hospitalization scenarios are not considered to be AEs: An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:~~

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

The patient has not experienced an AE

- Hospitalization due solely to progression of the underlying cancer

~~The following hospitalization scenarios are not considered to be SAEs, but should be reported as AEs instead: An event that leads to hospitalization under the following circumstances is not considered to be a SAE, but should be reported as an AE instead:~~

- Hospitalization for an AE that would ordinarily have been treated in an outpatient setting
- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

6.4 EFFICACY ANALYSES

{...}

The primary efficacy analysis will determine the BOR for all patients of a cohort who received a dose of study medication in the selected treatment regimen and will take place 12-10 weeks after the last patient of an individual cohort has been recruited (following a tumor assessment after 6 weeks [2 cycles] with a *confirmation of BOR performed no less than 4 weeks after the criteria for response are first met*). ~~confirmation of BOR within 4 weeks~~.

6.6 IMMUNOGENICITY ANALYSES

{...}

Corresponding analyses will be performed for immune checkpoints ~~inhibitors~~ and e.g. infiltrating lymphocytes in the tumor before and after treatment by the assessment of immune-related biomarkers such as PDL1 and CD8.

8.2 INFORMED CONSENT

The Sponsor's sample ICF, *including the sample ICF for the HER2 screening test, will be provided to each site and ancillary sample ICFs such as a Child's Informed Assent Form or Mobile Nursing ICF, if applicable*) will be provided to each site. If applicable, the ICFs will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be

provided to the Sponsor for health authority submission purposes according to local requirements.

{...}

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.5 PUBLICATION OF DATA AND PROTOECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

<http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf>

{...}

10. REFERENCES

Kimura K, et al. Antitumor effect of trastuzumab for pancreatic cancer with high HER-2 expression and enhancement of effect by combined therapy with gemcitabine. Clin Cancer Res. 2006;12(16):4925-32.

Safran H, Iannitti D, Ramanathan R, et al. Herceptin and gemcitabine for metastatic pancreatic cancers that overexpress HER-2/neu. Cancer Invest. 2004;22(5):706-12

Schedule of Activities: The Schedule of Activities has been revised for Regimen A and B separately, to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: PHASE II, EXPLORATORY, MULTICENTER, NON RANDOMIZED, SINGLE AGENT COHORT STUDY TO DETERMINE BEST TUMOR RESPONSE WITH TRASTUZUMAB EMTANSINE IN HER2 OVEREXPRESSING SOLID TUMORS

PROTOCOL NUMBER: MO29694

VERSION NUMBER: 2

EUDRACT NUMBER: 2015-001377-40

IND NUMBER: N/A

TEST PRODUCT: Trastuzumab Emtansine (RO5304020)

MEDICAL MONITOR: [REDACTED]

SPONSOR: F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE: PHASE II, EXPLORATORY, MULTICENTER, NON RANDOMIZED, SINGLE AGENT COHORT STUDY TO DETERMINE BEST TUMOR RESPONSE WITH TRASTUZUMAB EMTANSINE IN HER2 OVEREXPRESSING SOLID TUMORS

PROTOCOL NUMBER: MO29694

VERSION NUMBER: 2

EUDRACT NUMBER: 2015-001377-40

IND NUMBER: N/A

TEST PRODUCT: Trastuzumab Emtansine (RO5304020)

PHASE: Phase II

INDICATION: HER2 overexpressing solid tumors

SPONSOR: F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety and pharmacokinetics of trastuzumab emtansine in patients with *locally advanced (unresectable and not treatable with curative intent)* or metastatic urothelial bladder cancer (UBC) or *locally advanced (unresectable and not treatable with curative intent)* or metastatic pancreatic cancer/cholangiocarcinoma. Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of trastuzumab emtansine	• Best overall response rate (BOR) as determined by the investigator (using RECIST 1.1). BOR is defined as the best response recorded from the first day of study treatment until disease progression/recurrence or death. Responders, as assessed every 6 weeks, will be defined based on tumor assessment status as partial responder (PR) or complete responder (CR) at these time points. To be assigned a status of PR or CR (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder.

Secondary Efficacy Objective:	
• To evaluate the efficacy of trastuzumab emtansine	<ul style="list-style-type: none"> • Progression-free survival (PFS), defined as the time from beginning of treatment to the first occurrence of disease progression, as determined by the investigator (using RECIST 1.1), or death from any cause, whichever occurs first. • Overall survival (OS), defined as the time from beginning of treatment to death from any cause.
Safety Objective:	
• To evaluate the safety of trastuzumab emtansine	<ul style="list-style-type: none"> • Incidence, type and severity of all adverse events (AEs) and serious adverse events (SAEs) based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03). • Incidence and type of AEs leading to discontinuation, modification, or delay of trastuzumab emtansine dose. • Changes in vital signs, physical examination findings, and clinical laboratory results during and following trastuzumab emtansine administration. • Death and cause of death. • Cases of drug-induced liver injury meeting Hy's Law criteria. • Pneumonitis of all grades. • Change in left ventricular ejection fraction (LVEF) over the course of the study as measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA). • Incidence of congestive heart failure (CHF).
Pharmacokinetic Objective:	
• <i>To characterize the pharmacokinetics of trastuzumab emtansine</i>	<ul style="list-style-type: none"> • <i>Concentrations of trastuzumab emtansine in plasma/serum to determine exposure.</i>

(Exploratory) Immunogenicity Objective:	
• To evaluate the immune response to trastuzumab emtansine	<ul style="list-style-type: none"> Incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline. Exploratory assessment of immune checkpoints and infiltrating lymphocytes in the tumor before and after treatment by the assessment of immune-related biomarkers such as PDL1 and CD8.
Exploratory Biomarker Objective:	
• To identify biomarkers that are predictive of response, can provide evidence of trastuzumab emtansine activity, or can increase the knowledge and understanding of disease biology	<ul style="list-style-type: none"> <i>To further evaluate the HER2 status by other exploratory testing methods such as a novel gene-protein assay (GPA), e.g. immunohistochemistry (IHC) and in situ hybridization (ISH) combined in one assay on samples of all consenting screened patients.</i> Correlate levels of HER2 protein expression, HER2 gene amplification and circulating HER2 extracellular domain (HER2 ECD) to trastuzumab emtansine efficacy. To evaluate biomarkers that may be associated with response and/or safety on the protein, RNA and DNA level (e.g. by molecular subtyping and gene mutation analysis).

Study Design

Description of Study

This is an exploratory, multicenter, non-randomized, Phase II, single agent *cohort* study designed to evaluate the efficacy of trastuzumab emtansine in patients with *locally advanced (unresectable and not treatable with curative intent) or metastatic urothelial bladder cancer (UBC) or locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancer/cholangiocarcinoma.*

Number of Patients

In total, 32-38 patients will be enrolled per cohort; 64-76 patients in total.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Histologically centrally confirmed HER2-positive (IHC3+ in $\geq 30\%$ of tumor cells): *locally advanced (unresectable and not treatable with curative intent) or metastatic urothelial bladder cancer or locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancer/cholangiocarcinoma.*

HER2 status may be pre-screened at the participating site. However, HER2 determination at the referral center is not accepted to determine study eligibility. HER2 positivity needs to be prospectively confirmed with central laboratory HER2 testing before patient enrollment.

- There must be no standard treatment options available for patients with the above HER2 overexpressing tumors and they must have undergone at least one prior platinum-based treatment for *locally advanced (unresectable and not treatable with curative intent) or metastatic tumor.* (Note: for *pancreatic cancer/cholangiocarcinoma*, prior treatments are NOT required to be platinum-based.)
- The patient must have evaluable disease fulfilling all of the following imaging criteria:

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- a. On diagnostic computed tomography scan/magnetic resonance imaging: lesion should be measurable according to RECIST 1.1.
- b. Target lesion(s) should not have been previously irradiated.
- At least one formalin-fixed paraffin-embedded biopsy of the primary tumor and/or from a metastatic site is required.
- Age \geq 18 years.
- Eastern Cooperative Oncology Group performance status of 0-2.
- No significant cardiac history and a current LVEF \geq 50%. LVEF should be determined within 28 days before the start of trastuzumab emtansine treatment.
- Adequate organ function, evidenced by the following laboratory results (performed within 7 days prior to commencement of dosing):
 - a. Absolute neutrophil count $>$ 1,500 cells/mm³.
 - b. Platelet count $>$ 100,000 cells/mm³.
 - c. Hemoglobin $>$ 9 g/dL.
 - d. Aspartate aminotransferase and alanine aminotransferase $<$ 2.5 x upper limit of normal (ULN).
 - e. Total bilirubin \leq 1.5 x ULN unless the patient has documented Gilbert's syndrome, in which case direct (conjugated) bilirubin level needs to be within normal limits.
 - f. Serum alkaline phosphatase \leq 2.5 x ULN. Patients with bone metastases: alkaline phosphatase \leq 5 x ULN.
 - g. Serum creatinine $<$ 2.0 mg/dL or $<$ 177 μ mol/L.
 - h. International normalized ratio and activated partial thromboplastin time or partial thromboplastin time $<$ 1.5 ULN.
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the study.
- Negative serum pregnancy test for women of childbearing potential (including pre-menopausal women who have had a tubal ligation) and for all women not meeting the definition of postmenopausal (\geq 12 months of amenorrhea), and who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential.

For women of childbearing potential and men with partners of childbearing potential, agreement by the patient and/or partner to use a highly effective non-hormonal form of contraception such as surgical sterilization or two effective forms of non-hormonal contraception until 7 months after the last dose of trastuzumab emtansine.

Methods of birth control are considered highly effective forms of contraception in case they result in a low failure rate (i.e., $<$ 1% per year) when used consistently and correctly. The use of the following non-hormonal methods of contraception is acceptable:

- a. True abstinence, when this is the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, and symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.
- b. Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomized male partner should be the sole partner.

Alternatively, use of two of the following effective forms of contraception is acceptable:

- a. Placement of intrauterine device or intrauterine system. Consideration should be given to the type of device being used, as there are higher failure rates for certain types (e.g., steel or copper wire).
- b. Condom with spermicidal foam/gel/film/cream/suppository.

- c. Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted: Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection. However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

- Signed written informed consent approved by Ethics Committee and obtained prior to any study procedure.
- Life expectancy of at least 12 weeks.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Patients with previous exposure to HER2-targeted therapies in any setting.
- Patients showing histologically confirmed focal HER2-expression, i.e., < 30% of positively stained tumor cells.
- Patients with brain metastasis as the sole site of metastatic disease and are symptomatic or require therapy to control symptoms.

NB: Brain metastases are allowed provided they are asymptomatic and/or controlled by previous radiotherapy.

- Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg).
- Current unstable angina pectoris.
- History of symptomatic CHF of any New York Heart Association criteria or ventricular arrhythmia that requires treatment.
- History of myocardial infarction within the last 6 months.
- Peripheral neuropathy, Grade ≥ 3 .
- Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy.
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures).
- History of other malignancy within the last 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, stage I uterine cancer, or other cancers with a similar outcome as those previously mentioned.
- For female patients, current pregnancy and lactation.
- Concurrent, serious, uncontrolled infections or current known infection with human immunodeficiency virus, active hepatitis B and/or hepatitis C.
- Known prior severe hypersensitivity to trastuzumab and trastuzumab emtansine or the excipients of the investigational medicinal product (IMP).
- Clinically significant bleeding within 30 days before enrollment
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
- Concurrent participation in any other therapeutic clinical trial.

End of Study

Each cohort will close 18 months after the last patient was recruited or once all patients have died or withdrawn from study, whatever happens first.

End of study for a cohort will be declared at the last patient last visit (LPLV) as per definition is the last data collection point, which can be a clinic visit or a laboratory sample.

Length of Study

The total length of the study for an individual cohort, from screening of the first patient to the end of the study, is expected to be approximately 3 years (18 months of recruitment, *an expected* 6 months of treatment and a *further* 12 months of follow-up).

Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurs first.

The data cutoff for the primary analysis of BOR will take place 12 weeks after the last patient of an individual cohort has been recruited (following a tumor assessment after 6 weeks [2 cycles] with a confirmation of BOR *performed no less than 4 weeks after the criteria for response are first met*).

The data cutoff for the final analysis for each cohort of all primary and secondary efficacy measures will take place 18 months after the last patient of a cohort was recruited, or once all patients have reported a progression event, whichever occurs earlier.

Investigational Medicinal Products

Test Product (Investigational Drug)

The IMP for this study is trastuzumab emtansine (Kadcyla).

Trastuzumab emtansine will be administered by intravenous infusion

- Regimen A: trastuzumab emtansine 2.4 mg/kg, weekly
- Regimen B: trastuzumab emtansine 3.6 mg/kg every 3 weeks.

In a safety run-in, the first 6 patients of each cohort will enter Regimen A and receive 2.4 mg/kg weekly trastuzumab emtansine. These first 6 patients will be assessed on an ongoing and patient per patient basis – i.e. based on the tolerability criteria (as defined in the Independent Data Monitoring Committee [iDMC] charter) and in consultation with the Steering Committee (SC) and iDMC if needed. Recruitment for the respective cohort will be suspended until all 6 of these patients have completed the 2nd cycle (6 weeks) and the ‘regimen decision point’ has been reached. Based on tolerability and safety aspects, the iDMC will decide for each cohort if the study is to continue on Regimen A (2.4 mg/kg qw), extending recruitment to a total of 32 patients (additional 26 patients) per cohort, or if the dose switches to Regimen B (3.6 mg/kg q3w). If the regimen is changed to Regimen B, 32 additional patients will be included per cohort; if the regimen remains unchanged (i.e., Regimen A), only 26 additional patients will be recruited.

Statistical Methods

The first 6 patients of each cohort will be analyzed on an ongoing and patient per patient basis – i.e. based on the tolerability criteria (as defined in the iDMC charter) and in consultation with the SC and iDMC if needed.

Primary Analysis

The primary efficacy endpoint BOR will be analyzed as follows:

Responders as assessed every 6 weeks will be defined based on tumor assessment status of PR or CR at these time points. Only patients with measurable disease at baseline will be included in the analysis of the response rate. Patients without a post-baseline tumor assessment will be considered to be non-responders. BOR is defined as the best response recorded from the first day of study treatment until disease progression/recurrence or death. To be assigned a status of PR or CR (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder. The primary analysis will be based on the BOR result after 12 weeks (an assessment after 6 weeks [2 cycles] with a confirmation of BOR *performed no less than 4 weeks after the criteria for response are first met*).

The null hypothesis (H_0) is that the best response rate is 5% or less, which would yield a low activity profile. The alternative hypothesis (H_1) is that the best response rate is greater than or equal to 20%, which would yield an encouraging activity profile:

H_0 : best response rate $\leq 5\%$ vs H_1 : best response rate $\geq 20\%$

A Simon's two-stage design (Simon 1989) will be used to allow the study to stop early if there is no evidence of efficacy. The null hypothesis that the true response rate (BOR) is $\leq 5\%$ will be

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tested against a one-sided alternative. In the first stage, 13 patients in each cohort will be accrued. If there are 0 responses (CR or PR) in these 13 patients, the study will be stopped for the respective cohort. Otherwise, 14 additional patients will be accrued per cohort for a total of 27. Recruitment may be suspended after the 13th patient in a cohort has been enrolled in the selected treatment regimen. This suspension will occur if there are no responses observed in the previous 12 patients (since the decision will be made to stop the study only if there are no responses in the first 13 patients).

In the primary analysis of efficacy the null hypothesis will be rejected if 4 or more responses are observed in 27 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is $\geq 20\%$.

It is planned to recruit more than the required 27 patients per cohort to allow for drop-outs. If there are no drop-outs amongst the 32 enrolled patients in a certain cohort then the decision rule will be revised as necessary to retain the same alpha and power. For example, if 32 patients have evaluable efficacy data, then if 5 or more responders are observed then we will reject H_0 and accept H_1 – i.e., accept that the best response rate $\geq 20\%$. If 4 or fewer responders are observed then we will accept H_0 .

A response rate of less than 5% will be considered of no clinical interest. A response rate of more than 20% will be considered of interest to potentially start a further study, which will not be part of this protocol.

Determination of Sample Size

The sample size estimation is based on the method of A'Hern (2001) and Simon (1989) and corresponding Statistical Analysis System programs.

To test the null hypothesis (H_0) that the best BOR is 5% or less (which would yield a low activity profile) against the alternative hypothesis (H_1) that the BOR is greater than or equal to 20% (which would yield an encouraging activity profile), 27 patients per cohort would be required to perform the test with 80% power, at the one-sided alpha=0.05 level. To allow for drop-outs (10-15%) and to ensure that at least 27 patients will have efficacy data available, 32 patients will be recruited per cohort on the respective treatment regimen.

Assuming a preferable BOR of 20% is observed, then with 27 patients, the 95% confidence limits would range from 7.2% to 39.8% (Clopper-Pearson exact confidence intervals).

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ADC	antibody-drug conjugate
AGC	advanced gastric cancer
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATA	anti-therapeutic antibody
BC	breast cancer
BOR	best overall response rate
CHF	congestive heart failure
CI	confidence interval
CNS	central nervous system
CR	complete responder
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DNA	deoxyribonucleic acid
EBC	early breast cancer
EC	Ethics Committee
ECD	extracellular domain
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GC	gastric cancer
GGT	gamma-glutamyl-transferase
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation

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iDMC	Independent Data Monitoring Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	Institutional Review Board
ISH	in-situ hybridization
ITT	intent-to-treat
IV	intravenous
IxRS	interactive voice/web recognition system
KM	Kaplan-Meier
LABC	locally advanced breast cancer
LDH	lactate dehydrogenase
LPI	last patient in
LPLV	last patient last visit
LVEF	left ventricular ejection fraction
MBC	metastatic breast cancer
MRI	magnetic resonance imaging
MTD	maximum tolerable dose
MUGA	multiple-gated acquisition scan
NCI	National Cancer Institute
NGS	next-generation sequencing
NRH	nodular regenerative hyperplasia
NYHA	New York Heart Association
PD	pharmacodynamics / progressive disease
PDAC	<i>pancreatic ductal adenocarcinoma</i>
PET	positron emission tomography
PFS	progression free survival
PK	pharmacokinetic
PR	partial responder
PS	performance status
PT	preferred term
PTT	partial thromboplastin time
PVC	polyvinylchloride
RBC	red blood cells
RBR	Research Biosample Repository
RECIST	Response Evaluation Criteria In Solid Tumors

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RNA	ribonucleic acid
RNA-seq	RNA sequencing
SAE	serious adverse event
SC	steering committee
SmPC	Summary of medicinal Product Characteristics
SOC	system organ class/standard of care
SOP	standard operating procedure
SP	safety population
SWFI	sterile water for injection
TPC	treatment of physician's choice
UBC	urothelial bladder cancer
ULN	upper limit of normal
US	United States
WBC	white blood cells
WGS	whole genome sequencing

1. BACKGROUND

1.1 BACKGROUND ON HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR HER2

The human epidermal growth factor receptor 2 (HER2) gene is a proto-oncogene, which is located on chromosome 17q11.2-12 and encodes a transmembrane tyrosine kinase receptor, which is responsible for cell growth, differentiation, migration and apoptosis (Normanno et al 2005).

Amplification of the HER2 gene occurs in approximately 20% to 25% of primary human breast cancers (BC) and typically results in overexpression of the HER2 protein at > 1 million copies per cell (Slamon et al 1987, Slamon et al 1989, Pegram et al 2000). Such tumors are considered “HER2-positive” and are associated with aggressive growth and poor clinical outcome (Slamon et al 1987, Slamon et al 1989).

Recently, new results on the role of HER2-targeted therapies in antitumor therapy for BC were published (refer to the Investigator's Brochure [IB] for further information). In other tumors like gastric cancer (GC) trastuzumab is approved as well, which is not the case for trastuzumab emtansine (e.g., Lewis et al 2013).

HER2 aberrations (gene amplification, gene mutations and protein overexpression) are reported in diverse other malignancies for instance esophagus, colorectal, pancreatic, bladder and prostate cancer (Yan et al 2014, Yoon et al 2014, Sato-Kuwabara et al 2009,

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Seo et al 2014, Stoecklein et al 2004, Minner et al 2010, Carneiro et al 2015, Hansel et al 2008). *Urothelial bladder cancer (UBC) and pancreatic cancer/cholangiocarcinoma* are areas of high unmet medical need, and a more efficacious and less toxic therapy is desired. For UBC, it is currently estimated that the incidence of HER2 overexpression (immunohistochemistry [IHC]3+ and IHC2+/in situ hybridization [ISH]+) ranges from 22-37% (Internal Data, Dendreon DN24-02, Hayashi et al 2014). In *pancreatic ductal adenocarcinoma (PDAC)*, the *HER2 gene locus* was frequently (24%) amplified and the rate of overexpression (2+ and 3+) was 10%, but no prognostic significance was found (Stoecklein et al 2004). In addition, Safran et al (2004) have reported 30 patients (88%) with IHC2+ and 4 patients (12%) with IHC3+ HER2 status in a Phase II study of trastuzumab in HER2-positive metastatic pancreatic adenocarcinoma. In another Phase II study it has been shown that in contrary to breast and gastric cancer, where HER2 protein overexpression and HER2 gene amplification are highly concordant, only 7 out of 11 (64%) patients with IHC3+ and 1 out of 22 (5%) with IHC2+ HER2 expression showed gene amplification (Harder et al 2012). Maybe HER2 overexpression in pancreatic cancer is regulated by other mechanisms on the transcriptional or translational level rather than gene amplification as postulated by Ukita et al (2002) for intrahepatic biliary tract cancer. The role of HER2 targeting therapy in these and potentially other indications is still unclear and needs to be further explored.

1.2 BACKGROUND ON STUDY DRUG

Four HER2-targeted therapies have been approved for HER2-positive BC: Two monoclonal antibodies (trastuzumab and pertuzumab), an antibody-drug conjugate (trastuzumab emtansine/ado trastuzumab emtansine), and a small molecule kinase inhibitor (lapatinib) (Giordano et al 2014).

1.2.1 Background on Trastuzumab

Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of HER2. Trastuzumab mediates antibody-dependent cellular cytotoxicity, inhibits HER2 extracellular domain shedding, and inhibits the phosphatidylinositol 3 kinase signaling pathway.

Trastuzumab is currently approved and it is part of the current standard of care (SOC) in HER2-positive BC for both the early breast cancer (EBC) and the metastatic breast cancer (MBC) setting, as shown in the pivotal randomized phase III study (Slamon et al 2001). The American Society of Clinical Oncology (ASCO) guidelines 2014 recommend HER2 targeted therapy for all patients with advanced HER2-positive BC, except for those with clinical congestive heart failure or significantly compromised left ventricular ejection fraction (LVEF, Giordano et al 2014).

Trastuzumab is also currently approved for the treatment of first-line HER2 overexpressing GC (including gastroesophageal [GE] junction adenocarcinoma), the second most common cause of cancer related deaths worldwide (Kamangar et al 2006).

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One study ([Peyromaure et al 2005](#)) explored the activity of trastuzumab in six patients with metastatic urothelial tract carcinoma. All of these patients had a positive immunohistochemistry for HER2. Four cases were treated with trastuzumab, paclitaxel, and carboplatin; one case with trastuzumab and paclitaxel; and the other case with trastuzumab monotherapy. The six patients achieved a partial response, ranging from 30 to 80% reduction in the size of the metastatic lesions. Interval between trastuzumab initiation and death varied from 8 to 22 months. This study showed a potential role for anti-HER2 strategies in metastatic bladder carcinoma with HER2 overexpression. In 2007, a phase II trial conducted by [Hussain et al \(2007\)](#) tested the combination of carboplatin, paclitaxel, gemcitabine, and trastuzumab in advanced urothelial carcinoma. A total number of 44 patients with HER2-positive tumors were treated with this combination. Five of these patients (11%) achieved a complete response, 26 (59%) a partial response, 5 (11%) had stable disease, and 5 (11%) had no response assessment, with an overall response rate of 70%. Median time to progression was 9.3 months, and median survival was 14.1 months. ([Marin et al 2010](#))

1.2.2 Background on Trastuzumab Emtansine

Trastuzumab emtansine (Kadcyla, also known as T-DM1, trastuzumab emtansine/ado-trastuzumab emtansine) is a novel antibody-drug conjugate (ADC) that is specifically designed for the treatment of HER2-positive malignancies. Trastuzumab emtansine is composed of trastuzumab; an average of 3.5 molecules of DM1, an anti-microtubule agent derived from maytansine; and MCC, a linker that conjugates each molecule of DM1 to trastuzumab. Trastuzumab emtansine recognizes an epitope on the extracellular domain (ECD) of HER2 and binds to HER2 with an affinity similar to that of trastuzumab. It is hypothesized that after binding to HER2, trastuzumab emtansine undergoes receptor-mediated internalization. Following internalization, the endosome is fused with the lysosomal compartment, the ADC undergoes lysosomal degradation and the active metabolites lys-MCC-DM1 and DM1 are released ([Erickson et al 2006, Erickson et al 2012](#)). DM1 is a highly potent thiol-containing derivative of maytansine and is synthesized from ansamitocin P3. It is an inhibitor of tubulin polymerization; it binds to tubulin competitively with vinca alkaloids but is 20-100 times more potent than vincristine in its cytotoxic effect against tumor cell lines. Its parent molecule, maytansine, was studied in approximately 800 patients, with responses seen in patients with BC and lung cancer ([Issell et al 1978](#)); however, because of its narrow therapeutic index, clinical development was not continued ([Cassady et al 2004](#)).

In vitro studies of trastuzumab emtansine demonstrate enhanced cytotoxicity in HER2-overexpressing BC cell lines compared to BC cell lines with low HER2 expression. The requirement for receptor binding for trastuzumab emtansine activity has been demonstrated in vivo where a non-HER2-binding isotype-matched ADC served as a control. In these experiments, the control antibody-MCC-DM1 had no anti-tumor activity in the HER2-positive BC model whereas trastuzumab emtansine exhibited significant anti-tumor activity.

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Trastuzumab emtansine has been approved globally as a single agent and is indicated for the treatment of adult patients with HER2-positive, unresectable locally advanced breast cancer (LABC) or MBC who previously received trastuzumab and a taxane.

1.2.2.1 Nonclinical and Clinical Development of Trastuzumab Emtansine in Breast Cancer

The nonclinical development of trastuzumab emtansine was designed to provide proof of concept for the mechanism of action of trastuzumab emtansine as a single agent and in combination with other therapies. Detailed summaries of nonclinical data for BC are provided in the IB.

Data are available from six completed clinical studies assessing the safety and/or efficacy of single-agent trastuzumab emtansine: in MBC the dose-finding Phase I study TDM3569g ([Krop et al 2010](#)), two single-arm Phase II studies TDM4258g (Burris et al 2010) and TDM4374g ([Krop et al 2012](#)), the single-arm Phase II study TDM4688g, which evaluated effects of trastuzumab emtansine on cardiac safety, the randomized Phase II study TDM4450g/BO21976, comparing single-agent trastuzumab emtansine with trastuzumab plus docetaxel and the expanded access, open-label study TDM4884g.

Efficacy and safety data are also available from three Phase III studies evaluating single-agent trastuzumab emtansine in MBC. Study TDM4370g/BO21977 (EMILIA) compared trastuzumab emtansine with lapatinib plus capecitabine ([Verma et al 2012](#)), and study TDM4997g/BO25734 (TH3RESA) evaluated trastuzumab emtansine versus treatment of physician's choice (TPC): standard treatment with chemotherapy, hormone therapy and/or biologic agents ([Krop et al 2014](#)). A Phase IIIb safety study (MO28231; KAMILLA) is also ongoing.

Trastuzumab emtansine treatment, with or without pertuzumab, is being compared with trastuzumab plus taxane (docetaxel or paclitaxel) in an ongoing Phase III study (TDM4788g/BO22589; MARIANNE). The primary results were presented at a recent medical congress and demonstrated non-inferiority of trastuzumab emtansine containing arms in progression free survival (PFS) compared to control. Trastuzumab emtansine was better tolerated than trastuzumab plus taxane, and no new safety issues were identified.

1.2.2.2 Nonclinical and Clinical Development of Trastuzumab Emtansine in Gastric Cancer

Detailed summaries of nonclinical data for GC are provided in the IB.

In terms of clinical studies in GC, one Phase II/III study evaluating trastuzumab emtansine versus taxane in patients with HER2-positive locally advanced or metastatic GC (BO27952; GATSBY) was published recently. While trastuzumab emtansine 2.4 mg/kg qw did not show an efficacy benefit (with no improvement in overall survival [OS], PFS, overall response rate, or duration of response with trastuzumab emtansine in

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the primary analysis population or subgroups), it was well tolerated and the safety profiles were comparable. The lack in efficacy benefit was even more accentuated in the non-IHC3+ population as per subgroup analyses (Kang et al 2016).

1.2.2.3 Nonclinical and Clinical Development of Trastuzumab Emtansine in Lung Cancer

Detailed summaries of nonclinical data for lung cancer are provided in the IB.

In two models of HER2-overexpressing (HER2 IHC3+) lung cancer, Calu-3 and NCIH2170, a single 7 mg/kg dose of trastuzumab emtansine resulted in tumor stasis. An additional lung cancer model, with HER2 expressed at the 1+ level, was tested for response to trastuzumab emtansine. In this model, 10 mg/kg trastuzumab emtansine administered every three weeks resulted in tumor stasis. In the Calu-3 HER2-positive lung cancer model, the combination of trastuzumab emtansine with pertuzumab was more efficacious than treatment with either single-agent trastuzumab emtansine or pertuzumab (Lewis et al 2013).

HER2Lung (BO29389) is an ongoing Phase II study of trastuzumab emtansine in patients with HER2-positive advanced non-small cell lung cancer who have received at least one prior chemotherapy regimen.

1.2.2.4 Nonclinical Development of Trastuzumab Emtansine in Bladder Cancer

Trastuzumab emtansine showed promising antitumor effects in preclinical models of HER2-overexpressing UBC. The bladder cell line with the highest HER2-expression (RT4V6), showed modest sensitivity to trastuzumab emtansine at concentrations less than 1 μ M but 24% higher growth inhibition compared to trastuzumab at a concentration of 1 μ M (Hayashi et al 2014). In an orthotopic bladder cancer xenograft model tumor growth of cisplatin resistant RT112 was significantly inhibited by trastuzumab emtansine via the induction of apoptosis compared to treatment with control IgG or trastuzumab.

1.2.2.5 Nonclinical Development of Trastuzumab Emtansine in Pancreatic Cancer/Cholangiocarcinoma

In a study by Buechler et al (2005) the effect of a combination therapy consisting of Herceptin, gemcitabine and docetaxel on anchorage-independent growth of different human pancreatic cancer cell lines was tested. Monotherapy with Herceptin had shown some tumor suppressive activity particularly in those cell lines, which overexpress the HER2 receptor (Buechler et al 2001) and gemcitabine is the current standard chemotherapeutic agent for therapy of pancreatic cancer (Slamon 2000). Because of the promising results in BC where the combination therapy of Herceptin plus taxanes has been clinically effective, the combination of Herceptin with docetaxel and gemcitabine was tested (Slamon et al 2001; Pegram et al 2004, Kimura et al 2006). In order to test whether this therapeutic regimen was also effective *in vivo*, a murine model for

pancreatic cancer in which tumor xenografts were grown in an orthotopic location within the pancreatic parenchyma was used. Two different human pancreatic cancer cell lines with different characteristics of HER2 expression were tested. According to the clinical grading of HER2 expression, the MIA PaCa-2 cell line would be graded as HER2 3+ whereas the HPAF-II cell line would be graded as HER2 (+/-). Monotherapy with individual substances improved the survival benefit moderately. In contrast, there was a dramatic survival improvement upon combination therapy of gemcitabine and docetaxel or both substances plus Herceptin compared to monotherapy alone. More importantly, the metastatic score was reduced when Herceptin was added to gemcitabine and docetaxel in the high HER2-expressing cell line, MIA PaCa-2.

1.2.2.6 Pharmacokinetic Properties of Trastuzumab Emtansine in Breast Cancer

The PK of trastuzumab emtansine and its analytes (i.e., the trastuzumab emtansine conjugate [hereafter referred to as trastuzumab emtansine], total trastuzumab and DM1) have been evaluated in a Phase I study (TDM3569g), four Phase II studies (Studies TDM4258g, TDM4374g, TDM4688g, TDM4450g/BO21976), and two Phase III studies (Study TDM4370g/BO21977 and TDM4997g/BO25734).

The recommended dose of trastuzumab emtansine for BC is 3.6 mg/kg given as an IV infusion q3w. The PK analysis from the Phase I study (TDM3569g) following administration of 0.3 mg/kg to 4.8 mg/kg trastuzumab emtansine q3w showed that at the dose of 3.6 mg/kg q3w, the systemic clearance was approximately 12.7 mL/day/kg and the elimination half-life was approximately 3.1 days. The clearance of trastuzumab emtansine was nonlinear at doses less than or equal to 1.2 mg/kg. At doses ranging from 2.4 to 4.8 mg/kg q3w, trastuzumab emtansine exhibited linear PK.

A qw dosing regimen was also evaluated in Study TDM3569g, and 2.4 mg/kg qw was identified as the maximum tolerable dose (MTD). Key trastuzumab emtansine PK parameters (i.e., CL, V_{ss} and t_{1/2}) at 2.4 mg/kg qw were similar to those observed at 3.6 mg/kg q3w dosing. Measurable levels of free DM1 are found, but are approximately 10,000 fold (by mass ratio) and approximately 50 fold (by molar ratio) lower than trastuzumab emtansine levels.

In the Phase II and III studies in MBC patients (TDM4258g, TDM4374g, TDM4688g, TDM4450g/BO21976, and TDM4370g/BO21977 and TDM4997g/BO25734), PK parameter values for trastuzumab emtansine after a 3.6 mg/kg dose given q3w were similar to those observed for the q3w dosing regimen in the Phase I study regardless of lines of therapy.

A robust population PK (popPK) model has been developed based on single-agent trastuzumab emtansine PK data from 671 HER2-positive MBC patients in five Phase I, II, and III studies (TDM3569g, TDM4258g, TDM4374g, TDM4450g/BO21976, and TDM4370g/BO21977). The estimated total body clearance, central volume of distribution,

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and elimination half-life for trastuzumab emtansine was 0.676 L/day, 3.127 L, and 3.94 days, respectively. Among ~30 covariates tested in the model, body weight, sum of longest dimension of target lesions, serum HER2 ECD concentration, baseline serum aspartate aminotransferase (AST), serum albumin, and baseline trastuzumab concentrations were identified as statistically significant covariates for trastuzumab emtansine PK but, with the exception of body weight, none had any clinically meaningful effect on trastuzumab emtansine exposure. Therefore, the weight-based dose of 3.6 mg/kg q3w is considered appropriate in BC patients.

1.2.2.7 Pharmacokinetic Properties of Trastuzumab Emtansine in Gastric Cancer

An important observation from the ToGA study (described in the IB) was the difference in the PK of trastuzumab in patients with advanced GC (AGC) compared with the PK of trastuzumab in patients with BC ([Cosson et al 2014](#)).

Two regimens of trastuzumab emtansine were evaluated in the GATSBY trial (BO27952). The 3.6-mg/kg every-3-weeks regimen (MTD in Phase I studies) has been tested in several Phase II studies in MBC and is the regimen being studied in several Phase III BC studies and the approved regimen for MBC. The 3.6 mg/kg dose has a reasonable amount of clinical safety and efficacy data that can be found in greater detail in the IB. GATSBY used the 3.6-mg/kg every-3-weeks regimen as one of the trastuzumab emtansine doses in the study. However, because of the lower exposure of trastuzumab in gastric cancer patients in the ToGA study (BO18255) versus the exposure observed in BC studies ([Bang et al 2010](#)), the trial was also exploring an alternative regimen of trastuzumab emtansine (2.4 mg/kg weekly), which may provide a higher cumulative exposure of trastuzumab emtansine than the every-3-weeks schedule.

The dosing of trastuzumab emtansine has been established in BC and recently in GC. It was demonstrated that 2.4 mg/kg dosing was well tolerated by patients and that event rates were comparable to taxane. This suggests 2.4 mg/kg to be the preferred dose as benefit-risk appears acceptable. However, as an additional safety measure and following the same process as GATSBY, an Independent Data Monitoring Committee (iDMC) will be used during this study that will provide additional safety monitoring.

1.2.2.8 Pharmacokinetic Properties of Trastuzumab Emtansine in Lung Cancer

Currently, there are no PK data available for trastuzumab emtansine in lung cancer.

1.2.2.9 Pharmacokinetic Properties of Trastuzumab Emtansine in Urothelial Bladder Cancer

Currently, there are no PK data available for trastuzumab emtansine in UBC.

1.2.2.10 Pharmacokinetic Properties of Trastuzumab Emtansine in Pancreatic Cancer/Cholangiocarcinoma

Currently, there are no PK data available for trastuzumab emtansine in *pancreatic cancer/cholangiocarcinoma*.

1.2.2.11 Clinical Safety with Trastuzumab Emtansine

The following section summarizes the experience with trastuzumab emtansine in several BC studies to date (described in the trastuzumab emtansine IB). Trastuzumab emtansine has demonstrated a favorable toxicity and tolerability profile to date across several studies. This safety profile of trastuzumab emtansine in MBC is based on data from 1871 patients receiving single-agent trastuzumab emtansine treatment at 3.6mg/kg q3w (Studies TDM3569g, TDM4258g, TDM4374g, TDM4688g, TDM4450g/BO21976, TDM4370g/BO21977 and TDM4529g/BO25430) and combined treatment with pertuzumab in 87 patients (Studies TDM4373g/BO22495 and TDM4688g), with a clinical cut-off date of 31 July 2012. ([Dieras et al 2014](#)).

Thrombocytopenia: Thrombocytopenia, or decreased platelet counts, was reported in patients in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events ($\geq 50,000/\text{mm}^3$), with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 ($\geq 75,000/\text{mm}^3$) by the next scheduled dose. In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients. Cases of bleeding events with a fatal outcome have been observed. Severe cases of hemorrhagic events, including central nervous system (CNS) hemorrhage, have been reported in clinical trials with trastuzumab emtansine; these events were independent of ethnicity. In some of the observed cases the patients were also receiving anti-coagulation therapy.

Hepatotoxicity: Hepatotoxicity, predominantly in the form of asymptomatic increases in the concentrations of serum transaminases, has been observed while on treatment with trastuzumab emtansine in clinical trials. Grade 1–2 events have been observed frequently; Grade 3–4 events have been observed less commonly.

Transaminase elevations were generally transient. A cumulative effect of trastuzumab emtansine on transaminases has been observed; elevated transaminases improved to Grade 1 or normal within 30 days of the last dose of trastuzumab emtansine in the majority of the patients. Serious hepatobiliary disorders, including nodular regenerative hyperplasia (NRH) of the liver and some resulting in fatal liver failure, have been observed in patients treated with trastuzumab emtansine in clinical trials. Some of the observed cases may have been confounded by comorbidities and/or concomitant medications with known hepatotoxic potential.

Cases of NRH of the liver have been identified from liver biopsies in patients presenting with signs and symptoms of portal hypertension. NRH was also observed in one fatal case of hepatic failure. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules; NRH may lead to

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non-cirrhotic portal hypertension. Diagnosis of NRH can only be confirmed by histopathology. NRH should be considered in patients who develop clinical symptoms of portal hypertension and/or a cirrhosis-like pattern seen on computed tomography (CT) scan of the liver, but with normal transaminases and no other manifestations of cirrhosis or liver failure following long-term treatment with trastuzumab emtansine.

Infusion-Related Reactions and Hypersensitivity Reactions: Infusion-related reactions, characterized by one or more of the following symptoms: flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia, have been reported in clinical trials of trastuzumab emtansine. In general, these symptoms were not severe. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated. Hypersensitivity reactions, including serious anaphylactic-like reactions, have been observed in clinical trials with treatment of trastuzumab emtansine.

Pulmonary Toxicity: Severe cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or a fatal outcome, have been reported in clinical trials with trastuzumab emtansine. Signs and symptoms include dyspnea, cough, fatigue, and pulmonary infiltrates. These events may or may not occur as sequelae of infusion reactions. Treatment has included administration of steroids, oxygen, and study drug discontinuation. In some patients with multiple lung metastases, ventilatory support (mechanical ventilation) was required. Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at increased risk of pulmonary events.

Neurotoxicity: Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine.

Left Ventricular Dysfunction: Patients treated with trastuzumab emtansine are at increased risk of developing left ventricular dysfunction. LVEF < 40% has been observed in patients treated with trastuzumab emtansine, and therefore symptomatic congestive heart failure (CHF) is a potential risk. Treatment with trastuzumab emtansine has not been studied in patients with LVEF <50% prior to initiation of treatment.

Extravasation: In trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and comprised erythema, tenderness, skin irritation, pain, or swelling at the infusion site. These reactions have been observed more frequently within 24 hours of infusion.

Full details regarding the clinical safety of trastuzumab emtansine are presented in the IB and in the Summary of Medicinal Product Characteristics (SmPC)/US data sheet for trastuzumab emtansine.

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1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

A number of anti-HER2 therapies have proven efficacy, are approved and part of the SOC for HER2-positive BC and GC (see Sections 1.1 and 1.2). However, this is not yet the case for trastuzumab emtansine which currently is only available for BC. HER2 overexpression has been identified in some other tumors as described in Section 1.1. These findings pose the intriguing question if trastuzumab emtansine could improve patient outcomes in those tumor types and beyond BC and GC. There is currently no clinical data on the potential therapeutic effect of trastuzumab emtansine treatment in HER2-positive tumors such as esophageal-, colorectal-, pancreatic/cholangio-, prostate and bladder carcinoma.

UBC seems to be an interesting target that shows a similar HER2 overexpression rate as in breast cancer, although the IHC staining pattern is expected to be more heterogeneous. HER2 expression in UBC is associated with high-grade tumors and advanced local disease (Hussain et al 2007, Simon et al 2003, Gehani et al 2012, Chen et al 2013), more metastatic sites and visceral metastases (Hussain et al 2007), higher recurrence risk (Chen et al 2013) and shorter OS and disease specific survival (Krueger et al 2002, Simon et al 2003).

Trastuzumab and lapatinib in combination with chemotherapeutic agents showed activity in bladder cancer cell lines (Pegram et al 1999, McHugh et al 2007, McHugh et al 2009) and trastuzumab emtansine showed growth inhibition in cisplatin-resistant, HER2 overexpressing bladder cell lines and orthotopic xenograft models (Hayashi et al 2015).

This proof of effectiveness of HER2-targeted therapies in bladder cell lines as well as some activity of trastuzumab in combination with chemotherapeutic agents in metastatic bladder cancer (Hussain et al 2007) – although in small non-controlled studies – suggests further clinical assessment in a clearly defined UBC population.

Harder et al (2012) conducted a study to investigate the efficacy and safety of trastuzumab and capecitabine as first-line treatment in patients with IHC3+ HER2 expressing advanced pancreatic cancer or cancer with HER2 gene amplification of stage IVB (T1-4N0-1M1). The objective was to show activity of the combination of trastuzumab and capecitabine in these patients. Median PFS was 65 days, with an estimated PFS rate after 6 months of 11.8% (95% CI: 0-27.1) and of 0% after 12 months. Median OS was 6.9 months, with an estimated OS probability after 6 months of 52.9% (95% CI: 29.2-76.7), and after 12 months of 29.4% (95% CI: 7.8-51.1). Even though these were promising results, capecitabine in combination with trastuzumab anti-HER2 therapy did not seem to significantly improve treatment effects in comparison with historical capecitabine monotherapy (mean OS 6.0 months; Cartwright et al 2002). However, as found in a post-hoc analysis, one-third of IHC3+ HER2-positive tumors did not show HER2 amplification and thus may be an explanation for the findings in patients with treated with trastuzumab plus capecitabine.

Therefore, focusing on non-focal expressers in the current study may eliminate some of these limitations and lead to better results.

At a later point in time additional HER2 positive tumors might be evaluated and further assessed as well.

1.3.1 Rationale for Patient Selection

Trastuzumab emtansine is proven to be efficacious in HER2 positive BC tumors.

In patients with HER2-positive LABC or MBC who had received prior taxane and trastuzumab-based therapy (TDM4370g/BO21977), statistically significant and clinically meaningful improvements in PFS and OS were observed in patients receiving trastuzumab emtansine compared with patients receiving lapatinib plus capecitabine. This benefit was supported by improvements in all secondary efficacy endpoints, including overall response rate, time to treatment failure, and in the patient-reported outcome of time to symptom progression.

Consistent with these results, in patients with HER2-positive MBC (see Section 1.2.2) who had received at least two HER2-directed regimens in the metastatic setting (TDM4997g/BO25734), trastuzumab emtansine gave a significant improvement in PFS compared with TPC, and a strong positive trend at the first interim analysis of OS. At the second interim analysis of OS, treatment with trastuzumab emtansine resulted in a statistically significant and clinically meaningful improvement in OS compared with TPC. Since the related p-value crossed the OS efficacy stopping boundary, the results were considered final. Patients receiving trastuzumab emtansine also showed a consistent treatment benefit compared with the subgroup of patients receiving a trastuzumab-containing TPC.

The comparison of trastuzumab emtansine treatment, with or without pertuzumab with trastuzumab plus taxane (docetaxel or paclitaxel) in HER2-positive, progressive or recurrent LABC or MBC (TDM4788g/BO22589) demonstrated PFS non-inferiority for both trastuzumab emtansine-containing regimens compared with trastuzumab plus taxane: The addition of pertuzumab to trastuzumab emtansine did not result in a statistically significant increase in PFS.

The indication of trastuzumab emtansine in BC is limited to patients with HER2-positive, unresectable LABC or MBC who have received prior treatment with trastuzumab and a taxane.

UBC: UBC is a major global health challenge with an estimated 429,000 new cases resulting in 165,000 deaths annually ([Ferlay et al 2013](#)). In males, UBC represents the fourth most frequent diagnoses of new cancer yearly. Over the past two decades, there has been no significant improvement in survival of UBC with 5-year relative survival rates for locally advanced and metastatic disease of 33% and 5%, respectively ([Siegel et](#)

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al 2014). Around 5% of the patients have metastases at diagnosis. 75% are non-muscle invasive (whereas around 20-30% progress) and 20% are muscle-invasive (of these around 50% progress to the metastatic stage) at diagnosis. In urothelial carcinoma of the bladder, different levels of HER2 expression have been reported, between 22% and 37% (Internal Data; Dendreon DN24-02; Hayashi et al 2013) and there is a high concordance between overexpression (IHC) and amplification (ISH). This makes them an interesting potential group for trastuzumab emtansine treatment. However, UBC has a more heterogeneous HER2-expression than for example BC and GC (Internal Data; Sauter et al 1993, Lae et al 2010). It was therefore decided to only include non-focal expressers with $\geq 30\%$ of HER2 IHC3+ positively stained cells as efficacy of trastuzumab emtansine in more heterogeneous cancers is currently unknown.

Pancreatic cancer/cholangiocarcinoma: Pancreatic adenocarcinoma is the 5th most frequent cause of cancer related deaths (Hartwig et al 2013). Survival rates remain disappointing (median OS with palliative chemotherapy 11.1 months) and many patients will develop distant metastases (Conroy et al 2011). The HER2 overexpression rate is as high as 11% (and varies widely between patients). Interestingly, overexpression of the HER2 protein does not correlate well to amplification of the HER2 locus; especially it was shown, that HER2 IHC3+ protein expression did not correlate with gene amplification (Harder et al 2012). HER2 overexpression in pancreatic cancer may be due to gene deregulation rather than gene amplification as postulated by Ukita et al (2002) for intrahepatic biliary tract cancer (Harder et al 2012). Nevertheless an approach with an ADC such as trastuzumab emtansine may be considered a potential treatment option.

Cholangiocarcinomas may be considered related tumors and these patients can be included in later stages of this study. The incidence and mortality rates of cholangiocarcinoma, especially those of *intrahepatic cholangiocarcinoma*, are increasing worldwide (Khan et al 2005). Complete resection is the only way to cure the disease at present. However, because cholangiocarcinoma are difficult to diagnose at an early stage and extend diffusely, most patients have unresectable disease at clinical presentation, and prognosis is very poor (5-year survival is 0–40% even in resected cases) (Yoshikawa et al 2008). Approximately 8% of patients have HER2 overexpression (Yan et al 2015) and may therefore benefit from a HER2-targeted therapeutic approach.

Patients diagnosed with *locally advanced (unresectable and not treatable with curative intent)* or metastatic UBC or *locally advanced (unresectable and not treatable with curative intent)* or metastatic pancreatic cancer/cholangiocarcinoma have very limited treatment options to date, especially if they present in an advanced stage of their cancer, with a high mortality and low long-time survival rates. New therapeutic approaches are therefore needed for these patients with a high unmet medical need and limited other treatment options, especially in late stage.

1.3.2 Rationale for Study Design

KAMELEON is a Phase II, proof of concept, single arm study, designed to estimate the efficacy of trastuzumab emtansine in HER2 overexpressing *locally advanced (unresectable and not treatable with curative intent) or metastatic* UBC, *locally advanced (unresectable and not treatable with curative intent) or metastatic* pancreatic *cancer/cholangiocarcinoma* in patients with advanced disease where cure is no longer possible and where no other treatment options are available anymore. The *trial* might be opened up to a diverse range of other HER2 overexpressing tumors as described further above. Trastuzumab emtansine has proven efficacious in HER2-positive BC and has a tolerable safety profile (see Section [1.2.2.10](#)). Therefore, the risk benefit in this study is deemed positive.

The study design will allow for the examination of *locally advanced (unresectable and not treatable with curative intent) or metastatic* UBC and pancreatic *cancer/cholangiocarcinoma* with enough statistical power to determine whether further examination may be warranted in these indications or potential additional indications. To investigate a potential difference in treatment efficacy for UBC and pancreatic *cancer/cholangiocarcinoma* with homogeneous HER2 expression and the carcinoma with a more focal HER2 expression, patients will be stratified according to the HER2 *IHC* pattern in their baseline tissue biopsy (e.g., 30-70% vs 71-100% of tumor cells expressing HER2). Patients with very focal HER2 *IHC* pattern (e.g., < 30%) will be excluded from this study. The open-label, uncontrolled design is appropriate since the trial will only enroll patients with HER2-positive cancers and who in the opinion of the investigator have trastuzumab emtansine as their best treatment option. The study is intended as a proof of concept.

Recruitment might be expanded to combination treatments and a broader range of patients if a response rate has been demonstrated in Phase II as defined in the protocol and/or a clear clinical benefit for patients is observed based on RECIST 1.1. The sponsor in discussion with the study steering committee (SC) and the iDMC will decide on the expansion. The data from these additional patients will help further characterize the safety and efficacy of trastuzumab emtansine in the specific indication and potentially in combination with other agents.

1.3.3 Rationale for Dose Selection

A 2.4 mg/kg qw dose has been chosen as the starting dose for this study as it has already been explored in BC and GC patients and it is considered that it will provide the highest exposure with an acceptable safety profile in UBC patients. If tolerability is poor, the dose will be changed to 3.6 mg/kg q3w dose.

The weight-based dose of 3.6 mg/kg q3w for trastuzumab emtansine in BC was considered appropriate based on the Phase I dose-finding study and established by Phase II/III trials as shown in Section [1.2.2.6](#) in BC patients.

However, the dose chosen for the current study was explored in a Phase I dosing study in MBC (Beeram et al 2012), which determined the MTD to be 2.4 mg/kg qw. There are currently no data on alternative dosing such as a lower dose weekly or a higher dose every 2 weeks.

In a trastuzumab PK analysis (Cosson et al 2014), it was shown that the PK profiles for trastuzumab in the GC population are lower than what was observed in the BC population (see Sections 1.2.2.6 and 1.2.2.7) and patients with the lowest Cmin had a shorter OS and the highest progressive disease (PD) rate.

1.3.4 Rationale for Translational Research Program

This study will generate a unique data set of patients with HER2 expressing *locally advanced (unresectable and not treatable with curative intent) or metastatic* UBC or *locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancer/cholangiocarcinoma* treated with trastuzumab emtansine. It will create a comprehensive data set of markers that will be informative about differences and similarities between tissues, treatment outcome in these patients. Therefore, the mandatory archival tumor biopsies from all patients included in this study and the optional biopsy collected at disease progression may be used for exploratory protein, deoxyribonucleic acid (DNA)-based analyses and ribonucleic acid (RNA)-based expression analyses. In addition, mandatory plasma samples at baseline and at various timepoints during treatment will be collected (see Schedule of Activities, [Appendix 1](#)). These plasma samples will be used for exploratory biomarker assays which may include but are not limited to analysis of circulating protein and circulating tumor DNA. All exploratory biomarker analyses will be performed retrospectively and are clearly defined in the patient's informed consent.

1.3.5 Benefit Risk Assessment

Anti HER2-therapies have shown clinical utility and are approved in both BC and GC (trastuzumab) or BC (trastuzumab emtansine, see Section 1.2.2). Trastuzumab emtansine has demonstrated a favorable toxicity and tolerability profile to date across several phase I-III studies in BC patients (see Section 1.2.2.11).

HER2 overexpression has been shown in a number of other tumor types. The tumor types investigated in this study have poor prognosis in the advanced setting. Despite some recent progresses in the treatment of these cancers, the current standard of care still results in modest prolongation of survival in the advanced setting. Therefore the prognosis for this advanced-staged cancer types is still poor. Targeted therapies for *locally advanced (unresectable and not treatable with curative intent) or metastatic* UBC or *locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancer/cholangiocarcinoma* must not only demonstrate anti-tumor activity but should also minimize the toxicities commonly associated with currently available treatment options. Based on the clinical experience in MBC to date, trastuzumab

emtansine has the potential to fulfill this need as therapy for advanced HER2 IHC-positive urothelial and/or *pancreatic cancer/cholangiocarcinoma*, with the option to subsequently include other tumor types as well. A safety plan for this study, including appropriate eligibility criteria, dose modification and/or discontinuation guidelines for each identified and potential risk (see Section 5.1), monitoring of patients at risk as well as regular monitoring of patient safety data by an iDMC, has been put into place to minimize any potential risk in the study patient population.

Based on all of the above it is considered that the benefit risk for patients participating in this study is positive.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of trastuzumab emtansine in patients with *locally advanced (unresectable and not treatable with curative intent) or metastatic UBC* or *locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancer/cholangiocarcinoma*. Specific objectives and corresponding endpoints for the study are outlined in [Table 1](#) below.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of trastuzumab emtansine	• Best overall response rate (BOR) as determined by the investigator (using RECIST 1.1). BOR is defined as the best response recorded from the first day of study treatment until disease progression/recurrence or death. Responders, as assessed every 6 weeks, will be defined based on tumor assessment status as partial responder (PR) or complete responder (CR) at these time points. To be assigned a status of PR or CR (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder.
Secondary Efficacy Objective:	
• To evaluate the efficacy of trastuzumab emtansine	• PFS, defined as the time from beginning of treatment to the first occurrence of disease progression, as determined by the investigator (using RECIST 1.1), or death from any cause, whichever occurs first. • OS, defined as the time from beginning of treatment to death from any cause.
Safety Objective:	
• To evaluate the safety of trastuzumab emtansine	• Incidence, type and severity of all adverse events (AEs) and serious adverse events (SAEs) based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03). • Incidence and type of AEs leading to discontinuation, modification, or delay of trastuzumab emtansine dose. • Changes in vital signs, physical examination findings, and clinical laboratory results during and following trastuzumab emtansine administration. • Death and cause of death. • Cases of drug-induced liver injury meeting Hy's Law criteria. • Pneumonitis of all grades. • Change in LVEF over the course of the study as measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA). • Incidence of CHF.

Table 1 Objectives and Corresponding Endpoints (cont.)

Pharmacokinetic Objective:	
• To characterize the pharmacokinetics of trastuzumab emtansine	• Concentrations of trastuzumab emtansine in plasma/serum to determine exposure.
(Exploratory) Immunogenicity Objective:	
• To evaluate the immune response to trastuzumab emtansine	• Incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline. • Exploratory assessment of immune checkpoints e.g. infiltrating lymphocytes in the tumor before and after treatment by the assessment of immune-related biomarkers such as PDL1 and CD8.
Exploratory Biomarker Objective:	
• To identify biomarkers that are predictive of response, can provide evidence of trastuzumab emtansine activity, or can increase the knowledge and understanding of disease biology	• To further evaluate the HER2 status by other exploratory testing methods such as a novel Gene-Protein-Assay (GPA), e.g. IHC and ISH combined in one assay on samples of all consenting screened patients • Correlate levels of HER2 protein expression, HER2 gene amplification and circulating HER2 extracellular domain (HER2 ECD) to trastuzumab emtansine efficacy. • To evaluate biomarkers that may be associated with response and/or safety on the protein, RNA and DNA level (e.g. by molecular subtyping and gene mutation analysis).

3. STUDY DESIGN

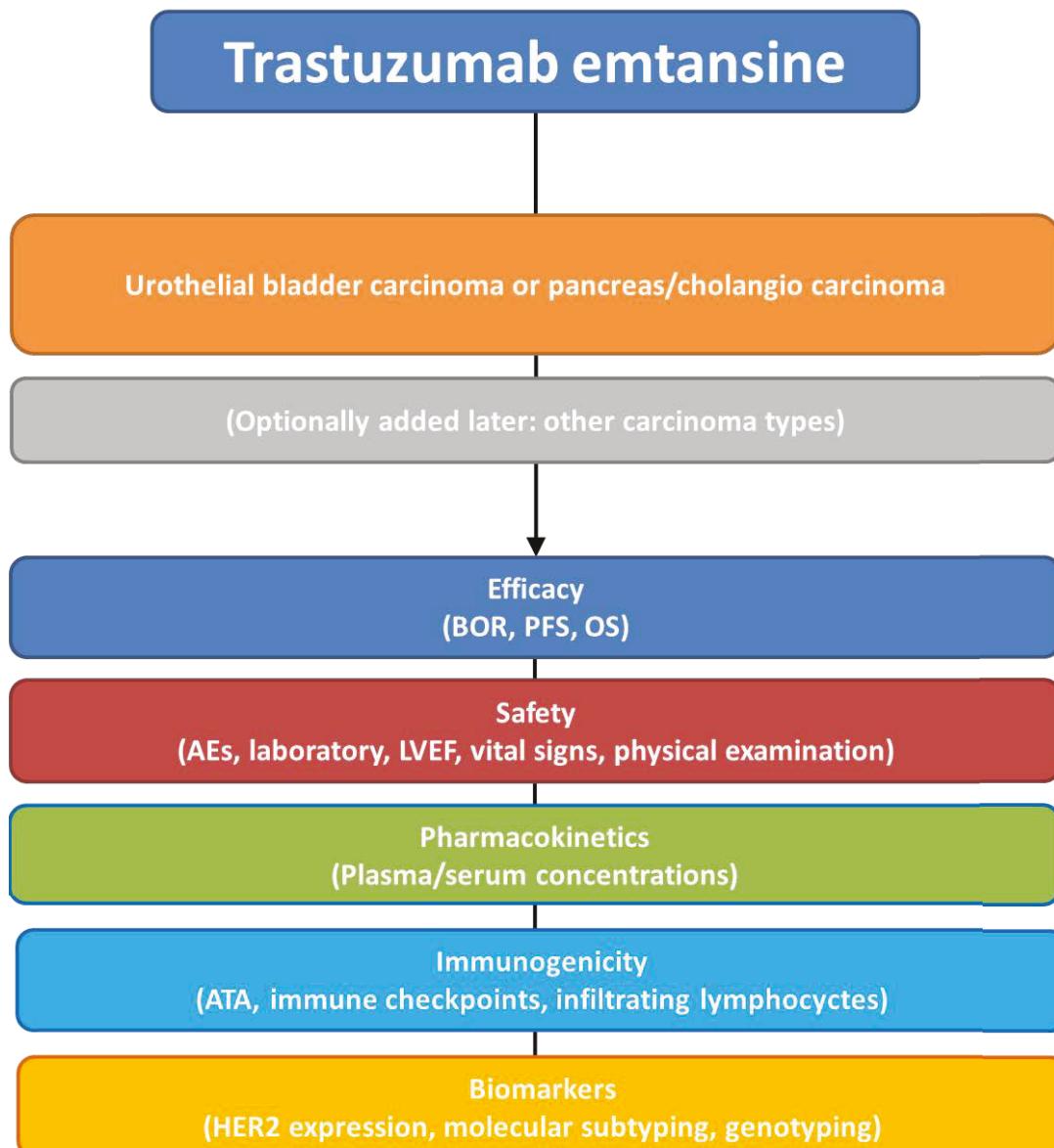
3.1 DESCRIPTION OF THE STUDY

This is an exploratory, multicenter, non-randomized, Phase II, single agent *cohort* study designed to evaluate the efficacy of trastuzumab emtansine in patients with *locally advanced (unresectable and not treatable with curative intent) or metastatic UBC or locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancer/cholangiocarcinoma*, with other tumor types being potentially explored at a later point in time.

If no patients are enrolled in an individual cohort one year after enrolment started, then enrolment for that cohort will be stopped.

The accrual inclusion time for this study is expected to be 18 months per cohort.

Figure 1 Schematic illustration of the KAMELEON study with trastuzumab emtansine treatment in HER2 IHC3+ *locally advanced (unresectable and not treatable with curative intent)* or metastatic urothelial bladder cancer and pancreatic cancer/cholangiocarcinoma



The percentage of HER2 positive UBC differs in the literature and ranges between 22 and 37%, (see Section 1.1). For HER2 IHC3+ with expression equal to 30% and above, the prevalence is between 7 and 18%, for pancreas cancer it is 11% and 8% for cholangiocarcinoma (see Section 1.3.1), depending on the tumor sample, pre-study biopsy or archived tissue. Best tumor response on trastuzumab emtansine treatment will be evaluated; also PFS and OS will be studied as secondary endpoints.

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Patients who fulfill the inclusion/exclusion criteria will be screened for HER2 status and enrolled in the study; a total of 32-38 patients per cohort will be enrolled; 64-76 patients in total.

In a safety run-in, the first 6 patients of each cohort will enter Regimen A and receive 2.4 mg/kg weekly trastuzumab emtansine. These first 6 patients will be assessed on an ongoing and patient per patient basis – i.e. based on the tolerability criteria (as defined in the iDMC charter) and in consultation with the SC and iDMC if needed. Recruitment for the respective cohort will be suspended until all 6 of these patients have completed the 2nd cycle (6 weeks) and the ‘regimen decision point’ has been reached. Based on tolerability and safety aspects (see [Figure 2](#) and [Figure 3](#)), such as lack of unacceptable toxicities (e.g., drug-related fatal case(s), severe drug-induced liver injury [confirmed Hy’s Law cases], Grade ≥ 3 pneumonitis, or other relevant severe toxicities determined by the iDMC) a decision will be made by the iDMC if the cohort is to continue on Regimen A (2.4 mg/kg qw), extending recruitment to a total of 32 patients (additional 26 patients) per cohort, or if the dose switches to Regimen B (3.6 mg/kg q3w). If the regimen is changed to Regimen B in an individual cohort, 32 additional patients will be included in this cohort; if the regimen remains unchanged (i.e., Regimen A), only 26 additional patients will be recruited.

If treatment in a cohort is switched to Regimen B, the 6 patients that were initially started on Regimen A will be allowed to switch if an additional benefit can be expected. However, for patients of a cohort who showed initial response on Regimen A, it is recommended to keep them on Regimen A. If any of these patients experiences PD, no switch is allowed and the patient will be discontinued from the study. Irrespective of these potential changes, these patients will not be included in the primary efficacy analysis.

The primary (and final) analysis for efficacy would be based only on those patients of a cohort who started on the selected treatment regimen. If the decision is made to switch to Regimen B then those patients who started on Regimen A would not be included in the primary or final efficacy analyses (whether they stay on Regimen A or switched to Regimen B) but their results would be included in a supplementary descriptive analysis.

An extensive flow chart is given below and in Figure 3. Decision on expansion of the study to include other carcinoma types will be made via collaboration of the SC and iDMC. The iDMC has to look at the initial tolerability data before the decision to include more carcinoma types is being made. Efficacy data will not be considered for this decision.

Figure 2 Schematic illustration of the KAMELEON study with trastuzumab emtansine treatment in *locally advanced (unresectable and not treatable with curative intent) or metastatic urothelial bladder cancer and pancreatic cancer/cholangiocarcinoma*

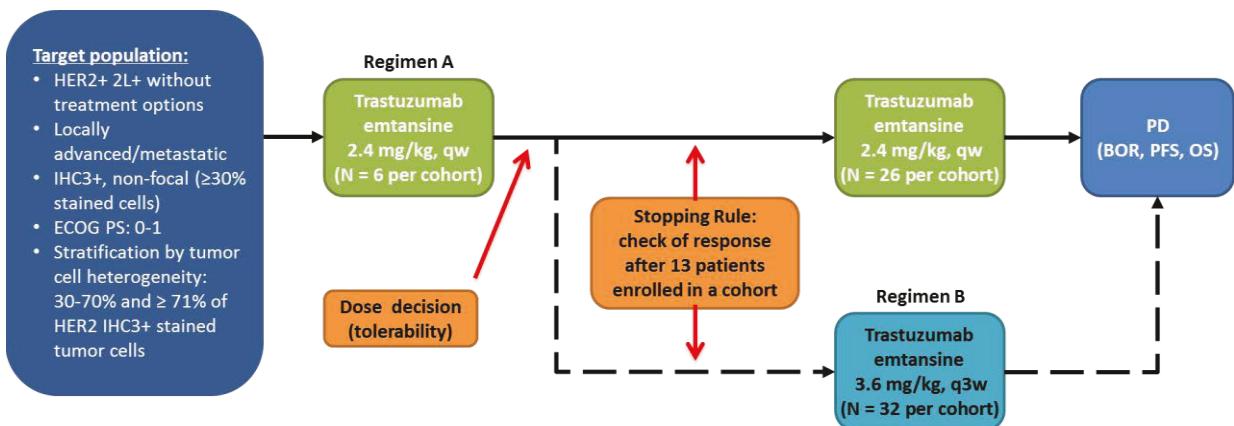
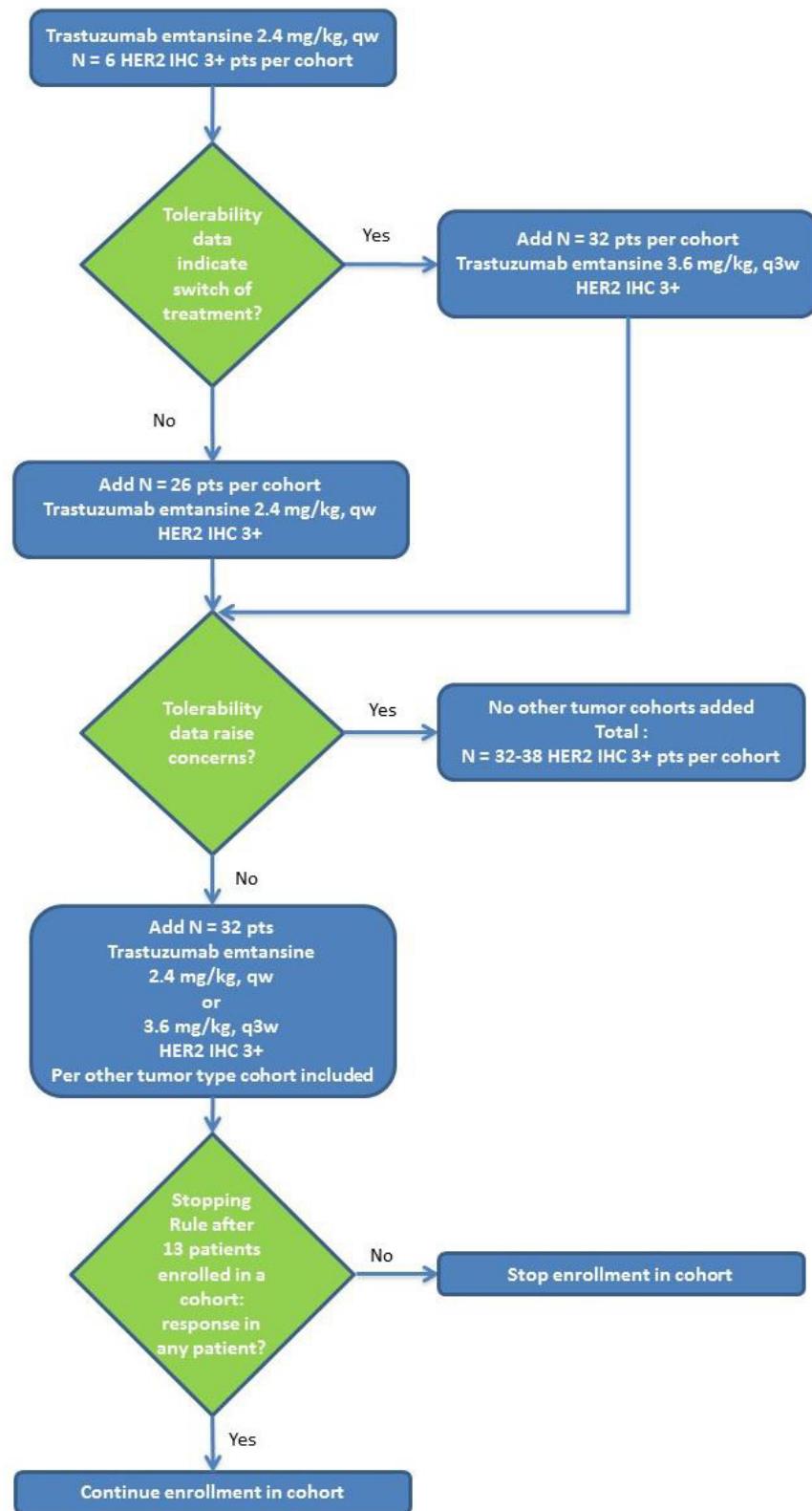


Figure 3 Extensive flow-chart regarding study design and decision points



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Study Procedures

General screening assessment will be performed as per the Schedule of Activities ([Appendix 1](#)). Mandatory pre-treatment tumor samples for HER2 status assessment and biomarkers will be taken. Exploratory biomarker analysis will be performed at the end of the study. Optional informed consent will be asked as well for the collection of a second biopsy at PD and long-term storage for further exploratory research under Research Biosample Repository (RBR) guidelines.

Tumor Assessments

Tumor responses will be measured according to RECIST 1.1 as per the Schedule of Activities ([Appendix 1](#)). Objective response (complete, partial) and progression will be assessed by CT and, in case of brain metastases, also by magnetic resonance imaging (MRI).

Tumor Sampling

Mandatory Tumor Samples

Pre-treatment formalin-fixed tumor tissue embedded in paraffin blocks (or parts of tumor blocks) or alternatively 20 freshly cut slides will be taken for the assessment of HER2 positivity and e.g. for DNA/RNA extraction and/or assessment of biomarkers by protein expression. These procedures are necessary to obtain reliable biomarker and translational research information. For further exploratory assessment of HER2 positivity of consenting patients, additional HER2 testing methods assessing the HER2 protein expression and the gene amplification with tests that are new and under development will be applied. However, these additional assessments will not be relevant for patient screening and selection. All tissue samples will be stored in the central laboratory where HER2 positivity for patient inclusion is assessed for up to 5 years after the date of final closure of the associated clinical database.

Optional Tumor Samples

Besides the mandatory baseline biopsy, patients will also be asked to undergo optional post-treatment biopsies. Post-treatment biopsies will take place at discontinuation of trastuzumab emtansine, either due to PD, unacceptable toxicity of systemic treatment or any other reason. This allows to determine long-term effects of the systemic therapy on the mutational profile (in case of discontinuation of treatment due to disease control) and to observe new mutations that cause insensitivity to systemic treatment (PD after multiple cycles).

Standardized collection of adequate tissue samples is important in performing biomarker research and will be defined in a Sampling Manual.

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After the protocol-defined biomarker analysis will be completed, residual tissue and extracted DNA and RNA samples may be transferred to the RBR if the patient signs the optional informed consent for RBR. These samples can be used for further exploratory research and for long-term storage. All RBR specimen(s) will be destroyed no later than 15 years after the final freeze of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period.

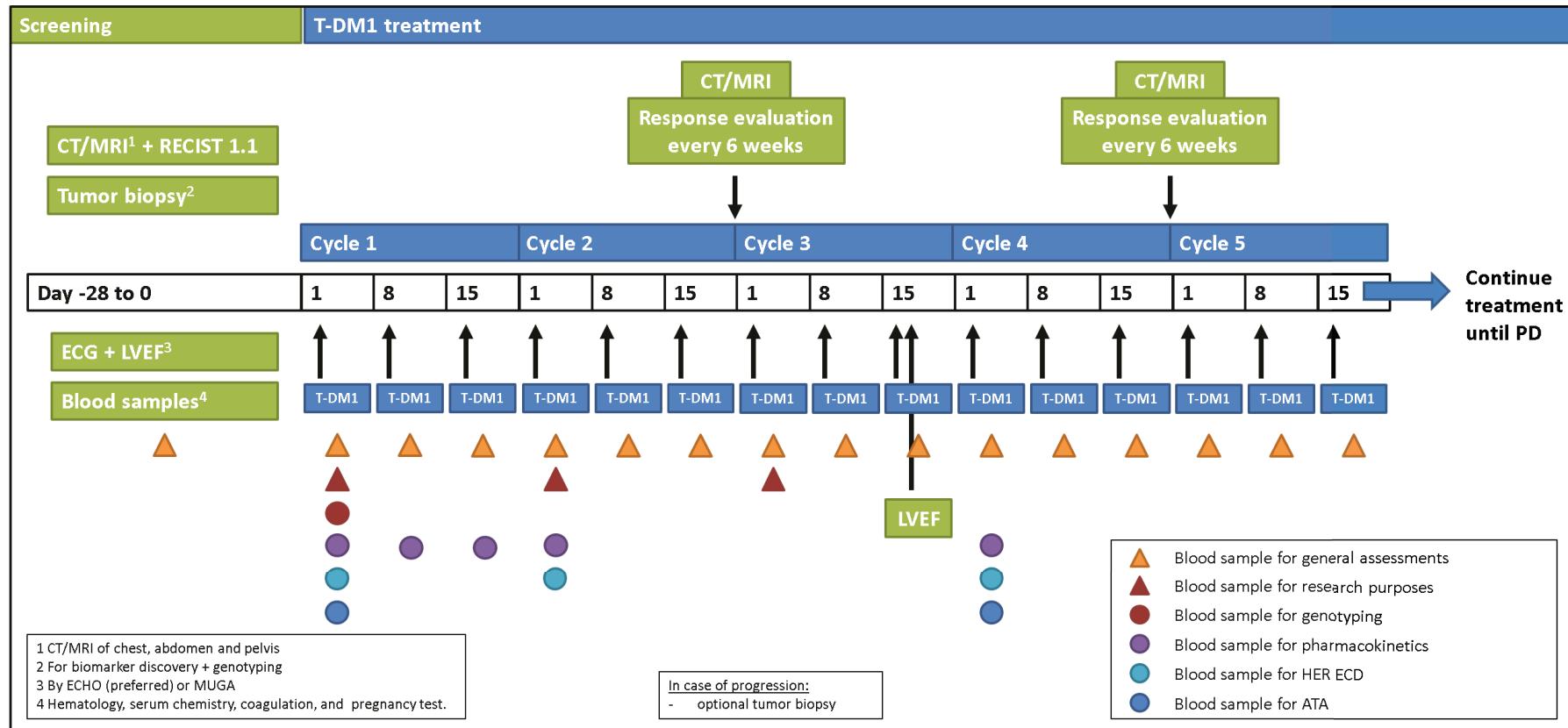
Blood Sampling

Mandatory plasma samples for general assessments will be collected at baseline (Cycle 1, Day 1), every study visit and at PD for all patients. Further samples at baseline will be collected for biomarkers, PK, HER2 ECD, ATAs and genotyping, for PK at each subsequent visit during Cycle 1 and at Cycle 4, Day 1, for HER2 ECD at Cycle 2 and Cycle 4, Day 1 and for ATAs at Cycle 4, Day 1, drug completion and every 3 months thereafter. These specimens will be used for research purposes to identify biomarkers that correlate to response to trastuzumab emtansine treatment (in terms of dose, safety and tolerability) and will help to better understand the pathogenesis, course, and outcome of the carcinomas under investigation and related diseases. Serial serum and plasma samples will be used for example to evaluate changes in circulating protein markers or circulating tumor DNA during course of treatment until progression to better understand (duration of) response to treatment. In addition, one 6 mL blood sample for retrospective genotyping of inherited genes will be collected at baseline from all patients (see [Appendix 1](#), Schedule of Activities).

Administration of Study Drug and Selected Study Assessments

Trastuzumab emtansine will be administered weekly at the dose of 2.4 mg/kg (Regimen A, see [Figure 4](#)) or every 3 weeks at the dose of 3.6 mg/kg (Regimen B, see [Figure 5](#)). Patients will be treated until PD, intolerable toxicity, death, and patient or investigator decision to discontinue treatment.

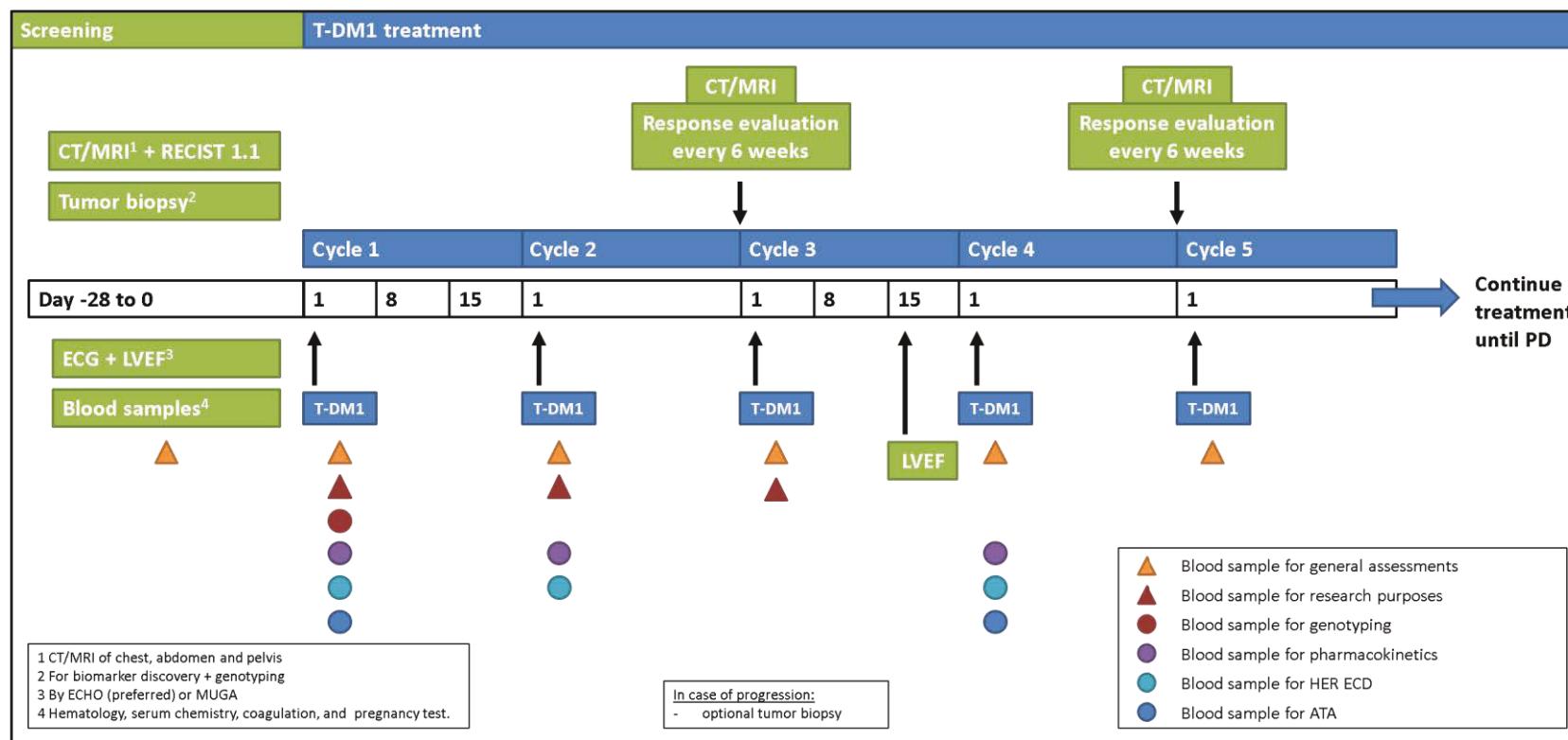
Figure 4 Study scheme of 2.4 mg/kg weekly trastuzumab emtansine administration (Regimen A)



T-DM1=trastuzumab emtansine

Figure refers to Cycles 1 to 5, for Cycle 6 onwards please refer to the SoA (Appendix 1.1)

Figure 5 Study scheme of 3.6 mg/kg 3-weekly trastuzumab emtansine administration (Regimen B)



T-DM1=trastuzumab emtansine

Figure refers to Cycles 1 to 5, for Cycle 6 onwards, please refer to the SoA (Appendix 1.2)

3.2 END OF STUDY AND LENGTH OF STUDY

The total length of the study for an individual cohort, from screening of the first patient to the end of the study, is expected to be approximately 3 years (18 months of recruitment, 6 months of treatment and 12 months of follow-up).

Each cohort will close 18 months after the last patient was recruited or once all patients have died or withdrawn from the study, whichever happens first. End of study in a cohort will be declared at the last patient last visit (LPLV) as per definition is the last data collection point, which can be a clinic visit or a laboratory sample.

Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurs first. After completion of treatment, patients will be followed up in a 3 monthly schedule until study close (18 months after last patient in each cohort). *The treatment period is expected to be 6 months.*

The data cutoff for the primary analysis of BOR will take place 12 weeks after the last patient of an individual cohort has been recruited (following a tumor assessment after 6 weeks [2 cycles] with a confirmation of BOR performed no less than 4 weeks after the criteria for response are first met).

The data cutoff for the final analysis for each cohort of all primary and secondary efficacy measures will take place 18 months after the last patient was recruited, or once all patients have reported a progression event, whichever occurs earlier.

Interim analyses will take place as described in Section 6.8.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Trastuzumab Emtansine Dose and Schedule

In this study, patients will be treated with trastuzumab emtansine. No comparator or placebo will be used. Trastuzumab emtansine is considered the investigational medicinal product (IMP) in this study.

The weight-based doses of 2.4 mg/kg qw and 3.6 mg/kg q3w for trastuzumab emtansine are considered appropriate based on the Phase I dose-finding study and established by Phase II/III trials. PK characteristics of trastuzumab (backbone antibody of trastuzumab emtansine) differ between different tumor types ([Cosson et al 2014](#)). Current knowledge of trastuzumab emtansine PK derives mostly from BC. For further information see Sections [1.2.2.5](#) and [1.3.3](#).

3.3.2 Rationale for Patient Population

Trastuzumab emtansine is proven to be efficacious in HER2 positive BC. Recently published results in locally advanced or metastatic GC (BO27952; GATSBY) showed that, though not demonstrating a direct efficacy benefit over taxane, trastuzumab

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emtansine was well tolerated and the safety profile was acceptable. It is currently being under evaluation for the treatment of HER2 lung cancer (Lewis et al 2013).

There is currently no clinical data on the potential therapeutic effect of trastuzumab emtansine treatment in other HER2 positive tumors such as *locally advanced (unresectable and not treatable with curative intent) or metastatic UBC or locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancer/cholangiocarcinoma*. Further information on this disease is presented in Section 1.3.1.

4. **MATERIALS AND METHODS**

4.1 **PATIENTS**

Up to 38 patients per cancer type, i.e. *locally advanced (unresectable and not treatable with curative intent) or metastatic UBC and locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancer/cholangiocarcinoma*, will be enrolled in this study.

4.1.1 **Inclusion Criteria**

Patients must meet the following criteria for study entry:

1. Histologically centrally confirmed HER2-positive (IHC3+ in $\geq 30\%$ of tumor cells): *locally advanced (unresectable and not treatable with curative intent) or metastatic UBC or locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancer/cholangiocarcinoma*.

HER2 status may be pre-screened at the participating site. However, HER2 determination at the referral center is not accepted to determine study eligibility. HER2 positivity needs to be prospectively confirmed with central laboratory HER2 testing before patient enrollment.

2. There must be no standard treatment options available for patients with the above HER2 overexpressing tumors and they must have undergone at least one prior platinum-based treatment for *locally advanced (unresectable and not treatable with curative intent) or metastatic tumor*. (Note: for *pancreatic cancer/cholangiocarcinoma*, prior treatments are NOT required to be platinum-based.)
3. The patient must have evaluable disease fulfilling all of the following imaging criteria:
 - a. On diagnostic CT scan/MRI: lesion should be measurable according to RECIST 1.1.
 - b. Target lesion(s) should not have been previously irradiated.
4. At least one formalin-fixed paraffin-embedded (FFPE) biopsy of the primary tumor and/or from a metastatic site is required.
5. Age ≥ 18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2.

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7. No significant cardiac history and a current LVEF \geq 50%. LVEF should be determined within 28 days before the start of trastuzumab emtansine treatment.
8. Adequate organ function, evidenced by the following laboratory results (performed within 7 days prior to commencement of dosing):
 - a. Absolute neutrophil count $>$ 1,500 cells/mm³.
 - b. Platelet count $>$ 100,000 cells/mm³.
 - c. Hemoglobin $>$ 9 g/dL.
 - d. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $<$ 2.5 \times upper limit of normal (ULN).
 - e. Total bilirubin \leq 1.5 \times ULN unless the patient has documented Gilbert's syndrome, in which case direct (conjugated) bilirubin level needs to be within normal limits.
 - f. Serum alkaline phosphatase \leq 2.5 \times ULN. Patients with bone metastases: alkaline phosphatase \leq 5 \times ULN.
 - g. Serum creatinine $<$ 2.0 mg/dL or $<$ 177 μ mol/L.
 - h. International normalized ratio (INR) and activated partial thromboplastin time or partial thromboplastin time (aPTT or PTT) $<$ 1.5 ULN.
9. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the study.
10. Negative serum pregnancy test for women of childbearing potential (including premenopausal women who have had a tubal ligation) and for all women not meeting the definition of postmenopausal (\geq 12 months of amenorrhea), and who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential (see Section 5.4.3).
11. For women of childbearing potential and men with partners of childbearing potential, agreement by the patient and/or partner to use a highly effective non-hormonal form of contraception such as surgical sterilization or two effective forms of non-hormonal contraception until 7 months after the last dose of trastuzumab emtansine.
A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (\geq 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
Methods of birth control are considered highly effective forms of contraception in case they result in a low failure rate (i.e., $<$ 1% per year) when used consistently and correctly. The use of the following non-hormonal methods of contraception is acceptable:
 - a. True abstinence, when this is the preferred and usual lifestyle of the patient.
Periodic abstinence (e.g., calendar, ovulation, and symptothermal post

ovulation methods) and withdrawal are not acceptable methods of contraception.

- b. Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomized male partner should be the sole partner.

Alternatively, use of two of the following effective forms of contraception is acceptable:

- a. Placement of intrauterine device or intrauterine system. Consideration should be given to the type of device being used, as there are higher failure rates for certain types (e.g., steel or copper wire).
- b. Condom with spermicidal foam/gel/film/cream/suppository.
- c. Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted: Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection. However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

12. Signed written informed consent approved by Ethics Committee (EC) and obtained prior to any study procedure.
13. Life expectancy of at least 12 weeks.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Patients with previous exposure to HER2-targeted therapies in any setting.
2. Patients showing histologically confirmed focal HER2-expression, i.e., < 30% of positively stained tumor cells.
3. Patients with brain metastasis as the sole site of metastatic disease and/or are symptomatic or require therapy to control symptoms.

NB: Brain metastases are allowed provided they are asymptomatic and controlled by previous radiotherapy.

4. Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg).
5. Current unstable angina pectoris.
6. History of symptomatic CHF of any New York Heart Association (NYHA) criteria or ventricular arrhythmia that requires treatment.
7. History of myocardial infarction within the last 6 months.
8. Peripheral neuropathy, Grade ≥ 3.

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9. Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy.
10. Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures).
11. History of other malignancy within the last 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, stage I uterine cancer, or other cancers with a similar outcome as those previously mentioned.
12. For female patients, current pregnancy and lactation.
13. Concurrent, serious, uncontrolled infections or current known infection with human immunodeficiency virus (HIV), active hepatitis B and/or hepatitis C.
14. Known prior severe hypersensitivity to trastuzumab and trastuzumab emtansine or the excipients of the investigational medicinal product (IMP).
15. Clinically significant bleeding within 30 days before enrollment
16. Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
17. Concurrent participation in any other therapeutic clinical trial.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a single arm open label study. All patients will be treated with trastuzumab emtansine single agent.

4.3 STUDY TREATMENT

The IMP for this study is trastuzumab emtansine (Kadcyla).

- Trastuzumab emtansine will be administered by intravenous (IV) infusion
 - Regimen A: trastuzumab emtansine 2.4 mg/kg, weekly or
 - Regimen B: trastuzumab emtansine 3.6 mg/kg every 3 weeks.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Trastuzumab Emtansine

Trastuzumab emtansine is provided as a single-use, lyophilized formulation in a colorless 20 mL Type I glass vial containing 160 mg of trastuzumab emtansine closed by means of a FluroTec coated stopper and an overseal with flip-off cap. Upon receipt of trastuzumab emtansine, vials should be refrigerated at 2–8°C (36–46°F) until use. Do not use the product beyond the expiration date provided by the manufacturer.

All vials of trastuzumab emtansine should be handled by appropriately trained site staff wearing gloves and using appropriate procedures in place at the clinical site for preparation of chemotherapeutic drugs. Vials should be visually inspected upon receipt

to ensure that they are intact without exterior contamination. Discard any cracked vials and report vials with surface contamination to the clinical site manager for assessment.

The lyophilized product should be reconstituted using sterile water for injection (SWFI). Using a new syringe, 8 mL SWFI should be added to the vial and the vial swirled gently until the product is completely dissolved. THE VIAL SHOULD NOT BE SHAKEN. The resulting product contains 20 mg/mL trastuzumab emtansine, 10 mM sodium succinate, pH 5.0, 60 mg/mL sucrose, and 0.02% (w/v) polysorbate 20. Each 20 mL vial contains enough trastuzumab emtansine to allow delivery of 160 mg trastuzumab emtansine. The reconstituted product contains no preservative and is intended for single use only. The reconstituted lyophilized vials should be used within one hour of reconstitution with SWFI. If not used within this time frame, the reconstituted vials can be stored for up to 24 hours in a refrigerator at 2°C-8°C. Vials stored beyond this time period should be discarded.

The vial should be inspected to ensure the reconstituted product is a clear colorless solution, and is free of particulates before proceeding. Drug from any vial that appears abnormal upon inspection should not be administered to patients. Using a new syringe, the indicated volume of trastuzumab emtansine solution should be removed from the vial(s) and added to the IV bag containing at least 250 mL of 0.45% sodium chloride (preferred) or 0.9% sodium chloride injection and gently inverted to mix the solution. A 0.2 or 0.22 micron non-protein adsorptive polyethersulfone in-line filter is recommended when using 0.45% sodium chloride and required when using 0.9% sodium chloride injection. The solution of trastuzumab emtansine should not be shaken.

Once reconstituted, trastuzumab emtansine solution is diluted into polyvinylchloride (PVC), latex-free PVC-free, polyolefin, polypropylene or polyethylene bags containing 0.45% or 0.9% NaCl. From a microbiological point of view, the diluted trastuzumab emtansine in infusion bags should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should not be longer than 24 hours at 2°C-8°C. For additional information, refer to the IB.

4.3.2 Dosage, Administration, and Compliance

4.3.2.1 Trastuzumab Emtansine

Trastuzumab emtansine treatment only starts after a successfully completed screening period. There are two treatment regimens:

- Regimen A: trastuzumab emtansine 2.4 mg/kg weekly, IV or
- Regimen B: trastuzumab emtansine 3.6 mg/kg every 3 weeks, IV.

The iDMC will recommend a trastuzumab emtansine regimen based on tolerability data available at the time of the regimen-selection analysis.

If the timing of a protocol mandated procedure (e.g., infusion of study drug) coincides with a holiday and/or weekend that preclude the procedure, the procedure should be

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performed on the nearest following date, with subsequent protocol-specified procedures rescheduled accordingly.

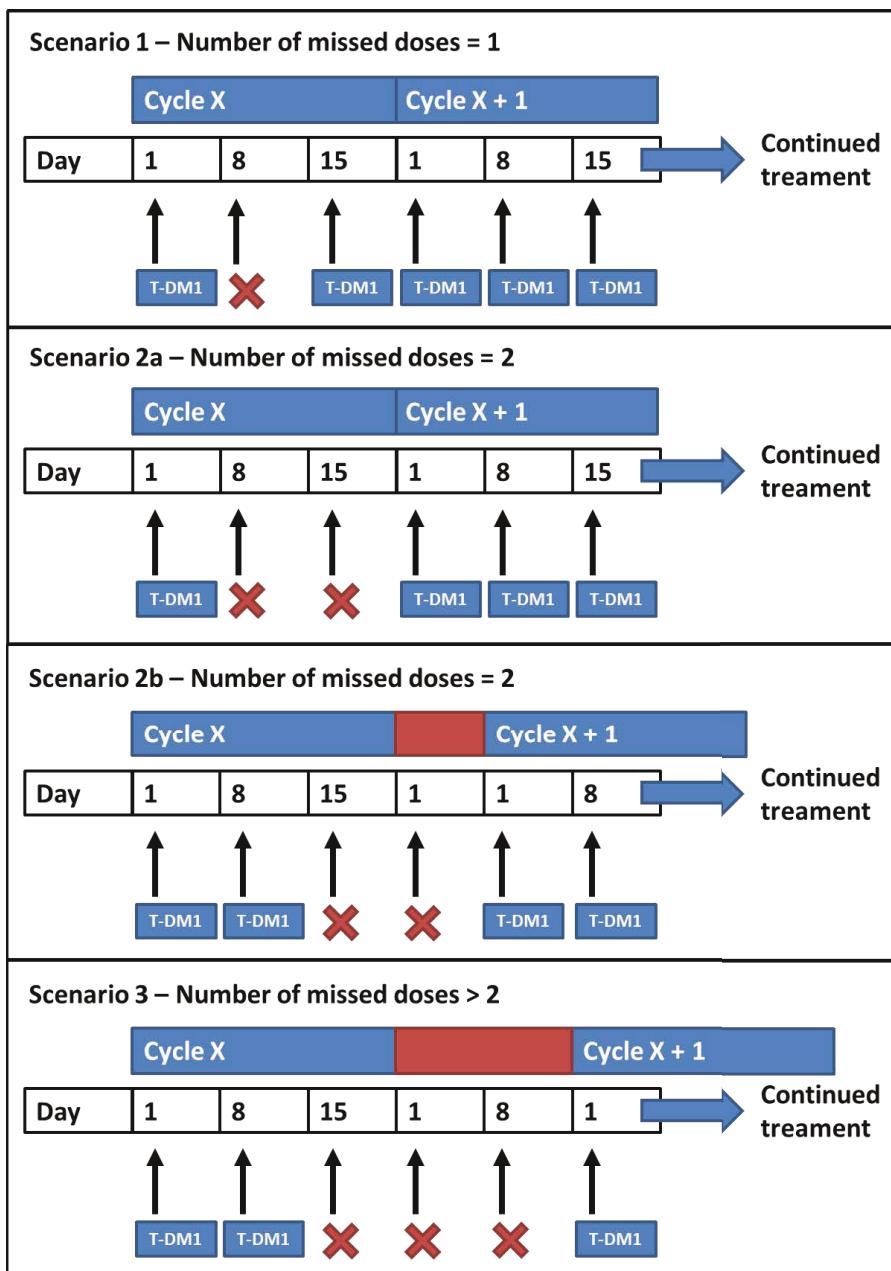
Each treatment cycle is 21 days in length.

Patients on a weekly regimen (Regimen A) will receive three weekly doses of study therapy every 21 days (on Days 1, 8, and 15 of a 21-day cycle).

Patients on the every 3-week regimen will receive one dose of study therapy every 21 days (on Day 1 of a 21-day cycle).

If a patient is not dosed on a cycle day because of toxicity, the dose will be held on that cycle dosing day, and dosing will resume on the next appropriate cycle dosing day when the toxicity has resolved. For example, if the patient received study treatment at Cycle X, Day 1, but is not dosed on Day 8 because of toxicity and she or he can be dosed again on Day 15, then for that cycle the patient will have received dosing on Days 1 and 15, with Day 8 held because of such an event. Similarly, if a patient received dosing on Days 1 and 8 but Day 15 was held because of toxicity and he or she is able to start dosing again the next week, then next week begins a new cycle (see [Figure 6](#)). Every effort should be made to keep to the 21-day cycle for weekly dosing.

Figure 6 Cycles and missed dosing



All patients will be closely monitored for safety and tolerability during all cycles of therapy and during the follow-up period. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and laboratory test values are acceptable. Dose delays up to 21 days (+/- 3 days) will be allowed for trastuzumab emtansine. It will be defined in the Schedule of Activities; in addition, dose reductions are further outlined in Section 5.1.2. During study drug infusion patients will be monitored, as described below.

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Please refer to [Figure 2](#) for a general overview of the study and [Figure 3](#) for a more detailed description of decision points.

Regimen A: Trastuzumab emtansine 2.4 mg/kg, weekly dosing in a 3-weekly cycle

The regimen selection will be performed for each cohort individually after 6 patients have been enrolled under Regimen A and followed for at least 6 weeks. If – based on tolerability data – the dosing regimen of 2.4 mg/kg every week is considered unfavorable then future patients of the respective cohort will be switched to the Regimen B with 3-weekly dosing of trastuzumab emtansine 3.6 mg/kg.

The administered dose will depend on the patient's weight on Day 1 (or up to 3 days before) of each trastuzumab emtansine cycle. The actual dose administered should be +/-10% of the dose calculated for the patient. Trastuzumab emtansine will be administered on Days 1, 8 and 15 of a 21 day cycle.

If the timing of a protocol-mandated procedure such as administration of trastuzumab emtansine coincides with a holiday that precludes the procedure, the procedure should be performed on the earliest following date, with subsequent protocol-specified procedures rescheduled accordingly. The weekly schedule allows for -1/+3 days. The interval between trastuzumab emtansine weekly dosing is 7 days, and should not be < 6 days.

Treatment continues until disease progression, unacceptable toxicity or request of the patient to withdraw of the study. Also in the event of an intercurrent illness – which would in the judgment of the investigator affect patient safety – treatment will be discontinued.

The only available route of administration for trastuzumab emtansine is IV infusion. Trastuzumab emtansine infusion time may be decreased, depending on the patient's tolerability of the infusion. For the first cycle, trastuzumab emtansine should be administered as a 90 (+/- 10) minutes IV infusion. Following the initial dose, patients will be observed for at least 90 minutes for fever, chills, or other infusion-associated symptoms. If the 90 minutes infusion is well tolerated, subsequent infusions may be delivered over 30 (+/- 10) minutes with a minimum 30 minute observation period after the infusion. The volume contained in the administration tubing should be completely flushed with saline after administration of trastuzumab emtansine. The line should not be used for any other drug administration, but it can be used to administer IV fluids. A filter should be used in conjunction with the infusion set when using 0.9% sodium chloride for dilution.

Premedication for nausea and infusion reactions (e.g., acetaminophen or other analgesics, antihistamines or corticosteroids) may be given at the investigator's discretion.

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If infiltration of the trastuzumab emtansine infusion site occurs, the following steps should be taken:

- Discontinue the IV infusion.
- If a significant volume of the trastuzumab emtansine infusion remains, re-start the IV infusion elsewhere.
- Treat the infiltration according to institutional guidelines for infiltration of a non caustic agent.

Patients will be carefully monitored during study drug infusion.

Regimen B: Trastuzumab emtansine 3.6 mg/kg, 3-weekly cycle of dosing

Trastuzumab emtansine will be given at a dose of 3.6 mg/kg every 3 weeks (21 days +/- 3 days) until disease progression, unacceptable toxicity or request of the patient to withdraw from the study. Also in the event of an intercurrent illness – which would in the judgment of the investigator affect patient safety – treatment will be discontinued.

The total dose will depend on the patient's weight on Day 1 (or up to 3 days before) of each trastuzumab emtansine cycle. The actual dose administered should be +/-10% of the dose calculated for the patient.

The only available route of administration for trastuzumab emtansine is IV infusion. Trastuzumab emtansine infusion time may be decreased, depending on the patient's tolerability of the infusion. For the first cycle, trastuzumab emtansine should be administered as a 90 (+/- 10) minutes IV infusion. Following the initial dose, patients will be observed for at least 90 minutes for fever, chills, or other infusion-associated symptoms. If the 90 minutes infusion is well tolerated, subsequent infusions may be delivered over 30 (+/- 10) minutes with a minimum 30 minute observation period after the infusion. The volume contained in the administration tubing should be completely flushed with saline after administration of trastuzumab emtansine. The line should not be used for any other drug administration, but it can be used to administer IV fluids. A filter should be used in conjunction with the infusion set when using 0.9% sodium chloride for dilution.

Premedication for nausea and infusion related reactions (e.g., acetaminophen or other analgesics, antihistamines or corticosteroids) may be given at the investigator's discretion.

If infiltration of the trastuzumab emtansine infusion site occurs, the following steps should be taken:

- Discontinue the IV infusion.
- If a significant volume of the trastuzumab emtansine infusion remains, re-start the IV infusion elsewhere.

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- Treat the infiltration according to institutional guidelines for infiltration of a non-caustic agent.

Patients will be carefully monitored during study drug infusion.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

The IMP required for completion of this study (trastuzumab emtansine) will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, using the interactive voice/web recognition system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced.

The IMP either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Trastuzumab Emtansine

Currently, the Sponsor does not have any plans to provide trastuzumab emtansine or any other study treatments or interventions to patients who have completed the study. The Sponsor may evaluate whether to continue providing trastuzumab emtansine in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

The Sponsor will offer post-trial access to the study drug (trastuzumab emtansine) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to IMP, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being

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- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for *locally advanced (unresectable and not treatable with curative intent)* or *metastatic UBC or pancreatic cancer/cholangiocarcinoma*
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for *locally advanced (unresectable and not treatable with curative intent)* or *metastatic UBC or pancreatic cancer/cholangiocarcinoma*
- Provision of study drug is not permitted under the laws and regulations of the patient's country

The study will be concluded *18 months after the last patient has been enrolled in the last cohort*. Patients who have not progressed at the end of the trial and who are still on treatment will be offered the possibility to continue treatment in an extension study.

In case a patient decides to withdraw from the study, no post-trial access will be granted. Currently, the Sponsor does not have any plans to provide other study interventions to patients after conclusion of the study or any earlier patient withdrawal.

4.4 CONCOMITANT THERAPY

All concomitant medications and premedication therapies are considered non-IMPs. Concomitant therapy (non-investigational products) includes any prescription medication, over-the-counter preparation, herbal therapy, or radiotherapy used by a patient between the 28 days preceding study enrollment and the study follow-up or study drug completion visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Permitted concomitant therapy:

- Bisphosphonates and other bone supportive agents are allowed if the dose and renal function have been stable for at least 12 weeks before the enrollment and no related side effects of \geq CTCAE Grade 2 are present for at least 4 weeks prior to study drug treatment.

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- Premedication is allowed according to standard practice guidelines.
- No pre-medication for the first infusion of trastuzumab emtansine with steroids is specified or expected; any planned pre-medication for the first infusion with steroids should be discussed with the oncologist prior to administration.
- Premedication for nausea and infusion related reactions (e.g., acetaminophen) may be given at the investigator's discretion. Anti-emetics are allowed.
- Patients who experience nausea and trastuzumab emtansine infusion-related temperature elevations of 38.5°C or other minor infusion related symptoms may be treated symptomatically with acetaminophen or other analgesics, antihistamines or corticosteroids. Serious infusion-related events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies clinically indicated according to standard clinical practice (e.g., supplemental oxygen, β 2 agonists, and corticosteroids).
- Palliative radiotherapy is allowed to treat painful bone metastases.

Brain stereotactic radiosurgery is allowed if metastatic brain lesions become symptomatic during trastuzumab emtansine treatment. (Of note, patients with brain metastases are allowed to enter the study provided they are asymptomatic and controlled at beginning of the study, see exclusion criteria in Section 4.1.2). Please contact the Medical Monitor for approval.

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study treatment prior to documented disease progression and for at least 28 days prior to initiation of study treatment:

- Investigational therapy other than study drug.
- Cytotoxic chemotherapy.
- Biologic agents, e.g., trastuzumab.
- Any therapies intended for the treatment of the tumor type whether they are approved by national health authorities or experimental.
- Erythropoiesis stimulating agents.
- G-CSF.
- Strong CYP3A4 inhibitors including but not limited to ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, neflifinavir, ritonavir, saquinavir, telithromycin, voriconazole.
- Therapeutic agents that have a high risk of bleeding or might increase the risk of bleeding (e.g., clopidogrel, ASS, diclofenac), except therapeutic anticoagulation if absolutely needed by the patient.

Other medications considered necessary for the patient's safety and well-being may be given at the discretion of the investigator.

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4.5 STUDY ASSESSMENTS

Please see [Appendix 1](#) for the Schedule of Activities to be performed during the study.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study related procedures unless the assessments were performed as standard of care prior to obtaining informed consent and within 2 weeks prior to study entry. Informed Consent Forms (ICFs) for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

Screening is to be completed within 28 days prior to baseline, however HER2 testing can be performed up to a maximum of 2 years prior to baseline (see Appendices 1.1 and 1.2 for Regimen A and B, respectively).

A separate ICF can be used for HER2 testing. The HER2 screening test (determined by the central laboratory) may be performed as soon as a potential patient is identified, provided the HER2 Screening Informed Consent is signed.

4.5.2 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse; in addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal/homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to the screening visit.

Demographic data will include age, sex, and self-reported ethnicity.

4.5.3 Physical Examinations

A complete physical examination should be performed at screening and should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. Height and weight should also be recorded in the eCRF.

At subsequent visits (as shown in [Appendix 1](#)), a limited, symptom-directed physical examination should be performed. Changes from baseline abnormalities should be

recorded in patient notes. New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF. Weight should also be recorded in the eCRF.

As part of tumor assessment, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Any new or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs (including systolic and diastolic blood pressure, pulse rate, oxygen saturation, respiratory rate, temperature) should be collected at screening, pre-dose, every 15 (+/- 5) minutes during the first trastuzumab emtansine infusion, and 60 (+/- 10) minutes after the infusion. In subsequent cycles, vital signs should be recorded within 60 minutes pre- and post-infusion (see [Appendix 1](#)). Measurements should be taken with the patient in a supine position.

Vital signs will be measured at every visit in the first 3 cycles and at Day 1 of all subsequent cycles.

Abnormal or significant changes to vital signs from baseline should be recorded as AEs, if appropriate.

4.5.5 Tumor and Response Evaluations

All known sites of disease (measurable and immeasurable) must be documented at screening and re-assessed at each subsequent tumor evaluation. Response will be assessed by the investigator on the basis of physical examinations, CT or MRI scans, and bone scans using RECIST v1.1, see [Appendix 2](#).

Assessments will be done every 6 weeks from the start date of the study drug, regardless of dose delay or early discontinuation, until disease progression or study termination. Tumor assessments obtained within 30 days of Cycle 1, Day 1 may be used for screening purposes. Response must be assessed through physical examination and imaged-based evaluation, using RECIST 1.1. The same radiographic procedure used to define measurable disease sites at baseline must be used throughout the study.

CT scans should include chest, abdomen, and pelvic scans; CT scans of the neck should be included if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if PD is suspected.

CT or MRI of the brain and baseline radioisotope bone scan must be obtained at screening. If an isotope-based scan was performed \geq 28 days but \leq 60 days prior to first treatment the bone scan does not need to be repeated and non-isotopic radiographic modalities should be utilized to document the extent of bony metastatic disease. Tumor assessments should include an evaluation of all known and/or suspected sites of

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disease, whenever possible. Patients should have lesions selected that can be evaluated at every tumor assessment. The same radiographic procedure used at screening must be used throughout the study for the same patient (e.g., the same contrast protocol for CT scans).

4.5.6 LVEF Evaluation

LVEF assessments will be performed, according to the Schedule of Activities (see [Appendix 1](#)), by either ECHO or MUGA scan. ECHO is the preferred method.

ECHO/MUGA will be performed at screening and between Days 15 and 21 *in Cycles 1 and 3 at every third cycle thereafter (Cycles 6, 9 etc) and* at the study drug completion visit. *The same method used at screening should be used throughout the study.*

Patients will be reassessed with the same technique used for baseline cardiac evaluation throughout the study and, to the extent possible, will be obtained at the same institution for an individual patient. If treatment is delayed for any reason, LVEF assessments can be postponed to allow them to be performed within 7 days prior to the next treatment administration.

For extensive follow-up instructions, see 'cardiotoxicity' in Section [5.1.1.3](#).

4.5.7 ECOG Performance Status

Performance status will be measured using the ECOG performance status scale, according to the Schedule of Activities (see [Appendix 1](#)).

It is recommended, where possible, that a patient's performance status will be assessed by the same person throughout the study.

4.5.8 Laboratory, Biomarker, and Other Biological Samples

4.5.8.1 Samples for General Assessments

Blood samples for hematology, biochemistry, coagulation, urinalysis, serology, and pregnancy testing will be collected as per the Schedule of Activities (see [Appendix 1](#)) and will be analyzed at the study site's local laboratory:

- Hematology (hemoglobin, hematocrit, red blood cells [RBC], platelet count, white blood cells [WBC] with differential [including neutrophils, lymphocytes, monocytes, eosinophils and basophils])
- Serum chemistry (glucose, blood urea nitrogen [BUN], creatinine, sodium, potassium, bicarbonate, phosphorus, chloride, calcium, uric acid, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, lactate dehydrogenase [LDH], AST, ALT, gamma-glutamyl-transferase [GGT])
- Coagulation (INR and aPTT)

- Urinalysis (dipstick including pH, specific gravity, glucose, protein, ketones, blood, bilirubin and microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- Viral serology, performed at screening only (HIV, hepatitis B surface antigen [HBsAg], total hepatitis B core antibody [HBcAb], and hepatitis C virus [HCV] antibody)
- Pregnancy test: All women of childbearing potential will have a serum pregnancy test within 7 days prior to the first administration of study drug (Day 1, Cycle 1). Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

During the study, blood samples will be taken before each trastuzumab emtansine administration to secure adequate organ function and safety (see [Appendix 1](#), Schedule of Activities).

4.5.8.2 Blood Samples for Pharmacokinetic Assessments

Samples for evaluation of trastuzumab emtansine, DM1, and total trastuzumab will be collected as shown in [Figure 4 \(Regimen A\)](#) and [Figure 5 \(Regimen B\)](#).

Limited PK assessments *will be made*:

- *Regimen A: with 6 sampling timepoints in Cycle 1 (Day 1, Day 8, and Day 15, each predose and 15-30 minutes postdose), 1 sampling timepoint in Cycle 2 (Day 1, predose), and 2 sampling timepoints in Cycle 4 (Day 1, predose and 15-30 minutes postdose).*
- *Regimen B: with 2 sampling timepoints in Cycle 1 (Day 1 predose and 15-30 minutes postdose), 1 sampling timepoint in Cycle 2 (Day 1, predose), and two sampling timepoints in Cycle 4 (Day 1, predose and 15-30 minutes postdose).*

4.5.8.3 Blood Samples for HER2 ECD Assessments

HER2 ECD serum samples will be obtained predose at baseline (Cycle 1, Day 1), at Cycle 2, Day 1 and at Cycle 4, Day 1; see Appendix 1.

4.5.8.4 Blood Samples for Evaluation of Antitherapeutic Antibodies

Serum samples for assessing trastuzumab emtansine ATAs will be collected for all patients dosed with trastuzumab emtansine. Samples for ATA assessment will be collected before dosing in Cycles 1 and 4, at the study drug completion visit, and 3 months after the last trastuzumab emtansine dose (see [Figure 4](#) and [Figure 5](#)). ATA samples will be aliquoted into 2 tubes: one to measure ATA levels, and one to measure trastuzumab emtansine concentrations if necessary in the case of interference in the ATA assay.

4.5.8.5 Samples for Research Purposes

A tumor tissue sample will be submitted at screening (see [Appendix 1](#)). Tissue samples for HER2 testing will be sent to a central laboratory (Targos, Kassel, Germany). In addition, an optional tissue biopsy is taken at discontinuation of trastuzumab emtansine, either due to PD, unacceptable toxicity of systemic treatment or any other reason. DNA and RNA will be extracted for exploratory research from these samples, protein expression may be assessed as well.

4.5.8.6 Translational Research Program

Biomarkers that may be associated with response and/or safety will retrospectively be evaluated on the protein, RNA and DNA level. Pathological scoring of HER2 and heterogeneity of the HER2 expression in the tumor will be evaluated.

Isolation of RNA and DNA will be performed in the central study laboratory. Gene expression analysis of tumors from all patients included in this study will be performed. In addition, tumor DNA mutation analysis may be performed using the most up to date technology. Depending on the technology used, the 6 mL blood sample collected at baseline may then be genotyped simultaneously as intrapatient reference of inherited genes.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see [Section 4.5.10](#)) biological samples will be destroyed no later than 5 years after the date of final closure of the clinical database.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Data arising from sample analysis will be subject to the confidentiality standards described in [Section 8.4](#).

4.5.9 Electrocardiograms

A 12-lead electrocardiogram (ECG) recording will be obtained at screening and as clinically indicated during the study, as outlined in the Schedule of Activities (see [Appendix 1](#)).

ECG recordings must be performed using a standard high quality, high fidelity digital electrocardiograph machine equipped with computer-based interval measurements. ECGs for each patient should be obtained from the same machine whenever possible. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. ECGs are to be obtained prior to other procedures scheduled at that same time (e.g.,

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vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre ECG resting period and during ECG recording.

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

4.5.10 Samples for Research Biosample Repository

4.5.10.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, AEs, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.10.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's Institutional Review Board (IRB) or EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.10) will not be applicable at that site.

4.5.10.3 Sample Collection

Patients who have been enrolled in the study will be asked to consent to the optional RBR program to allow residuals of the collected tissue, blood and plasma samples as described above in Section 3.1 to be stored for 15 years and also to be used for further, exploratory biomarker research.

For all samples, dates of consent should be recorded on the associated RBR page of the eCRF.

RBR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RBR storage period will be in accordance with the IRB/EC approved ICF and applicable laws (e.g., health authority requirements).

The above samples may be sent to one or more laboratories for DNA extraction to enable analysis of germline mutations, somatic mutations via whole genome sequencing (WGS), next-generation sequencing based analyses (NGS), or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., health authority requirements).

4.5.10.4 Confidentiality

Specimens and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR specimens is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses, data derived from RBR specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.10.5 Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RBR research.

4.5.10.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study MO29694 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study MO29694.

4.5.10.7 Monitoring and Oversight

RBR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the ICF. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.5.11 Follow-Up Assessments

After the safety follow-up visit, AEs should be followed as outlined in Sections [5.5](#) and [5.6](#).

After completion of treatment, patients will be followed up for survival in a 3 monthly schedule (\pm 7 working days) until 18 months after LPI. Patients who discontinue study treatment for reasons other than disease progression will continue to undergo tumor assessments every 6 weeks until disease progression, withdrawal of consent, loss to follow-up, death or study termination. If assessments cannot be done at survival visits, the study site is permitted to collect survival information by phone call. After disease progression, patients will be followed up for survival every 3 months (\pm 7 working days) until study closure (at 18 months after LPI) after completion of treatment or until death, loss to follow-up, withdrawal of consent or study discontinuation by the Sponsor (whichever occurs first).

Assessments are no longer required to evaluate new lesions, non-target lesions, and target lesions. However a visit to collect survival information is still required. If a visit cannot be done, the study site is permitted to collect survival information by phone call.

4.6 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

Patients must return for a follow-up visit within 30 days after the last dose of study drug; however, the visit at which a tumor assessment shows disease progression may be used as the early termination visit if it is within 30 days of the last administration of study drug. Every effort should be made to have patients return for this visit.

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. In case of premature withdrawal of non-evaluable patients, these patients will not be replaced. Follow-up of withdrawn subjects will be done by the referring physician/oncologist.

4.6.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

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- Pregnancy
- Disease progression
- Toxicities requiring permanent discontinuation as outlined in Section 5.1.2
- Sponsor's decision to stop study
- Commencement of another anticancer therapy before documented disease progression

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients who discontinue study treatment for any of the above reasons will continue to be followed for their survival status for 12 months after discontinuation of study treatment according to protocol or until one of the following outcomes occurs:

- Death
- Loss to follow-up
- Withdrawal from the study
- Study termination by the Sponsor

Patients who discontinue trastuzumab emtansine for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments every 6 weeks (\pm 7 days) for 12 months after discontinuation or until disease progression, withdrawal of consent, loss to follow-up, death, or study termination.

4.6.3 Study and Site Discontinuation

In case the study does not recruit at least 4 patients in the first year the Sponsor might decide to either amend the protocol for inclusion/exclusion, open more sites or stop the study.

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

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

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording

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- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. **ASSESSMENT OF SAFETY**

5.1 **SAFETY PLAN**

The safety plan for patients in this study is based on clinical experience with trastuzumab emtansine in completed and ongoing studies and knowledge of toxicities related to trastuzumab and maytansine (a parent compound of emtansine and DM1). The anticipated important safety risks of trastuzumab emtansine are outlined below. Please refer to the trastuzumab emtansine IB for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities (see Section 4.1). In addition, patients will undergo safety monitoring during the study including assessment of the nature, frequency, and severity of AEs (see Section 4.5). The first 6 patients of a cohort (i.e. during the safety run-in) will be assessed on an ongoing and patient per patient basis – i.e. based on the tolerability criteria (as defined in the iDMC charter) and in consultation with the SC and iDMC if needed.

Finally, guidelines for managing AEs, including criteria for dosage modification and treatment interruption or discontinuation, have been provided (see Section 5.1.2).

5.1.1 **Risks Associated with Trastuzumab Emtansine**

5.1.1.1 **Pulmonary Toxicity**

Cases of interstitial lung disease (ILD), including pneumonitis, some leading to acute respiratory distress syndrome or death, have been reported in patients receiving trastuzumab emtansine. Signs and symptoms may include dyspnea, cough, fatigue, and pulmonary infiltrates. Patients with dyspnea at rest due to complications of advanced malignancy and comorbidities may be at risk of pulmonary events.

Patients with clinically significant pulmonary symptoms or disease will be excluded from this study (see Section 4.1.2).

Guidelines for management of patients who develop ILD or pneumonitis are provided in Table 3.

5.1.1.2 **Hepatotoxicity**

The following events have been reported with administration of trastuzumab emtansine:

- Severe hepatotoxicity

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Rare cases of severe hepatotoxicity, including death due to drug-induced liver injury and associated hepatic encephalopathy, have been observed in patients treated with trastuzumab emtansine. Some of the observed cases may have been confounded by concomitant medications with known hepatotoxic potential.

- Increased serum transaminases

Increases in serum AST and ALT have been observed in all trastuzumab emtansine studies. Grade 1 and 2 events have been observed frequently; Grade 3 and 4 events have been observed less commonly. Increases in AST and ALT were commonly observed by Day 8 of each cycle and generally recovered to $\leq 2.5 \times$ ULN by Day 21. A cumulative effect of trastuzumab emtansine, that is, an increase in the proportion of patients with Grade 1 or 2 elevations in transaminases with successive cycles has been observed.

- NRH

Cases of NRH have been identified from liver biopsies in patients treated with trastuzumab emtansine who presented with signs and symptoms of portal hypertension. NRH is a rare liver condition characterized by widespread benign transformation of hepatic parenchyma into small regenerative nodules. NRH may lead to non-cirrhotic portal hypertension. Diagnosis of NRH can only be confirmed by histopathology. Biopsy-confirmed NRH leading to fatal hepatic failure has been reported.

NRH should be considered in all patients with clinical symptoms of portal hypertension, even with normal transaminases, and no other manifestations of cirrhosis; in patients with a cirrhosis-like pattern seen on a CT scan of the liver; and/or in patients with liver failure following long-term treatment with trastuzumab emtansine.

Patients must meet specified hepatic laboratory test requirements to be included in this study (see Section 4.1).

Hepatic laboratory parameters will be monitored as described in Section 4.5 and the Schedule of Activities (see Appendix 1).

Guidelines for management of trastuzumab emtansine in patients who develop increased serum transaminases, increased serum bilirubin, or NRH are provided in Table 3.

5.1.1.3 Left Ventricular Dysfunction

Patients treated with trastuzumab emtansine are at risk of developing left ventricular dysfunction. To date, significant cardiac events, including LVEF of $<40\%$, have been observed infrequently in clinical trials of trastuzumab emtansine.

Patients must meet specified LVEF requirements to be included in this study (see Section 4.1).

Left ventricular function will be monitored by measurement of ejection fraction using ECHO or MUGA scans as described in Section 4.5 and the Schedule of Activities (see Appendix 1).

Guidelines for management of patients who develop left ventricular dysfunction are provided in Table 3.

5.1.1.4 Infusion-Related Reactions and Hypersensitivity Reactions

Infusion-related reactions (IRRs) and hypersensitivity reactions have been reported with administration of trastuzumab emtansine. Despite the different pathophysiology of IRRs (reactions involving cytokine release) and hypersensitivity (allergic) reactions, the clinical manifestations are the same. In general, IRRs are expected to be more frequent and severe with the first infusion and to decrease in number and severity over time. The severity of true hypersensitivity reactions would be expected to increase with subsequent infusions.

IRRs, characterized by one or more of the following symptoms - flushing, chills, pyrexia, dyspnea, hypotension, wheezing, bronchospasm, and tachycardia - have been reported in clinical trials of trastuzumab emtansine. In general, these symptoms were not severe. In most patients, these reactions resolved over the course of several hours to a day after the infusion was terminated.

Hypersensitivity reactions, including serious anaphylactic-like reactions, have been observed in clinical trials of trastuzumab emtansine.

Patients with a history of intolerance to trastuzumab or trastuzumab emtansine will be excluded from this study (see Section 4.1).

Administration of trastuzumab emtansine will be performed in a setting with access to emergency facilities and staff who are trained to monitor and respond to medical emergencies. Patients should be closely monitored for infusion-related reactions during and after each infusion of trastuzumab emtansine, as described in Section 4.3.2.1.

Guidelines for management of patients who experience IRRs or hypersensitivity reactions are provided in Table 3.

5.1.1.5 Hematologic Toxicity

Thrombocytopenia has been reported in patients in clinical trials of trastuzumab emtansine. The majority of these patients had Grade 1 or 2 events (platelet count $\geq 50,000/\mu\text{L}$), with the nadir occurring by Day 8 and generally improving to Grade 0 or 1 (platelet count $\geq 75,000/\mu\text{L}$) by the next scheduled dose (i.e., within 3 weeks). In clinical trials, the incidence and severity of thrombocytopenia were higher in Asian patients.

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Cases of bleeding events with a fatal outcome have been observed. Severe cases of hemorrhagic events, including central nervous system hemorrhage, have been reported in clinical trials of trastuzumab emtansine; these events were independent of ethnicity. In some of the observed cases, the patients were also receiving anti-coagulation therapy. In addition, severe hemorrhagic events have been reported in the absence of thrombocytopenia.

Declines in other hematopoietic lineages, for example, leukopenia, neutropenia, and anemia, were less frequent than that observed for platelets.

Patients must meet specified hematologic laboratory test requirements to be included in this study (see Section 4.1).

Hematologic laboratory parameters will be monitored as described in Section 4.5 and the Schedule of Activities (see [Appendix 1](#)). Patients on anticoagulant or antiplatelet treatment should be monitored closely.

Guidelines for management of trastuzumab emtansine in patients who develop hematologic toxicity are provided in [Table 3](#).

5.1.1.6 Neurotoxicity

Peripheral neuropathy, mainly Grade 1 and predominantly sensory, has been reported in clinical trials of trastuzumab emtansine.

Patients with Grade ≥ 3 peripheral neuropathy must be excluded}} peripheral neuropathy will be excluded from this study (see Section 4.1).

Patients will be clinically monitored on an ongoing basis for signs or symptoms of peripheral neuropathy as described in Section 4.5 and the Schedule of Activities (see [Appendix 1](#)).

Guidelines for management of trastuzumab emtansine in patients who develop peripheral neuropathy are provided in [Table 3](#).

5.1.1.7 Extravasation

In trastuzumab emtansine clinical studies, reactions secondary to extravasation have been observed. These reactions were usually mild and consisted of erythema, tenderness, skin irritation, pain, or swelling at the infusion site. These reactions have been observed more frequently within 24 hours of infusion. Rare reports of more severe events, such as cellulitis, pain (tenderness and burning sensation), and skin irritation, have been received.

The infusion site will be closely monitored for possible subcutaneous infiltration during drug administration, as described in Section 4.3.2.1. Specific treatment for trastuzumab

emtansine extravasation is unknown at this time. Patients should be managed symptomatically per local institutional guidelines.

5.1.2 Management of Patients Who Experience Specific Adverse Events

Guidelines for trastuzumab emtansine dose reductions are provided in Table 2.

Table 2 Guidelines for Trastuzumab Emtansine Dose Reductions

	Regimen A	Regimen B
Dose Level	Dose	
0 (starting dose)	2.4 mg/kg	3.6 mg/kg
-1 (first reduction)	2 mg/kg	3.0 mg/kg
-2 (second reduction)	1.6 mg/kg	2.4 mg/kg

Note: The dose of trastuzumab emtansine, once reduced, may not be re-escalated. A maximum of two dose reductions is allowed; patients with any further requirement for dose reduction will discontinue treatment with trastuzumab emtansine.

Guidelines for management of patients who experience specific AEs are provided in [Table 3](#). Guidelines for managing trastuzumab emtansine-related toxicities other than the ones specified in Table 3 are as follows:

- If significant trastuzumab emtansine-related toxicities have not recovered to Grade 1 or baseline, the study drug may be delayed for 42 days from the last dose for the every 3 weeks regimen and 28 days from the last dose for the weekly regimen to assess or treat AEs. “Significant” and “related” will be based on the judgment of the investigator (in consultation with the Medical Monitor or designee when appropriate). For example, alopecia, even if considered related to trastuzumab emtansine, would most likely not be considered significant. Fatigue may or may not be considered either related or significant. Patients should be re-evaluated weekly during the delay, whenever possible.
- In general, when a toxicity resolves to Grade 1 or baseline, the patient may resume trastuzumab emtansine if the delay has not exceeded 42 days (Regimen B) or 28 days (Regimen A) after the date of the last dose received. If dosing resumes, the patient may receive trastuzumab emtansine either at the same dose level as before or at one dose level lower (see [Table 2](#)), at the discretion of the investigator. The dose of trastuzumab emtansine, once reduced, may not be re-escalated. If possible, subsequent cycles should continue at 21 day intervals.
- Trastuzumab emtansine must be discontinued for patients who experience an AE requiring a dose delay of > 28 days (Regimen A) or > 42 days (Regimen B) after the last dose received and for patients who experience an AE requiring dose reduction while being treated at the 2.4 mg/kg dose.

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Pulmonary toxicity	
ILD	Discontinue trastuzumab emtansine.
Pneumonitis	Discontinue trastuzumab emtansine.
Hepatotoxicity	
ALT or AST increase that meets Hy's law criteria: ALT or AST $>3 \times$ ULN in combination with TBIL $>2 \times$ ULN or clinical jaundice	Discontinue trastuzumab emtansine.
ALT or AST increase that does not meet Hy's law criteria:	
$>1 \times$ ULN to $\leq 5 \times$ ULN	Continue trastuzumab emtansine at the same dose level.
$>5 \times$ ULN to $\leq 20 \times$ ULN	Withhold trastuzumab emtansine until recovery to $\leq 5 \times$ ULN. Following recovery, resume trastuzumab emtansine with one dose level reduction. Discontinue trastuzumab emtansine if the event has not resolved to $\leq 5 \times$ ULN within 42 days after the last dose received.
$>20 \times$ ULN	Discontinue trastuzumab emtansine. Laboratory tests may be repeated (within 24 hours) to exclude laboratory error prior to discontinuing trastuzumab emtansine.
TBIL increase that does not meet Hy's law criteria	
$>1.5 \times$ ULN to $\leq 3 \times$ ULN	Withhold trastuzumab emtansine until recovery to $\leq 1.5 \times$ ULN. Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to $\leq 1.5 \times$ ULN within 42 days after the last dose received.
$>3 \times$ ULN to $\leq 10 \times$ ULN	Withhold trastuzumab emtansine until recovery to $\leq 1.5 \times$ ULN. Following recovery, resume trastuzumab emtansine with one dose level reduction. Discontinue trastuzumab emtansine if the event has not resolved to $\leq 1.5 \times$ ULN within 42 days after the last dose received.
$>10 \times$ ULN	Discontinue trastuzumab emtansine.
NRH	Discontinue trastuzumab emtansine.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; NRH = nodular regenerative hyperplasia; TBIL = total bilirubin; ULN = upper limit of normal.

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Left ventricular dysfunction	
Symptomatic CHF	Discontinue trastuzumab emtansine.
Asymptomatic LVEF decrease	
LVEF >45%	Continue trastuzumab emtansine at the same dose level.
LVEF 40% to ≤45% and decrease from baseline of ≥10% points	Withhold trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF decrease from baseline of ≥10% points is confirmed, discontinue trastuzumab emtansine.
LVEF 40% to ≤45% and decrease from baseline of <10% points	Continue trastuzumab emtansine at the same dose level. Repeat LVEF assessment within 3 weeks.
LVEF <40%	Withhold trastuzumab emtansine. Repeat LVEF assessment within 3 weeks. If LVEF <40% is confirmed, discontinue trastuzumab emtansine.
Infusion-related reaction (caused by cytokine release) or hypersensitivity (allergic) reaction	
Grade 2 reaction	<p>Decrease trastuzumab emtansine infusion rate or interrupt infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms.</p> <p>May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine.</p> <p>Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.</p>
Grade 3 reaction	<p>Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β-agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms.</p> <p>May continue trastuzumab emtansine at the same dose level at the investigator's discretion. In the event of a true hypersensitivity reaction (in which severity of reaction increases with subsequent infusions), discontinue trastuzumab emtansine.</p> <p>Premedication for infusion reactions (e.g., antihistamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.</p>

CHF = congestive heart failure; LVEF = left ventricular ejection fraction; TBILI = total bilirubin; ULN = upper limit of normal.

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Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Infusion-related reaction (caused by cytokine release) or hypersensitivity (allergic) reaction (cont.)	
Grade 4 reaction	Stop trastuzumab emtansine infusion. Administer supportive care with oxygen, β -agonists, antihistamines, antipyretics, or corticosteroids, as appropriate, at the investigator's discretion. Monitor patient until complete resolution of symptoms. Discontinue trastuzumab emtansine.
Hematologic toxicity	
Grade 3 thrombocytopenia (25,000 to <50,000/ μ L)	Withhold trastuzumab emtansine until recovery to Grade \leq 1 (\geq 75,000/ μ L). Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade \leq 1 within 42 days after the last dose received.
Grade 4 thrombocytopenia (<25,000/ μ L) at any time	Withhold trastuzumab emtansine until recovery to Grade \leq 1 (\geq 75,000/ μ L). Following recovery, resume trastuzumab emtansine with one dose level reduction. Discontinue trastuzumab emtansine if the event has not resolved to Grade \leq 1 within 42 days after the last dose received.
For all patients on anticoagulation therapy:	Withhold study drug until platelet count is Grade \leq 1 ($>75,000/\text{mm}^3$) – irrespective of the grade of thrombocytopenia
Grade \geq 3 hematologic toxicity other than thrombocytopenia	Withhold trastuzumab emtansine until recovery to Grade \leq 2. Following recovery, resume trastuzumab emtansine at the same dose level. Discontinue trastuzumab emtansine if the event has not resolved to Grade \leq 2 within 42 days after the last dose received.
Grade 2 Neutropenia:	Withhold study drug until neutrophil count \geq 1500 cells/ mm^3 (Grade \leq 1). No dose reduction is required.
Grade 3 Neutropenia:	Withhold study drug until neutrophil count \geq 1500 cells/ mm^3 (Grade \leq 1). No dose reduction required.
Grade 4 Neutropenia:	Withhold study drug until neutrophil count \geq 1500 cells/ mm^3 (Grade \leq 1). If the duration of Grade 4 neutropenia is >7 days, then either reduce one dose level for subsequent doses. No dose modification is required for a Grade 4 neutropenia lasting 7 or fewer days.
Patients who experience any of these toxicities should be reassessed at least weekly for recovery.	
Neurotoxicity	
Grade \geq 3 peripheral neuropathy	Withhold trastuzumab emtansine until recovery to Grade \leq 2. Following recovery, resume trastuzumab emtansine at the same dose level or with one dose level reduction, at the investigator's discretion. Discontinue trastuzumab emtansine if the event has not resolved to Grade \leq 2 within 42 days after the last dose received.

LVEF = left ventricular ejection fraction; TBIL = total bilirubin; ULN = upper limit of normal.

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5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and AEs of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section [5.4](#).

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section [5.3.5.10](#)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death)

This does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section [5.3.5.11](#))
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug

- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

SAEs are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see [Section 5.4.2](#) for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

AEs of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see [Section 5.4.2](#) for reporting instructions). AEs of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see [Section 5.3.5.7](#))
- Suspected transmission of an infectious agent by the study drug, as defined below
Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in [Sections 5.4–5.6](#).

For each AE recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see [Section 5.2.2](#) for seriousness criteria), severity (see [Section 5.3.3](#)), and causality (see [Section 5.3.4](#)).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section [5.4.2](#) for instructions for reporting SAEs).

After initiation of study drug, all AEs will be reported until 28 days after the last dose of study drug.

Instructions for reporting AEs that occur after the AE reporting period are provided in Section [5.6](#).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v4.03) will be used for assessing AE severity. [Table 4](#) will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living ^a
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living ^{b,c}
4	Life-threatening consequences or urgent intervention indicated ^d
5	Death related to AE ^d

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.03), which can be found at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- ^a Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- ^b Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
- ^c If an event is assessed as a "significant medical event," it must be reported as an SAE (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2.
- ^d Grade 4 and 5 events must be reported as SAEs (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly.

The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

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5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

AEs that occur during or within 24 hours after study drug administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For AEs other than infusion-related reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, AEs that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary AE that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.

- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. Details regarding any increases or decreases in severity will be captured on the Adverse Event Intensity or Grade Changes eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAE.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an AE. A laboratory test result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

Note: For oncology trials, certain abnormal values may not qualify as AEs.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

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

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section [5.3.5.4](#) for details on recording persistent AEs).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an AE. A vital sign result must be reported as an AE if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section [5.3.5.4](#) for details on recording persistent AEs).

5.3.5.7 Hepatic Events

Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an AE the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$

- Treatment-emergent ALT or AST $>3 \times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or an AE of special interest (see Section 5.4.2).

Nodular Regenerative Hyperplasia

NRH, whether or not accompanied by abnormal liver function tests, should be reported to the Sponsor as a SAE.

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified AE reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of *locally advanced (unresectable and not treatable with curative intent) or metastatic UBC or pancreatic cancer/cholangiocarcinoma* should be recorded on the Death Attributed to Progressive Disease eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). An independent monitoring committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, "**unexplained death**" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

Deaths that occur after the AE reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

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5.3.5.10 Lack of Efficacy or Worsening of Urothelial Bladder Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

The patient has not experienced an AE

- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a SAE, but should be reported as an AE instead:

- Hospitalization for an AE that would ordinarily have been treated in an outpatient setting
- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

AEs associated with an overdose of trastuzumab emtansine in previous clinical studies include thrombocytopenia and increased ALT. There was one case of overdose in which the patient died.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- SAEs (see Section 5.4.2 for further details)
- AEs of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, SAEs and AEs of special interest will be reported until 28 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting SAEs that occur >28 days after the last dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 7 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Additional information on any trastuzumab emtansine-exposed pregnancy and infant will be requested by Roche Drug Safety at specific time points (i.e., after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as an SAE (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For SAEs, AEs of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case. Pathology materials (e.g., pathology specimens and reports), if already obtained to evaluate the event, may be requested for review.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the AE reporting period (defined as 28 days after the last dose of study drug), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF. In addition, if the investigator becomes aware of an SAE that is believed to be related to prior study drug treatment, the event should be reported through use of the Adverse Event eCRF.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and AEs of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Trastuzumab emtansine IB

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary efficacy objective of this study is to determine the best tumor response (BOR).

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Based on the results of the tolerability analysis, a decision will be made for each individual cohort as to whether to continue with the trastuzumab emtansine regimen of 2.4 mg/kg every week (Regimen A) or switch to the trastuzumab emtansine regimen of 3.6 mg/kg every 3 weeks (Regimen B). Once the preferred trastuzumab emtansine dosing regimen has been determined for a cohort, the primary efficacy objective is to determine BOR.

The main analysis population for the analysis of safety will be the safety population (SP), which will include all patients who received at least one dose of the study drug (Regimen A and/or B). The main analysis population for the analysis of efficacy will be the intent-to-treat (ITT) population and will include all patients enrolled who started on the selected treatment regimen. If the decision is made to switch to Regimen B then those patients who started on Regimen A would not be included in the primary or final efficacy analyses (whether they stay on Regimen A or switched to Regimen B) but their results would be included in a supplementary descriptive analysis.

Biomarker analyses will be of exploratory nature.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size estimation is based on the method of [A'Hern \(2001\)](#) and [Simon \(1989\)](#) and corresponding SAS programs.

To test the null hypothesis (H_0) that the best BOR is 5% or less (which would yield a low activity profile) against the alternative hypothesis (H_1) that the BOR is greater than or equal to 20% (which would yield an encouraging activity profile):

$$H_0: \text{BOR} \leq 5\% \quad \text{vs.} \quad H_1: \text{BOR} \geq 20\%.$$

27 patients per cohort would be required to perform the test with 80% power, at the one-sided alpha=0.05 level. To allow for drop-outs (10-15%) and to ensure that at least 27 patients will have efficacy data available, 32 patients will be recruited per cohort on the respective treatment regimen.

Assuming a preferable BOR of 20% is observed, then with 27 patients in a cohort, the 95% confidence limits would range from 7.2% to 39.8% (Clopper-Pearson exact confidence intervals).

The 95% confidence intervals for different BOR rates, and with 27 patients per cohort, were determined using SAS (Version 9.2) and the results are presented in [Table 5](#) below.

Table 5 Estimation of Confidence Intervals for a Sample Size N = 27 (per cohort)

Sample Size	BOR	95% Clopper Pearson Exact Confidence Intervals
27 patients	15%	4.4% – 34.2%
	20%	7.2% – 39.8%
	25%	10.6% – 45.5%
	30%	14.0% – 50.6%
	35%	17.9% - 55.8%

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race, cancer characteristics, medical history and prior cancer treatment) will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate.

Concomitant therapy will be summarized by frequency tables and percentages.

Medical history will be summarized.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will include all enrolled and treated patients in the selected treatment regimen.

There are two efficacy analyses – a primary and a final analysis.

The primary efficacy analysis will determine the BOR for all patients of a cohort who received a dose of study medication in the selected treatment regimen and will take place 12 weeks after the last patient of an individual cohort has been recruited (following a tumor assessment after 6 weeks [2 cycles] with a *confirmation of BOR performed no less than 4 weeks after the criteria for response are first met*).

The final efficacy analysis will include all primary (BOR) and secondary efficacy measures.

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Results may also be presented according to cell heterogeneity, i.e., by percentage of positively stained tumor cells: 30-70% and $\geq 71\%$.

Number and percentage of responders with corresponding Clopper-Pearson 95% confidence intervals will be provided. Estimates for the survivor function for the time-to-event variables, such as PFS and OS will be obtained by using the Kaplan-Meier (KM) approach together with associated 95% CI.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is:

- BOR

Responders as assessed every 6 weeks will be defined based on tumor assessment status of PR or CR at these time points. Only patients with measurable disease at baseline will be included in the analysis of the response rate. Patients without a post-baseline tumor assessment will be considered to be non-responders. BOR is defined as the best response recorded from the first day of study treatment until disease progression/recurrence or death. To be assigned a status of PR or CR (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder.

The null hypothesis (H_0) is that the best response rate is 5% or less, which would yield a low activity profile. The alternative hypothesis (H_1) is that the best response rate is greater than or equal to 20%, which would yield an encouraging activity profile.

H_0 : best response rate $\leq 5\%$ vs H_1 : best response rate $\geq 20\%$

A Simon's two-stage design ([Simon 1989](#)) will be used to allow the study to stop early if there is no evidence of efficacy. The null hypothesis that the true response rate (BOR) is $\leq 5\%$ will be tested against a one-sided alternative. In the first stage, 13 patients in each cohort will be accrued and their BOR results will be evaluated 12 weeks after the 13th patient was enrolled. If there are 0 responses (CR or PR) in these 13 patients, the study will be stopped for the respective cohort. Otherwise, 14 additional patients will be accrued per cohort for a total of 27. Recruitment may be suspended after the 13th patient in a cohort has been enrolled in the selected treatment regimen. This suspension will occur if there are no responses observed in the previous 12 patients (since the decision will be made to stop the study for a cohort only if there are no responses in the first 13 patients).

Of the 27 patients with evaluable efficacy data, if 4 or more responders are observed then we will reject H_0 and accept H_1 – i.e., accept that the best response rate $\geq 20\%$. If 3 or fewer responders are observed then we will accept H_0 – i.e., accept that the best response rate $\leq 5\%$. If there are no drop-outs amongst the 32 enrolled patients in a

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certain cohort then the decision rule will be revised as necessary to retain the same alpha and power. For example, if 32 patients in a cohort have evaluable efficacy data, then if 5 or more responders are observed then we will reject H_0 and accept H_1 – i.e., accept that the best response rate $\geq 20\%$. If 4 or fewer responders are observed then we will accept H_0 .

A response rate of less than 5% will be considered of no clinical interest. A response rate of more than 20% will be considered of interest to potentially start a further study, which will not be part of this protocol.

This is an early phase II study, hence there will be no adjustment for multiplicity.

6.4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints will include:

- PFS
- OS

PFS is defined as the time from the first day of study treatment, until the first documented progression of disease (as determined by the investigator using RECIST 1.1), or death from any cause, whichever occurs first. Patients with no PFS events will be censored at the time of the last evaluable tumor assessment. Patients with no tumor assessment after the baseline visit will be censored at the time of the first day of study treatment plus 1 day.

OS (time to death) is defined as time between the first day of study treatment and date of death of any cause. Patients for whom no death is captured on the clinical database are censored at the most recent date they were known to be alive.

6.5 SAFETY ANALYSES

The safety variables will be summarized for the safety population at the same time as the final efficacy analysis. All safety variables will be summarized.

The analysis of AEs will focus on treatment-emergent AEs, i.e., AEs occurring on the day of or after first administration of study drug. Non-treatment emergent AEs (i.e., those occurring before commencement of study drug) will only be listed.

All AEs will be assessed according to the NCI CTCAE, v4.03, grading system. The incidence, type, and severity of AEs will be summarized according to the primary system organ class (SOC) and within each SOC, by MedDRA preferred term.

AEs Grade 3 or higher for hepatic events, allergic reactions, thrombocytopenia, hemorrhage events, and also all other AEs Grade 3 or higher related to trastuzumab emtansine will be summarized.

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Pneumonitis of all grades and the incidence of CHF will also be summarized.

AEs leading to treatment interruption and discontinuation and SAEs will be analyzed in a similar way to all AEs. Cause of death will also be summarized and listed.

The number of patients prematurely discontinued from the treatment with corresponding reason for discontinuation will be summarized and listed. The discontinuation from study will be also summarized and listed.

Descriptive statistics will be presented for cumulative trastuzumab emtansine doses and duration of exposure.

Laboratory parameters, hematology, and serum biochemistry will be presented in shift tables of NCI-CTCAE grade at baseline versus worst grade during the Treatment Period. The summary of laboratory parameters presented by means, standard deviation, minimum, and maximum will be also presented.

Vital signs (blood pressure, temperature, heart rate, and respiratory rate, oxygen saturation) and ECG findings will be also presented by frequency tables over time.

Change in LVEF over the course of the study as measured by ECHO or MUGA will be summarized.

Cases of drug-induced liver injury meeting Hy's Law criteria will be summarized.

The ECOG PS will be summarized by frequency tables over time and percentage of patients in different categories will be presented by bar charts at different time points.

Physical examination variables collected only at baseline (e.g., height) will be summarized for baseline only while other physical examination variables will be summarized over time by visits and reported in patients' listings.

6.6 IMMUNOGENICITY ANALYSES

The immunogenicity analyses will include patients with at least one pre-dose (baseline) and one post-dose ATA assessment.

The numbers and proportions of ATA-positive patients and ATA-negative patients during both the treatment and follow-up periods will be summarized by treatment group.

Patients are considered to be ATA positive if they are ATA negative at baseline but develop an ATA response following study drug administration (treatment-induced ATA response), or if they are ATA positive at baseline and the titer of one or more post-baseline samples is at least 4-fold greater (i.e., ≥ 0.60 titer units) than the titer of the baseline sample (treatment-enhanced ATA response). Patients are considered to be ATA negative if they are ATA negative at baseline and all post-baseline samples are negative, or if they are ATA positive at baseline but do not have any post-baseline

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samples with a titer that is at least 4 fold greater than the titer of the baseline sample (treatment unaffected).

The relationship between ATA status, and safety, efficacy, PK, and biomarker endpoints will be analyzed and reported descriptively via subgroup analyses.

Corresponding analyses will be performed for immune checkpoints e.g. infiltrating lymphocytes in the tumor before and after treatment by the assessment of immune-related biomarkers such as PDL1 and CD8.

6.7 BIOMARKER ANALYSES

Biomarkers that may be associated with response will be evaluated. These may include but are not limited to HER2 positivity analyses by IHC and ISH of all consenting screened patients, as well as circulating HER2 ECD and molecular subtyping by RNA expression, DNA analysis and/or protein analyses

6.8 INTERIM ANALYSIS

The first 6 patients of each cohort will be analyzed on an ongoing and patient per patient basis – i.e. based on the tolerability criteria (as defined in the iDMC charter) and in consultation with the SC and iDMC if needed. Further, there will be an analysis of the safety data after the first 6 patients of a cohort have completed 2 cycles of Regimen A. The results will be made available to the IDMC in order for them to make the decision as to whether to continue with Regimen A or to switch to Regimen B.

There will be analysis of the BOR results for the first 13 patients of a cohort (12 weeks after the 13th patient has been enrolled) in the selected treatment regimen. This will be done in order to decide whether to stop the study or not (as outlined in Section [6.4.1](#)).

6.8.1 Optional Interim Analysis

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel, who will have full access to the data.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), ICFs, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample ICF, *including the sample ICF for the HER2 screening test, will be provided to each site*. If applicable, the ICFs will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any

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proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the ICF will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

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

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements,

policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all AEs to the Sponsor, investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

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

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

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, subjects' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The study will have an iDMC, an SC, and a Pathology Panel to make crucial decisions at the above defined timepoints and to ensure patient safety. The study will be conducted with an IxRS and all study-related information and procedures documented in an eCRF. It will be run by a contract research organization (CRO) together with the Sponsor. Assessment of laboratory test results will be performed locally and confirmed centrally (HER2).

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data.

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application

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has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1.1 Schedule of Activities: *Regimen A (Trastuzumab emtansine, 2.4 mg/kg weekly)*

	Screening	Cycle 1 (day)			Cycle 2 (day)			Cycle 3 (day)			Cycle 4+ (day)			Study Drug Completion Visit ^d	Survival Follow-Up ^e
	-28 to 0	1	8	15	1	8	15	1	8	15	1	8	15		
		(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)		
Informed Consent ^a	x														
Assignment of patient numbers through the IwRS	x														
Tumor tissue for HER2 status testing ^b	x														
Medical history and demographics	x														
AEs	x ^c													x ^c	x ^c
Concomitant medications ^f	x ^f													x ^f	x ^f
Complete physical examination	x														
Limited physical examination ^g		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height	x														
Weight	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs ^h	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG PS	x	x			x			x			x			x	x
Hematology ^{i, j, k}	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum chemistry ^{j, k, m}	x ^m	x ^m	x ⁿ	x ⁿ	x ^m	x ⁿ	x ⁿ	x ^m	x ⁿ	x ⁿ	x ^m	x ⁿ	x ⁿ	x ^m	
INR and aPTT	x													x	
Pregnancy test ^l	x ^l							x ^l						x ^l	x ^l
Laboratory urinalysis ^o		x													
Blood sample for exploratory biomarker research	x			x			x							every 3 months	
Blood sample for PK ^p	x	x	x	x							x				
Blood sample HER2 ECD	x			x							x				
Blood sample for retrospective genotyping ^q	x														
ATA ^r		x							x			x		x	x
Hepatitis B/C serology, HIV	x														
12-lead ECG ^s	x														
LVEF by ECHO (or MUGA) ^t	x ^t			x ^t					x ^t		every 3 rd cycle		x ^t		
Tumor tissue for exploratory biomarker research¹	x													x ¹	
Tumor assessment ^{2, 3, 5}	x ^{2, 3, 5}													x ^{2, 3, 5}	x ^{2, 3, 5}
Bone scan ^{4, 5}	x ^{4, 6}														
Trastuzumab emtansine administration/distribution ⁶		x(A)	x(A)	x(A)											

^a Informed Consent must be obtained prior to performance of any study related procedure unless the assessments were performed as standard of care prior to obtaining informed consent and within 2 weeks prior to study entry.

^b HER2 status (IHC3+) should be completed within 28 days prior to baseline, however a maximum of 2 years is accepted unless otherwise stated.

^c After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs will be reported until 28 days after the last dose of study drug. After this period, the Sponsor should be notified in the investigator becomes aware of any SAE that is believed to be related to prior study drug treatment (see Section 5.6).

^d Performed 30 days (+/- 7 days) after the last dose of study treatment. Patients who discontinue study treatment will be asked to return to the clinic 4-6 weeks after the last dose of study drug for study drug completion visit. If the reason for study drug discontinuation is other than PD, tumor

Appendix 1.1

Schedule of Activities: *Regimen A (Trastuzumab emtansine, 2.4 mg/kg weekly)* (cont.)

assessments should be continued to be performed every 6 weeks from the first dose of study drug until PD or death

^e After completion of treatment, patients will be followed up for survival in a 3-monthly schedule until 18 months after LPI.

^f Record all concomitant therapy (non-investigational products), which includes prescription medication, over-the-counter preparation, herbal therapy, or radiotherapy used by a patient between the 28 days preceding date of first dose of study drug and the study drug completion/early termination visit.

^g Limited symptom-directed physical examination focusing on organ systems related to potential AEs based on patient's interim medical history and/or existing AE profiles of the study drug.

^h Systolic and diastolic blood pressure, pulse rate, oxygen saturation, respiratory rate, temperature should all be collected at screening, pre-dose, every 15 (+/- 5) minutes during the first trastuzumab emtansine infusion and 60 (+/-10) minutes after the infusion. In subsequent cycles, vital signs should be recorded within 60 minutes pre- and post-infusion. Abnormal or significant changes to vital signs from baseline should be recorded as an AE.

ⁱ Includes hemoglobin, hematocrit, platelet count, RBCs, WBCs; differentials including neutrophils, lymphocytes, monocytes, eosinophils and basophils.

^j Assessments should be performed at screening, on Day 1 of all cycles, and weekly following any hematologic AE. Local laboratory assessments should be performed within 72 hours preceding trastuzumab emtansine administration unless otherwise specified. Results of these local laboratory assessments must be reviewed and the review documented prior to trastuzumab emtansine administration.

^k For AEs associated with abnormal laboratory values, assessments should be performed at a minimum weekly until recovery to Grade \leq 2. Additional assessments may be done as clinically indicated.

^l For women of childbearing potential (including premenopausal women who have had a tubal ligation) and for women not considered post-menopausal, a serum b-HCG pregnancy test must be performed at a local laboratory within 7 days prior to the first administration of study drug (Day 1, Cycle 1). Urine pregnancy tests will be performed at specified subsequent visits (every 3 cycles, study completion visit, at 3 and 6 months (+/- 2 weeks) after last dose of study drug) within 7 days prior to receiving further study drug. All positive urine pregnancy tests must be confirmed by a serum b-HCG test.

^m Glucose, blood urea nitrogen (BUN)/urea, creatinine, sodium, potassium, bicarbonate, phosphorus, chloride, calcium, uric acid, total protein, albumin, total and direct bilirubin, alkaline phosphatase, LDH, ALT, AST, and GGT.

ⁿ AST, ALT, GGT, and total bilirubin only.

^o includes specific gravity, pH, protein, glucose, blood, ketones, bilirubin and microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria.

^p Six sampling timepoints in Cycle 1 (Day 1, Day 8, and Day 15, each predose and 15-30 minutes postdose), one sampling timepoint in Cycle 2 (Day 1, predose), and two sampling timepoints in Cycle 4 (Day 1, predose and 15-30 minutes postdose). .

^q To be taken at baseline (Cycle 1, Day 1)

^r Samples for ATA assessment will be collected before dosing in Cycles 1 and 4, at the study drug completion visit, and 3 months after the last trastuzumab emtansine dose.

^s ECGs for each patient should be obtained from the same machine whenever possible. One set of all ECG tracings should be printed and kept with the patient's record.

^t Cardiac monitoring (ECHO/MUGA) will be performed in all patients enrolled in the study. Assessments will occur during the screening period, between Days 15 and 21 in Cycles 1 and 3, and between Days 15 and 21 of every 3rd cycle thereafter (Cycle 6, 9 etc). ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed \geq 28 days after last study treatment administration or if no post-treatment evaluation was performed. The LVEF follows the actual treatment cycle. Dose modification of study drug will follow the algorithm/process described in [Table 2](#).

¹ An optional tissue biopsy is taken at discontinuation of trastuzumab emtansine, either due to PD, unacceptable toxicity of systemic treatment or any other reason.

² Every 6 weeks from the start date of the study drug, regardless of dose delay or early discontinuation, until PD or study termination. Tumor assessments obtained within 28 days of Cycle 1, Day 1 may be used for screening purposes. Tumor assessments with CT or MRI scans of the chest, abdomen, and pelvis are to be performed every 6 weeks (+/- 3 business days). Response must be assessed through physical examination and imaged-based evaluation,

Appendix 1.1

Schedule of Activities: *Regimen A (Trastuzumab emtansine, 2.4 mg/kg weekly) (cont.)*

using RECIST 1.1. Assessments should include an evaluation of all known or suspected sites of disease whenever possible. The same radiographic procedure used to define measurable disease sites at baseline must be used throughout the study.

³ If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessments, unless signs of clinical progression are present. In cases where there is suspicion of clinical progression before the next scheduled assessment, an unscheduled assessment should be performed.

⁴ A CT or MRI of the brain and an isotope bone scan will be performed at screening. The bone scan and/or X-ray should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions.

⁵ At the investigator's discretion, CT scans, MRI scans, and/or bone scans may be obtained at any time when clinically indicated or if PD is suspected.

⁶ A = Regimen A (trastuzumab emtansine weekly, 2.4 mg/kg). Trastuzumab emtansine should be given over 90 minutes for the first dose and, in the absence of infusion-related AEs, over 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

Appendix 1.2

Schedule of Activities: Regimen B (Trastuzumab emtansine 3.6 mg/kg 3-weekly)

	Screening	Cycle 1 (day)			Cycle 2 (day)			Cycle 3 (day)			Cycle 4+ (day)			Study Drug Completion Visit ^d	Survival Follow-Up ^e
		-28 to 0	1	8	15	1	8	15	1	8	15	1	8	15	
Informed Consent ^a	x				(-3,+3)			(-3,+3)			(-3,+3)				
Assignment of patient numbers through the IwRS	x														
Tumor tissue for HER2 status testing ^b	x														
Medical history and demographics	x														
AEs	x ^c													x ^c	x ^c
Concomitant medications ^f	x ^f													x ^f	x ^f
Complete physical examination	x														
Limited physical examination ^g		x			x			x		x			x	x	
Height	x														
Weight	x	x			x			x		x			x		
Vital signs ^h	x	x			x			x		x			x		x
ECOG PS	x	x			x			x		x			x		
Hematology ^{i, j, k}	x	x			x			x		x			x		
Serum chemistry ^{j, k, m}	x ^m	x ^m			x ^m			x ^m		x ^m			x ^m		
INR and aPTT	x												x		
Pregnancy test ^l	x ^l							x ^l					x ^l	x ^l	
Laboratory urinalysis ⁿ	x														
Blood sample for exploratory biomarker research	x				x			x					every 3 months		
Blood sample for PK ^o	x				x							x			
Blood sample HER2 ECD	x				x							x			
Blood sample for retrospective genotyping ^b	x														
ATA ^q	x									x			x	x	
Hepatitis B/C serology, HIV	x														
12-lead ECG ^r	x														
LVEF by ECHO (or MUGA) ^s	x ^s				x ^s					x ^s			x ^s		
Tumor tissue for exploratory biomarker research ¹	x												x ¹		
Tumor assessment ^{2, 3, 5}	x ^{2, 3, 5}												x ^{2, 3, 5}	x ^{2, 3, 5}	
Bone scan ^{4, 5}	x ^{4, 6}												As clinically indicated		
Trastuzumab emtansine administration/distribution ⁶		x(B)			x(B)			x(B)		x(B)					

^a Informed Consent must be obtained prior to performance of any study related procedure unless the assessments were performed as standard of care prior to obtaining informed consent and within 2 weeks prior to study entry.

^b HER2 status (IHC3+) should be completed within 28 days prior to baseline, however a maximum of 2 years is accepted unless otherwise stated.

^c After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs will be reported until 28 days after the last dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any SAE that is believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each AE until the event has

Appendix 1.2

Schedule of Activities: Regimen B (Trastuzumab emtansine 3-weekly, 3.6 mg/kg) (cont.)

resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

^d Performed 30 days (+/- 7 days) after the last dose of study treatment. Patients who discontinue study treatment will be asked to return to the clinic 4-6 weeks after the last dose of study drug for study drug completion visit. If the reason for study drug discontinuation is other than PD, tumor assessments should be continued to be performed every 6 weeks from the first dose of study drug until PD or death.

^e After completion of treatment, patients will be followed up for survival in a 3-monthly schedule until 18 months after LPI.

^f Record all concomitant therapy (non-investigational products), which includes prescription medication, over-the-counter preparation, herbal therapy, or radiotherapy used by a patient between the 28 days preceding date of first dose of study drug and the study drug completion/early termination visit.

^g Limited symptom-directed physical examination focusing on organ systems related to potential AEs based on patient's interim medical history and/or existing AE profiles of the study drug.

^h Systolic and diastolic blood pressure, pulse rate, oxygen saturation, respiratory rate, temperature should all be collected at screening, pre-dose, every 15 (+/- 5) minutes during the first trastuzumab emtansine infusion and 60 (+/-10) minutes after the infusion. In subsequent cycles, vital signs should be recorded within 60 minutes pre- and post-infusion. Abnormal or significant changes to vital signs from baseline should be recorded as an AE.

ⁱ Includes hemoglobin, hematocrit, platelet count, RBCs, WBCs; differentials including neutrophils, lymphocytes, monocytes, eosinophils and basophils. For Regimen B, laboratory assessments need only be performed in conjunction with a clinical visit, i.e. every 3 weeks on Day 1 of each cycle.

^j Assessments should be performed at screening, on Day 1 of all cycles, and weekly following any hematologic AE. Local laboratory assessments should be performed within 72 hours preceding trastuzumab emtansine administration unless otherwise specified. Results of these local laboratory assessments must be reviewed and the review documented prior to trastuzumab emtansine administration.

^k For AEs associated with abnormal laboratory values, assessments should be performed at a minimum weekly until recovery to Grade \leq 2. Additional assessments may be done as clinically indicated.

^l For women of childbearing potential (including premenopausal women who have had a tubal ligation) and for women not considered post-menopausal, a serum b-HCG pregnancy test must be performed at a local laboratory within 7 days prior to the first administration of study drug (Day 1, Cycle 1). Urine pregnancy tests will be performed at specified subsequent visits (every 3 cycles, study completion visit, at 3 and 6 months (+/- 2 weeks) after last dose of study drug) within 7 days prior to receiving further study drug. All positive urine pregnancy tests must be confirmed by a serum b-HCG test.

^m Glucose, blood urea nitrogen (BUN)/urea, creatinine, sodium, potassium, bicarbonate, phosphorus, chloride, calcium, uric acid, total protein, albumin, total and direct bilirubin, alkaline phosphatase, LDH, ALT, AST, and GGT.

ⁿ Includes specific gravity, pH, protein, glucose, blood, ketones, bilirubin and microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria.

^o Two sampling timepoints in Cycle 1 (Day 1 predose and 15-30 minutes postdose), one sampling timepoint in Cycle 2 (Day 1, predose), and two sampling timepoints in Cycle 4 (Day 1, predose and 15-30 minutes postdose). .

^p To be taken at baseline (Cycle 1, Day 1).

^q Samples for ATA assessment will be collected before dosing in Cycles 1 and 4, at the study drug completion visit, and 3 months after the last trastuzumab emtansine dose.

^r ECGs for each patient should be obtained from the same machine whenever possible. One set of all ECG tracings should be printed and kept with the patient's record.

^s Cardiac monitoring (ECHO/MUGA) will be performed in all patients enrolled in the study. Assessments will occur during the screening period, between Days 15 and 21 in Cycles 1 and 3, and between Days 15 and 21 of every 3rd cycle thereafter (Cycle 6, 9 etc). ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed \geq 28 days after last study treatment administration or if no post-treatment evaluation was performed. The LVEF follows the actual treatment cycle. Dose modification of study drug will follow the algorithm/process described in [Table 2](#).

¹ An optional tissue biopsy is taken at discontinuation of trastuzumab emtansine, either due to PD, unacceptable toxicity of systemic treatment or any other reason.

Appendix 1.2

Schedule of Activities: Regimen B (Trastuzumab emtansine 3-weekly, 3.6 mg/kg) (cont.)

² Every 6 weeks from the start date of the study drug, regardless of dose delay or early discontinuation, until PD or study termination. Tumor assessments obtained within 30 days of Cycle 1, Day 1 may be used for screening purposes. Tumor assessments with CT or MRI scans of the chest, abdomen, and pelvis are to be performed every 6 weeks (+/- 3 business days). Response must be assessed through physical examination and imaged-based evaluation, using RECIST 1.1. Assessments should include an evaluation of all known or suspected sites of disease whenever possible. The same radiographic procedure used to define measurable disease sites at baseline must be used throughout the study.

³ If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessments, unless signs of clinical progression are present. In cases where there is suspicion of clinical progression before the next scheduled assessment, an unscheduled assessment should be performed.

⁴ A CT or MRI of the brain and an isotope bone scan will be performed at screening. The bone scan and/or X-ray should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions.

⁵ At the investigator's discretion, CT scans, MRI scans, and/or bone scans may be obtained at any time when clinically indicated or if PD is suspected.

⁶ B = Regimen B (trastuzumab emtansine 3-weekly, 3.6 mg/kg). Trastuzumab emtansine should be given over 90 minutes for the first dose and, in the absence of infusion-related AEs, over 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

STATISTICAL ANALYSIS PLAN

TITLE: PHASE II, EXPLORATORY, MULTICENTER, NON RANDOMIZED, SINGLE AGENT COHORT STUDY TO DETERMINE BEST TUMOR RESPONSE WITH TRASTUZUMAB EMTANSINE IN HER2 OVEREXPRESSING SOLID TUMORS

PROTOCOL NUMBER: MO29694/NCT02999672

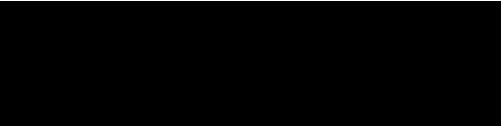
STUDY DRUG: Trastuzumab Emtansine (RO5304020)

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STATISTICAL ANALYSIS PLAN HISTORY

SAP Version / Date	Description
Version 1.0 / 23 March 2017	Initial version.
Version 2.0 / 5 June 2018	The Sponsor decided to prematurely terminate the study and to produce an abbreviated clinical study report (CSR). As a consequence, some of the analyses planned in the version 1.0 won't be performed and have been removed in this version.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse events
AESI	adverse events of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BOR	best overall response
CI	confidence interval
CR	complete response
CSR	clinical study report
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC	European Organization for the Research and Treatment of Cancer
FDA	Food and Drug Administration
GGT	gamma glutamyl transferase
IC	Informed Consent
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IV	Intra-Venous
INR	international normalized ratio
ITT	Intent-to-treat
KM	Kaplan Meier
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetic
PR	partial response
PS	performance status
PT	preferred term
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Definition
SAE	serious adverse event
SAF	safety population
SAP	statistical analysis plan
SC	Steering Committee
SD	stable disease
SI	System International
SOC	System Organ Class
TEAE	treatment emergent adverse event
MUBC	Metastatic Urothelial bladder cancer
WBC	white blood cell

2.

BACKGROUND

The human epidermal growth factor receptor 2 (HER2) gene is a proto-oncogene, which is located on chromosome 17q11.2-12 and encodes a transmembrane tyrosine kinase receptor, which is responsible for cell growth, differentiation, migration and apoptosis (Normanno et al 2005). Amplification of the HER2 gene occurs in approximately 20% to 25% of primary human breast cancers (BC) and typically results in overexpression of the HER2 protein at > 1 million copies per cell (Slamon et al 1987, Slamon et al 1989, Pegram et al 2000). Such tumors are considered "HER2-positive" and are associated with aggressive growth and poor clinical outcome (Slamon et al 1987, Slamon et al 1989).

A number of anti-HER2 therapies have proven efficacy, are approved and part of the SOC for HER2-positive Breast Cancer (BC) and Gastric Cancer GC. However, this is not yet the case for trastuzumab emtansine which currently is only available for BC. HER2 overexpression has been identified in some other tumors as esophagus, colorectal, pancreatic, bladder and prostate cancer (Yan et al 2014, Yoon et al 2014, Sato-Kuwabara et al 2009, Seo et al 2014, Stoecklein et al 2004, Minner et al 2010, Carneiro et al 2015, Hansel et al 2008). These findings pose the intriguing question if trastuzumab emtansine could improve patient outcomes in those tumor types and beyond BC and GC. There is currently no clinical data on the potential therapeutic effect of trastuzumab emtansine treatment in HER2-positive tumors such as esophageal-, colorectal-, pancreas/cholangio-, prostate and bladder carcinoma.

Urothelial bladder cancer (UBC) is an area of high unmet medical need. UBC seems to be an interesting target that shows a similar HER2 overexpression rate as in breast cancer, although the IHC staining pattern is expected to be more heterogeneous. HER2 expression in UBC is associated with high-grade tumors and advanced local disease (Hussain et al 2007, Simon et al 2003, Gehani et al 2012, Chen et al 2013), more metastatic sites and visceral metastases (Hussain et al 2007), higher recurrence risk (Chen et al 2013) and shorter OS and disease specific survival (Krueger et al 2002, Simon et al 2003).

Pancreatic adenocarcinoma is also an area of high unmet medical need with survival rates, which remain disappointing (median OS with palliative chemotherapy 11.1 months). The HER2 overexpression rate is as high as 11% (and varies widely between patients). Interestingly, overexpression of the HER2 protein does not correlate well to amplification of the HER2 locus. HER2 overexpression in pancreatic cancer may be due to gene deregulation rather than gene amplification as postulated by Ukita et al (2002) for intrahepatic biliary tract cancer (Harder et al 2012). Nevertheless an approach with an ADC such as trastuzumab emtansine may be considered a potential treatment option.

Cholangiocarcinomas may be considered related tumors and these patients can be included in later stages of this study. The incidence and mortality rates of cholangiocarcinoma, especially those of IHC, are increasing worldwide (Khan et al 2005). Complete resection is the only way to cure the disease at present. However, because cholangiocarcinoma are difficult to diagnose at an early stage and extend diffusely, most patients have unresectable disease at clinical presentation, and prognosis is very poor (5-year survival is 0–40% even in resected cases) (Yoshikawa et al 2008). Approximately 8% of patients have HER2 overexpression (Yan et al 2014) and may therefore benefit from a HER2-targeted therapeutic approach.

Patients diagnosed with metastatic UBC (MUBC) or metastatic pancreatic/cholangio cancer have very limited treatment options to date, especially if they present in an

advanced stage of their cancer, with a high mortality and low long-time survival rates. New therapeutic approaches are therefore needed for these patients with a high unmet medical need and limited other treatment options, especially in late stage.

This trial is a Phase II, proof of concept, single arm study, designed to estimate the efficacy of trastuzumab emtansine in HER2 overexpressing MUBC and metastatic pancreas/cholangio cancer in patients with advanced disease where cure is no longer possible and where no other treatment options are available anymore. This might be opened up to a diverse range of other HER2 overexpressing tumors as described further above. Trastuzumab emtansine has proven efficacious in HER2-positive BC and has a tolerable safety profile. Therefore, the risk benefit in this study is deemed positive.

The study design will allow for the examination of MUBC and metastatic pancreas/cholangio cancer with enough statistical power to determine whether further examination may be warranted in these indications or potential additional indications. To investigate a potential difference in treatment efficacy for MUBC and metastatic pancreas/cholangio cancer with homogeneous HER2 expression and the carcinoma with a more focal HER2 expression, patients will be stratified according to the HER2 IHC pattern in their baseline tissue biopsy (e.g., 30-70% vs 71-100% of tumor cells expressing HER2). Patients with very focal HER2 IHC pattern (e.g., < 30%) will be excluded from this study. The open-label, uncontrolled design is appropriate since the trial will only enroll patients with HER2-positive cancers and who in the opinion of the investigator have trastuzumab emtansine as their best treatment option. The study is intended as a proof of concept.

3. STUDY DESIGN

This trial is an exploratory, multicenter, non-randomized, Phase II, single agent study designed to evaluate the efficacy and safety of trastuzumab emtansine in two cohorts:

- patients with MUBC
- patients with metastatic pancreas/cholangio cancer.

Other tumor types may be potentially explored at a later point in time.

If no patients are enrolled in an individual cohort one year after enrolment started, then enrolment for that cohort will be stopped. A total of 32-38 patients per cohort will be enrolled i.e. 64-76 patients in total.

The accrual inclusion time for this study is expected to be 18 months per cohort.

In a safety run-in, the first 6 patients of each cohort will enter Regimen A and receive 2.4 mg/kg weekly trastuzumab emtansine intravenously (iv). Recruitment for the respective cohort will be suspended until all 6 of these patients have completed the 2nd cycle (6 weeks) and the 'regimen decision point' has been reached. Based on tolerability and safety aspects, a decision will be made by the idMC if the cohort is to continue on Regimen A (2.4 mg/kg qw), extending recruitment to a total of 32 patients (additional 26 patients) per cohort, or if the dose switches to Regimen B (3.6 mg/kg q3w). If the regimen is changed to Regimen B in an individual cohort, 32 additional patients will be included in this cohort; if the regimen remains unchanged (i.e., Regimen A), only 26 additional patients will be recruited.

If treatment in a cohort is switched to Regimen B, the 6 patients that were initially started on Regimen A will be allowed to switch if an additional benefit can be expected. However, for patients of a cohort who showed initial response on Regimen A, it is recommended to keep them on Regimen A. If any of these patients experiences PD, no switch is allowed and the patient will be discontinued from the study. Irrespective of

these potential changes, these patients will not be included in the primary efficacy analysis.

A Simon's two-stage design (Simon 1989) will be used to allow the study to stop early if there is no evidence of efficacy. In the first stage, 13 patients in each cohort will be accrued and their BOR results will be evaluated 12 weeks after the 13th patient was enrolled. If there are 0 objective responses (CR or PR) in these 13 patients, the study will be stopped for the respective cohort. Otherwise, 14 additional patients will be accrued per cohort for a total of 27.

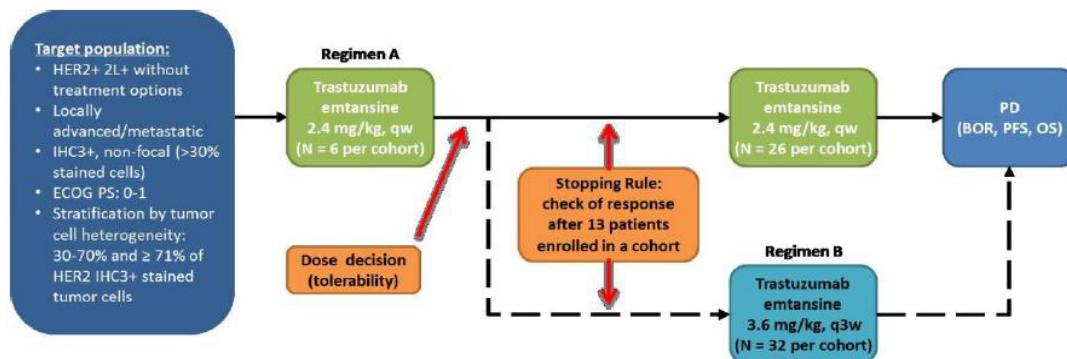
The data cutoff for the primary analysis will take place 12 weeks after the last patient of an individual cohort has been recruited (following a tumor assessment after 6 weeks [2 cycles] with a confirmation of BOR within 4 weeks).

The data cutoff for the final analysis for each cohort of all primary and secondary efficacy measures will take place 18 months after the last patient of a cohort was recruited, or once all patients have reported a progression event, whichever occurs earlier.

The primary (and final) analysis for efficacy would be based only on those patients of a cohort who started on the selected treatment regimen. If the decision is made to switch to Regimen B then those patients who started on Regimen A would not be included in the primary or final efficacy analyses (whether they stay on Regimen A or switched to Regimen B) but their results would be included in a supplementary descriptive analysis.

Decision on expansion of the study to include other carcinoma types will be made via collaboration of the SC and iDMC. The iDMC has to look at the initial tolerability data before the decision to include more carcinoma types is being made. Efficacy data will not be considered for this decision.

Figure 1 Trial design



ECOG PS = Eastern Cooperative Oncology Group Performance Status; PD = progressive disease;

Objectives of the study covered in the present statistical analysis plan:

The primary efficacy objective for this study is to evaluate the efficacy of trastuzumab emtansine in term of best tumor response.

The secondary efficacy objective for this study is to evaluate the efficacy of trastuzumab emtansine in term of progression-free survival, overall survival.

The safety objective is to evaluate the safety of trastuzumab emtansine in term of adverse events, vital signs and clinical laboratory results. An independent data monitoring committee (IDMC) will be responsible for reviewing periodically safety data.

Objectives of the study that will be covered in separate documents:

The pharmacokinetic objective is to characterize the pharmacokinetics of trastuzumab emtansine concentration in plasma and/or serum. This analysis will be handled by Clinical Pharmacology department at Roche.

The immunogenicity objective is to evaluate the immune response to trastuzumab emtansine. Endpoints for this objective will be the incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline, and immune-related biomarkers such PDL1 and CD8.

The biomarker objective is to identify biomarkers that are predictive of response, can provide evidence of trastuzumab emtansine activity, or can increase the knowledge and understanding of disease biology.

3.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in [Appendix 1](#). For additional details, see the Schedule of Assessments in [Appendix 2](#).

3.2 OUTCOME MEASURES

3.2.1 Primary Efficacy Outcome Measures

3.2.1.1 Best Overall Response

The best overall response will be assessed by investigator using the following definition.

The best overall response for a subject is defined as the most favorable outcome, according to RECIST v1.1 criteria, at any visit after first day of study treatment and up to the analysis data cut-off or the first disease progression, whichever occurs first.

The outcomes are ordered below from most to least favorable:

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)
- Non-Evaluable (NE)

Responses of Non CR/Non PD are treated as SD.

For investigator assessments, the best overall response will be derived programmatically, according to RECIST v1.1, based on the investigator overall subject response per visit collected on the eCRF. The investigator overall subject response per timepoint will not be re-derived programmatically. Best overall response is the first occurrence of the most favorable outcome, as detailed above. A best response of CR or PR cannot be assessed unless it is confirmed, no earlier than four (4) weeks (28 days) from the time a response of CR or PR is first suspected. Refer to the below table if the patient experienced at least one overall response of Complete Response (CR), Partial Response (PR) or Not Evaluable (NE) at any time on-treatment, the following conventions will be used to derive the confirmed best overall response:

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR ^a
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

^a If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the 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 timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

If a subject experienced only CR - NE - CR, BOR will be CR.

If a subject experienced only PR - NE - PR, BOR will be PR.

If a subject experienced only PR - SD - PR, BOR will be SD.

If a subject had only one tumor assessment post baseline with an overall response of NE, then the overall response will be set to NE.

A minimum interval of 5 weeks (35 days) will be considered for Stable Disease (SD) to be assigned as best overall response, i.e. in the case the single response is SD, PR or CR, this single response must have been assessed no less than 5 weeks (at least 35 days) after treatment start.

If the subject has a missing baseline tumor assessment, he/she will be excluded from the BOR calculation.

If the subject has no post-baseline tumor assessment, his/her best overall response will be Non-Evaluable (NE) and will be regarded as no responder.

3.2.1.2 **Overall Response Rate**

Overall response rate (ORR) as per investigator is defined as the percentage of patients who attain complete response (CR) or partial response (PR), as per RECIST v1.1. Only patients with measurable disease and with tumor assessment at baseline will be included in the denominator of the response rate. Patients without any post-baseline assessments will be assigned to the Non-Evaluable (NE) category and regarded as non-responders.

3.2.2 **Secondary Efficacy Outcome Measures**

3.2.2.1 **Progression-Free Survival**

Progression-free survival (PFS) as per investigator is defined as the time from start of treatment to the first documented disease progression, as determined using RECIST v1.1 from tumor assessments or reported in the eCRF follow-up pages, or death from any cause, whichever occurs first. Patients without an event will be censored at latest date between the last tumor assessment and the date of treatment start..

3.2.2.2 **Overall Survival**

Overall survival (OS) is defined as the time from start of treatment to death from any cause. Patients without an event will be censored at the last date known to be alive. Patients without any post-baseline information will be censored at the date of treatment start plus one day.

3.2.3 **Safety Outcome Measures**

The safety outcome measures for this study are as follows:

- Incidence, type and severity of all adverse events (AEs) and serious adverse events (SAEs) based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03).
- Incidence and type of AEs leading to discontinuation, modification, or delay of trastuzumab emtansine dose.
- Changes in vital signs and clinical laboratory results during and following trastuzumab emtansine administration.
- Death and cause of death.
- Cases of drug-induced liver injury meeting Hy's Law criteria.
- Pneumonitis of all grades.
- Change in LVEF over the course of the study as measured by echocardiogram (ECHO) or multiple- gated acquisition scan (MUGA).
- Incidence of congestive heart failure (CHF).

3.2.4 **Pharmacokinetic Outcome Measures**

Analysis of PK/PD will be handled by Clinical Pharmacology department at Roche. Details of statistical methods used for PK/PD exploratory analyses will be provided in a separate document.

3.3 **DETERMINATION OF SAMPLE SIZE**

The sample size estimation is based on the method of A'Hern (2001) and Simon (1989) and corresponding SAS programs.

To test the null hypothesis (H_0) that the best BOR is 5% or less (which would yield a low activity profile) against the alternative hypothesis (H_1) that the BOR is greater than or equal to 20% (which would yield an encouraging activity profile):

$$H_0: \text{BOR} \leq 5\% \quad \text{vs.} \quad H_1: \text{BOR} \geq 20\%.$$

27 patients per cohort would be required to perform the test with 80% power, at the one-sided alpha=0.05 level. To allow for drop-outs (10-15%) and to ensure that at least 27 patients will have efficacy data available, 32 patients will be recruited per cohort on the respective treatment regimen.

Assuming a preferable BOR of 20% is observed, then with 27 patients in a cohort, the 95% confidence limits would range from 7.2% to 39.8% (Clopper-Pearson exact confidence intervals).

The 95% confidence intervals for different BOR rates, and with 27 patients per cohort, were determined using SAS (Version 9.2) and the results are presented in [Table 1: Estimation of Confidence Intervals for a Sample Size N = 27 \(per cohort\)](#) below.

Table 1: Estimation of Confidence Intervals for a Sample Size N = 27 (per cohort)

Sample Size	BOR	95% Clopper Pearson Exact Confidence Intervals
27 patients	15%	4.4% – 34.2%
	20%	7.2% – 39.8%
	25%	10.6% – 45.5%
	30%	14.0% – 50.6%
	35%	17.9% – 55.8%

3.4 ANALYSIS TIMING

The following analyses are scheduled for each cohort (of note: timing of each analysis might differ for each cohort):

- **Safety analysis** for the review by iDMC of the accrued safety data of the first 6 patients treated for at least 6 weeks. This safety review will be based on individual patient listings provided by the data management vendor and is not covered by the present SAP.
- **Interim analysis** after Stage 1 for the review by iDMC of the BOR results of the first 13 patients treated at least 12 weeks
- **Primary analysis** with a data cutoff 12 weeks after the last patient of the cohort has been recruited.
- **Final analysis** with a data cutoff 18 months after the last patient of a cohort has been recruited, or once all patients have reported a progression event, whichever occurs earlier.

All data after cut-off date will be excluded from the analyses. Details of outputs to be produced for each analysis will be provided in [Appendix 3](#).

The interim, primary and final analyses for efficacy will be based only on those patients of a cohort who started on the selected treatment regimen. If the decision is made to switch to Regimen B then those patients who started on Regimen A will not be included in the primary or final efficacy tables (whether they stay on Regimen A or switched to Regimen B) but their results will be included in listings.

4. STUDY CONDUCT

4.1 DATA MONITORING

An independent data monitoring committee (iDMC) will be established to monitor the progress of the study, ensure that the safety of patients enrolled in the study is not compromised, make recommendation based on safety data whether each cohort can be continue with Regimen A or should switch to Regimen B and make recommendation at end of Stage 1 based on BOR results whether the cohort should be continued or not. Details of the composition, roles, responsibilities and processes of the iDMC are documented in a separate iDMC charter.

5. STATISTICAL METHODS

The analysis specifications described in this SAP supersede the specifications available in the protocol.

5.1 DEFINITIONS OF COHORT AND REGIMENS

Patients can enter into the study via two cohorts:

- **Metastatic urothelial bladder cancer:** This cohort consists of patients with locally advanced/ metastatic urothelial bladder cancer
- **Pancreas/cholangio cancer:** This cohort consists of patients with locally advanced/ metastatic pancreas/cholangio cancer

Cohort as recorded on the 'Cohort Assessment' eCRF page will be used for the analysis.

Patients may receive trastuzumab emtansine in two different regimens depending on the decision at end of safety run-in and when patients are enrolled:

- **Regimen A:** trastuzumab emtansine 2.4 mg/kg, weekly. This regimen will be administered to at least the first six patients in each cohort.
- **Regimen B:** trastuzumab emtansine 3.6 mg/kg every 3 weeks. This regimen will only be administered if decision at end of safety run-in is to switch to this regimen B.

Of note: For sake of completeness, the SAP and shells have been developed in case both regimens are used in the study. In case, only regimen A will be used then only one column will have to be displayed in the outputs.

The first received regimen (as entered in eCRF at the first treatment visit) will be used to classify each patient into one of the two possible regimens.

5.2 GENERAL DESCRIPTIVE METHODS

Descriptive statistics will be provided for each cohort separately and by first regimen received and overall (i.e. if patients starting on Regimen A switch to Regimen B then their data will still be displayed in Regimen A column). For safety data, all data will be included in tables and listings, including data reported when receiving non-selected regimen as well as data reported after potential switch of regimen. For efficacy data,

only data from patients who started on the selected regimen will be included in summary tables and figures, but all data will be included in listings.

For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. Percentage will be calculated by using as denominators the 'N' in column header and will be rounded to one decimal place, unless specified otherwise. Therefore, there may be cases where for instance the total of the percentages does not exactly equal 100%. If number of patients is '0' then 0 will be reported instead of '0 (0.0%)'.

For continuous variables, N, mean, median, standard deviation, 25th and 75th percentile, minimum and maximum values will be presented. The number of missing is displayed between brackets next to 'N'. Mean, standard deviation, and median will be presented with one more decimal place compared to the raw data, minimum and maximum will be presented with same number of decimal places as the raw data.

5.3 DEFINITION OF TREATMENT PERIOD

The first day of treatment is defined as the earliest day of non-null trastuzumab emtansine administration of the first regimen received.

The last day of treatment is defined as the latest day of non-null trastuzumab emtansine administration of any regimen received.

Baseline assessments are defined as the latest assessment performed prior to the first day of treatment, unless otherwise stated. For vital signs, ECG, laboratory examinations and ECOG PS the latest available assessment within 28 days prior to or on the first day of treatment (this latest assessment will be assumed to have been performed before drug was given) will be considered as baseline evaluation.

On-treatment evaluations will be evaluations performed on or after the first day of treatment and until 28 days from last day of treatment.

On-treatment laboratory, ECOG PS, vital signs and ECG will be all values collected after the first day of treatment and until 28 days from last day of treatment otherwise.

5.4 DATA CONVENTION

All data will be listed (e.g. pre-treatment serious adverse events), whereas only baseline and on-treatment evaluations will be considered for summary tables, except for Progression-Free and Overall Survival which will be summarized using data recorded during the follow-up period.

The following conversion factors will be used to convert days to months or years, where applicable:

- 1 week = 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days

Age at informed consent (yrs) = (date of informed consent – date of birth) / 365.25.

To calculate **duration / time between** two dates, the following convention will be used:
[Later date] – [earlier date] + 1 day.

Durations and times between two dates will be calculated only when both start and end dates are available (imputed dates cannot be used for computation, apart for overall survival when date of death has only day as missing).

The last known date to be alive will be the latest date among all dates specified in the eCRF except the following:

- Survival Follow-up date when status is either death or lost to follow-up
- Study Completion/Early Discontinuation Date when reason is either death or lost to follow-up
- A sample / record with test 'Not Done'.

Imputation of partial and missing dates is described in section [5.16](#).

5.5 COMPUTING ENVIRONMENT

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.2 or newer version), unless otherwise noted.

5.6 GRADING AND CODING OF ADVERSE EVENTS, LABORATORY PARAMETERS AND MEDICATIONS

Laboratory results, adverse events, and other symptoms will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE), version 4.03, except where CTC grades are not available.

Adverse events and relevant Medical History data fields (i.e. prior symptoms / AEs) will be coded using the most recent version of MedDRA dictionary available at the time of analysis.

Prior and concomitant anti-cancer therapy / other medications will be coded using the most up-to-date version of the in house Roche Drug Thesaurus dictionary.

Dictionary versions used will be displayed in analysis outputs.

5.7 ADJUSTMENTS FOR COVARIATES

No adjustment will be performed.

5.8 SUBGROUP ANALYSIS

Analysis of primary endpoint (BOR) will be performed according to cell heterogeneity (percentage of HER2 positively stained tumor cells: 30-70% versus $\geq 71\%$).

5.9 ANALYSIS POPULATIONS

5.9.1 Safety Population

Safety (SAF) Population: all patients who received at least one non-null dose of trastuzumab emtansine. The SAF population is the primary population for the analysis of safety parameters.

5.9.2

Screened Population

Screened (SCR) Population: all screened subjects who signed the optional informed consent for the additional gene protein assessment. The SCR population will be used for the analysis of biomarkers.

5.9.3

Efficacy Population

The analyses of efficacy parameter will be done on the SAF population as defined in section 5.9.1.

5.9.4

Per Protocol Population

Not applicable.

5.10

ANALYSIS OF STUDY CONDUCT

5.10.1

Patient Disposition

The overall subject disposition table will be based on the SAF population and will display the following information by first regimen received and overall:

- Number of subjects who signed informed consent
- Number of subjects who met all eligibility criteria: Yes/No
- Number of treated subjects with any regimen (SAF): Yes/No
- Number of treated subjects who switch from Regimen A to Regimen B (if applicable): Yes/No
- Number of patients in ITT: Yes/No

Summary of patient discontinuation and early termination will be tabulated on SAF population and will display the following information by first regimen received and overall:

- Number of subjects who discontinued from treatment phase and the reason
- Number of subjects who discontinued survival follow-up and the reason

The number of patients in SAF population by country and site will be summarized by first regimen started and overall.

Follow-up duration, defined as the time from start of treatment to the last date known to be alive, for patients who are still alive at the end of the study, will be estimated using Kaplan Meier product-method estimates. Patients who died during the study will be censored at the date of death. Follow-up duration will be summarized by displaying the following information:

- Number of patients with event (absence of death),
- Number of patients censored,
- Median and two-sided 95% CI computed according to Brookmeyer and Crowley method,
- 25th and 75th quantile, and the corresponding two-sided 95% CI computed according to Brookmeyer and Crowley method,
- Minimum and maximum for event time.

By-patient listing will be provided using SAF population for the following information:

- Date of start of treatment

- Date of completion/discontinuation and reason for completion/discontinuation for the treatment phase
- Date of completion/discontinuation and reason for completion/discontinuation for the follow-up phase
- Primary cause of death

5.10.2 **Protocol Deviations**

The protocol deviations as reported in the Protocol Deviation Management System (PDMS) will be considered. In PDMS, major protocol deviation is defined as any deviation impacting:

- Subject's rights, safety or well-being
- Study efficacy and/or safety results

The following major protocol deviations will be considered:

- Unfilled inclusion and/or exclusion criteria
- IMP dosing error
- Trastuzumab Emtansine dose not given according to weight assessed at D1 of each cycle
- Scheduling errors
- Failure to conduct Safety Follow-up visit 28 days (+-3 days) after end of study
- Failure to conduct Post-Treatment Follow-Up Visit, every 3 months
- Failure to provide full supportive care including transfusion of blood, blood products and antibiotics, according to standard of care
- Use of prohibited concomitant medication and/or procedures during course of treatment period including treatment with other systemic anticancer agents, concurrent investigational agents of any type, therapeutic agents that have a high risk of bleeding or might increase the risk of bleeding, and strong CYP3A4 inhibitors
- Failure to follow the Toxicity Management Guidelines
- Failure to perform baseline total tumor burden within 30 days before the first dose of study drug treatment, and post-baseline assessments every 6 weeks (+- 3 business days)
- Change in tumour assessment methods without medical rationale
- Treatment not discontinued after withdrawal criteria are met
- Failure to obtain informed consent at next scheduled protocol visit if protocol amendment or EC/IRB requires changes to ICF
- Failure to report a Serious Adverse Event in accordance with timelines
- Any screening assessment not done or not done within timelines without retrospective confirmation that the missed assessment was with normal range

Protocol deviations (as reported in PDMS) will be summarized by first regimen received and overall on SAF population:

- Number of patients having at least one major protocol deviations
- Number of subjects by major protocol deviations category as mentioned above.
- Number of patients having at least one non-major protocol deviations

- Number of subjects by non-major protocol deviations category as defined in PDMS

5.11 ANALYSIS OF TREATMENT GROUP

5.11.1 Demographics and Baseline Disease Characteristics

The following information will be summarized by first regimen received and overall on SAF population:

- Patient Demographics
 - Age
 - Age (categories: <18, 18-64, 65-84, >=85, missing)
 - Sex
 - Ethnicity
 - Race (if Asian, region will be specified)
 - ECOG Performance Status at baseline (0, 1, 2, 3, 4, 5)
 - HER2 positively stained tumor cells: <30%, 30-70%, > 70%.
 - Tobacco use history: Never, Current, Previous
 - Alcohol use history: Never, Current, Previous
 - Substance use: Yes, No
 - Female reproductive status (for female participants only. Percentage will be based on the total number of female patients)
 - Baseline weight (kg)
 - Baseline height (cm)
- Metastatic urothelial bladder cancer history (for the cohort of patients with metastatic urothelial bladder cancer)
 - Diagnosis confirmed histologically/ cytologically: Yes/No
 - Primary tumor site: Bladder/Ureter/Urethra/Renal Pelvis/Other
 - Intravesical therapy administered: Yes/No
 - Histology at time of enrollment: Transitional (urothelial) cell carcinoma/ Transitional (urothelial) cell carcinoma with mixed histology
 - Time from initial diagnosis to start of treatment date (weeks)
 - Staging at initial diagnosis: Pathological/ Clinical
 - Classification of primary tumor at initial diagnosis: (TX, T0,Ta etc...)
 - Classification of regional lymph nodes at initial diagnosis (NX, N0, N1 etc...)
 - Classification of distant metastasis at initial diagnosis (Mx, M0, M1 etc...)
 - Status of disease at time of enrollment: locally advanced disease/ metastatic disease
 - Staging at time of enrollment: Pathological/ Clinical
 - Classification of primary tumor at enrollment: (TX, T0,Ta etc...)
 - Classification of regional lymph nodes at enrollement (NX, N0, N1 etc...)
 - Classification of distant metastasis at enrollment (Mx, M0, M1 etc...)
 - Sites of metastatic disease
 - Time from first diagnosis of metastatic disease to start of treatment date (weeks)
- Pancreas/Cholangio cancer history (for the cohort of patients with pancreas/cholangio cancer)
 - Primary tumor site: Gallbladder/Intrahepatic/Vater Ampulla/Other
 - Histology: Adenocarcinoma, Squamous cell carcinoma/Small cell/ Undifferentiated carcinomas/Other

- Time from initial diagnosis to start of treatment date (weeks)
- Stage at primary diagnosis: Stage 0, Stage1 etc...
- Classification of primary tumor at primary diagnosis: (TX, T0,Ta etc...)
- Classification of regional lymph nodes at primary diagnosis (NX, N0, N1 etc...)
- Classification of distant metastasis at primary diagnosis (Mx, M0, M1 etc...)
- Stage at enrollment: Stage 0, Stage1 etc...
- Classification of primary tumor at enrollment: (TX, T0,Ta etc...)
- Classification of regional lymph nodes at enrollment (NX, N0, N1 etc...)
- Classification of distant metastasis at enrollment (Mx, M0, M1 etc...)
- Location of metastases
- Time from first metastasis to start of treatment date (weeks)

5.11.2 **Prior and Concomitant Treatments**

5.11.2.1 **Prior Anti-Cancer Treatment/Procedure**

Prior anti-cancer treatments/procedures summary on SAF population will present the following information by first regimen received and overall:

- Number of subjects with prior tumor surgery for the cancer of interest: Yes, No
- Number of patient by site of prior surgery for the cancer of interest
- Number of patients with prior radiotherapy: Yes, No
- Number of patients with prior systemic cancer therapy: Yes, No
- Number of lines of therapy by patient: 1 prior line, 2 prior lines, etc...
- Number of patients by type of prior therapy: chemotherapy, immunotherapy etc...

In addition, prior anti-cancer therapies will be tabulated on SAF by Drug/Medication Class and generic name/Standardized Medication Name using the in house Roche Drug Thesaurus dictionary. Drug Thesaurus Class will be sorted in a descending order of the total frequency count and the generic names with the highest frequency will be displayed first within each Drug Thesaurus class, unless otherwise indicated.

By-patient listing will be provided using SAF population for the following information:

- Prior tumor surgery other than cancer of interest
- Prior tumor surgery for cancer of interest
- Prior systemic cancer therapy
- Prior cancer radiotherapy

5.11.2.2 **Non Anti-Cancer Treatment/Procedure**

Prior medication is defined as any medication with end date prior to the start of the first day of treatment. Methods for handling partial or complete missing medication date are detailed in section [5.17](#).

Concomitant medication is defined as any medication/therapy with:

- start date until 28 days from last day of treatment
- end-date on or after first day of treatment or missing (ongoing).

Prior and concomitant therapies will be listed.

5.11.2.3 On-Study Anti-Cancer Treatment/Procedure

By-patient listing will be provided using SAF population for the following information coming from eCRF dedicated pages:

- On-study cancer radiotherapy (Brain Therapy)
- On-study cancer surgery

5.11.3 Subsequent Anti-Cancer Therapy

Subsequent anti-cancer therapies (as reported on the 'Subsequent anti-cancer therapies' CRF page) will be listed.

5.12 EFFICACY ANALYSIS

Efficacy analysis will be conducted on SAF population.

5.12.1 Primary Efficacy Endpoint

The primary efficacy objective of this study is to determine the best overall tumor response (BOR) as per RECIST 1.1 for all treated patients.

To answer the primary objective, the following hypotheses will be tested:

- H_0 : the best response rate is 5% or less, which would yield a low activity profile
- H_1 : the best response rate is greater than or equal to 20%, which would yield an encouraging activity profile

H_0 : best response rate $\leq 5\%$ vs H_1 : best response rate $\geq 20\%$

A Simon's two-stage design (Simon 1989) will be used to allow the study to stop early if there is no evidence of efficacy. The null hypothesis that the true response rate (BOR) is $\leq 5\%$ will be tested against a one-sided alternative.

- In the first stage, 13 patients in each cohort will be accrued and their BOR results will be evaluated 12 weeks after the 13th patient was enrolled. If there are 0 responses (CR or PR) in these 13 patients, the study will be stopped for the respective cohort. Otherwise, 14 additional patients will be accrued per cohort for a total of 27.
- In the second and last stage, H_0 will be rejected if the lower bound of the 90% confidence interval is greater than 5%. The minimum number of responders that will permit to reject H_0 will depend of the final number of patients with evaluable response data. For example, 4 or more responders will permit to reject H_0 if the number of patients is 27 or 28, where 5 or more responders will be needed if the number of patients between 29 and 32.

This is an early phase II study, hence there will be no adjustment for multiplicity.

Number and percentage of responders (i.e. subjects with objective response (CR or PR) as best overall response) with corresponding Clopper-Pearson 90% confidence interval will be provided. (Note: 90% CI (instead of 95% CI) will be used to be aligned with the testing at one-sided alpha level = 5%)

The following SAS code will be used:

```
PROC FREQ DATA= dataset;
  TABLE response/ binomial (clopperpearson level='1') alpha=0.1;
  * response represents the response variable;
```

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Further options to control the output may be added.

The number and percentage of each response category will also be presented.

Analysis will be repeated by subgroups of cell heterogeneity.

By-patient listing will be provided using SAF population for the following information:

- Tumor assessment and overall response per timepoint as per investigator
- Best overall response as per investigator

5.12.2 **Secondary Efficacy Endpoints**

5.12.2.1 **Progression-Free Survival**

PFS will be estimated using Kaplan Meier product-method estimates. PFS will be summarized by displaying the following information:

- Number of patients in the population (N),
- Number of patients with PFS event,
- Number of patients censored,
- Median and two-sided 95% CI computed according to Brookmeyer and Crowley method,
- 25th and 75th quantile, and the corresponding two-sided 95% CI computed according to Brookmeyer and Crowley method,
- Minimum and maximum for event time
- Minimum and maximum for censored time
- The event rates at certain time points (e.g. 3, 6, 9 and higher (every 3 months) if appropriate) with the relevant two-sided 95% CIs.

Kaplan-Meier estimates and median survival times are calculated with the PROC LIFETEST procedure in SAS. The CIs of the event rates will be calculated via log-log transformation method (default option CONFTYPE=LOGLOG in SAS) based on standard errors computed using the Greenwood's formula.

The following SAS code will be used:

```
PROC LIFETEST data=dataset METHOD=KM CONFTYPE=LOGLOG;
  TIME survtime*censor(1);
  RUN;
* survtime represents variable containing event/censor times;
* censor represents censoring variable (1=censored, 0=event);
Further options to control the output may be added.
```

Kaplan Meier (KM) plot of PFS will be generated.

PFS time will be listed on SAF population.

5.12.2.2 **Overall Survival**

The same analysis as for PFS will be repeated for OS.

5.12.2.3 **Duration of response**

Duration of response (DOR) is defined as the time from the first occurrence of response (complete response [CR] or partial response [PR], whichever is first reported) to disease progression, as determined by the investigator according to RECIST v1.1,

or death from any cause, whichever occurs first, among patients with a best overall response as CR or PR.

Patients who are alive and have not experienced disease progression will be censored at the time of the last tumor assessment date. If no tumor assessments were performed after the date of the first occurrence of a CR or PR, DOR will be censored at the date of the first occurrence of a CR or PR plus 1 day.

If there is a sufficient amount of responders (patients with a best overall response as CR or PR), DOR will be estimated using Kaplan Meier product-method estimates. DOR will be summarized by displaying the following information:

- Median and two-sided 95% CI computed according to Brookmeyer and Crowley method.

DOR time will be listed on SAF population.

5.12.3 **Sensitivity Analyses**

No sensitivity analysis are planned.

5.13 **PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES**

Analysis of PK/PD will be handled by Clinical Pharmacology department at Roche. Details of statistical methods used for PK/PD exploratory analyses will be provided in a separate document.

5.14 **SAFETY ANALYSES**

Safety summaries will be produced by first regimen received and overall on the SAF population.

5.14.1 **Exposure of Study Medication**

5.14.1.1 **Treatment Duration and Dose Exposure**

Definition of treatment duration, cycle initiated and dose exposure variables are in [Table 2](#).

Table 2: Exposure Definitions

	Regimen A (2.4 mg/kg weekly)	Regimen B (3.6 mg/kg every 3 weeks)
Time on Treatment (in weeks)	[min (last treatment day+7, death date, discontinuation date of treatment) – (first treatment day) +1] / 7. Note: Subjects still on treatment will be censored at minimum date between (cut-off date, last known drug administration date)	[min (last treatment day+21, death date, discontinuation date of treatment) – (first treatment day) +1] / 7. Note: Subjects still on treatment will be censored at minimum date between (cut-off date, last known drug administration date)
Number of cycles initiated	The number of cycle initiated will correspond to the number of non-null treatment dose administered at a “Day 1” visit in the eCRF.	The number of cycle initiated will correspond to the number of non-null treatment dose administered at a “Day 1” visit in the eCRF.

	Regimen A (2.4 mg/kg weekly)	Regimen B (3.6 mg/kg every 3 weeks)
Cumulative dose (in mg)	Sum of all dose administered (in mg) as reported on 'Trastuzumab Emtansine administration eCRF page'.	

Note: If patients switch from regimen A to regimen B, the different period of treatment will be summed for the time on treatment, number of cycles initiated and cumulative dose

Time on treatment (in weeks) and cumulative dose (in mg) will be summarized using descriptive statistics, by first regimen received and overall.

In addition, number of cycles initiated by patient considered as both continuous and categorical variables will also be summarized using descriptive statistics.

5.14.1.2 Infusion Interrupted or Delayed

Infusion interruption/ delayed as reported on the 'Trastuzumab Emtansine Administration' eCRF page will be summarized by first regimen received and overall. The following will be displayed:

- Number of patients with at least one infusion interrupted/delayed
- Infusion interrupted/delayed per patient: as continuous and as categorical (1, 2, 3, or ≥ 3).
- Reason for interrupted/delayed infusion

5.14.1.3 Infusion Rate Reduction

Infusion rate reduction as reported on the 'Trastuzumab Emtansine Administration' eCRF page will be summarized by first regimen received and overall. The following will be displayed:

- Number of patients with at least one infusion rate reduced
- Number of infusion rate reductions per patient: (1, 2).
- Reason for first infusion rate reduction
- Reason for second infusion rate reduction.

By patients listings will be provided for the following information.

- Drug administration.
- Drug exposure,
- Infusion rate interrupted delayed,
- Infusion rate reduction and reason.

5.14.2 Adverse Events

Adverse events variables are defined in [Table 3](#). Adverse events outputs will include all adverse events including those reported as infusion-related reactions.

Tables outputs will include only the Treatment Emergent Adverse Events. All events recorded in eCRF will be presented in listings, with a flag for emergence from the first day of treatment until last day of administration + 28 days.

Table 3 : Adverse Events Definitions

Variable	Definition
Treatment Adverse Events (TEAEs) ⁽¹⁾	Any adverse events (serious and non-serious) with an onset date on (only if the "Event occurred prior to first Trastuzumab Emtansine administration" from the AE eCRF page is not

Variable	Definition
	checked) or after the first day of treatment and until last day of administration +28 days
Adverse Events NCI CTCAE grade	The adverse events grade displayed in the AE summary table will be the one with tick box checked for "AE most extreme NCI CTCAE grade". Any AEs with a missing CTC grade will be reported in the "missing" category grade.
Serious Adverse Events (SAEs)	Any adverse events with "Serious" box checked for "Is this AE non-serious or serious?". In case of missing seriousness, TEAE will be considered serious.
Adverse events related to Trastuzumab Emtansine	Any adverse events with 'Yes' for "AE suspected to be caused by Trastuzumab Emtansine"
Adverse Events with fatal outcome	Any adverse events with tick box checked for "It resulted in death" or with a most extrement NCI CTCAE grade equal to 5
Adverse events leading to Trastuzumab Emtansine discontinuation	Any adverse events with an "Action taken with Trastuzumab Emtansine due to SAE/AE" of "drug withdrawn"
Adverse events leading to Trastuzumab Emtansine modification	Any adverse events with an "Action taken with Trastuzumab Emtansine due to SAE/AE" of "drug interrupted", "dose reduced", "drug withdrawn" or "dose delayed"
Adverse events of Special Interest (AESI) based on eCRF categories	Any adverse events with "Yes" box checked for "Is this an adverse event of special interest?" in the eCRF AESIs will be summarized based on the tick box from the eCRF. The categories from the AE eCRF page will be considered.
Selected Adverse events	Selected adverse events will be defined by Roche Safety group in Excel file. It will include (drug-induced liver injury meeting Hy's Law criteria., pneumonitis, congestive heart failure, hepatic events, allergic reactions, thrombocytopenia, hemorrhage events)

An overview table will be provided by first regimen received and overall, and will display number and percentage of patients with at least one:

- TEAE
- TEAE by CTC most extreme grade: 1, 2, 3, 4, 5, >=3,missing
- TEAE related to Trastuzumab Emtansine
- Serious TEAE
- Serious TEAE (SAE) related to Trastuzumab Emtansine
- TEAE with fatal outcome
- TEAEs leading to discontinuation of Trastuzumab Emtansine
- TEAEs leading to modification of Trastuzumab Emtansine
- TEAE of special interest

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- Serious TEAE of special interest

The incidence of TEAEs will be summarized by worst intensity (grade 1 - grade 5, missing, overall) and will display number of patients with at least one TEAE, for the following AEs:

- TEAE
- TEAE related to Trastuzumab Emtansine
- Selected TEAEs

The TEAE tables will include the number and percentage of patients with at least one TEAE, by MedDRA primary System Organ Classes (SOC) (sorted in descending order of the total frequency count) and MedDRA Preferred Terms (PT) (sorted in descending order of the total frequency count within each SOC) unless otherwise indicated. A patient with more than one occurrence of the same adverse event in a particular system organ class/preferred term will be counted only once in the total of those experiencing adverse events in that particular system organ class/preferred term.

The above summary tables will be repeated for the following categories of TEAEs; however the following tables will not be split by intensity.

- TEAE with NCI CTCAE grade ≥ 3
- TEAE of special interest based on the eCRF categories
- Serious TEAE
- Serious TEAE related to Trastuzumab Emtansine
- Serious TEAE of special interest
- TEAEs leading to discontinuation of Trastuzumab Emtansine
- TEAEs leading to modification of Trastuzumab Emtansine
- TEAE with fatal outcome

To address EudraCT requirements, the following tables by first regimen received and overall will be produced:

- Summary of serious treatment emergent adverse events, presenting number of subjects with event, number of events, number of treatment related events, number of events resulting in death, number of treatment related events resulting in death
- Summary of non-serious treatment emergent adverse events reported in at least 5% of subjects in any regimen, presenting number and percentage of subjects with event, number of events

For these specific EUdraCT tables, the SOC/PT categories will be sorted by alphabetical order.

In addition, by-patients listing will be provided. All AEs regardless of emergent status will be listed with the following items:

- All adverse events
- All adverse events with Missing or Partial Start Date
- All adverse events of grade 3 or more
- All serious adverse events
- All adverse events leading to treatment discontinuation
- All AESI based on the eCRF categories
- All selected adverse events

5.14.3 Infusions-Related Reactions (IRR)

Infusion-related reaction will also be described separately on SAF by first regimen received and overall.

Infusion-related reaction is defined as any adverse events with “Infusion Related Reaction” box checked in the eCRF.

An overview table will be provided by first regimen received and overall, and will display number and percentage of patients with at least one:

- IRR
- IRR by CTC most extreme grade: 1, 2, 3, 4, 5, >=3, missing
- IRR related to Trastuzumab Emtansine
- Serious IRR related to Trastuzumab Emtansine
- IRR with fatal outcome
- IRR leading to treatment discontinuation of Trastuzumab Emtansine
- IRR leading to treatment modification of Trastuzumab Emtansine

The summary tables by SOC and PT will be provided for:

- IRR by worst NCI CTCAE grade
- IRR related to Trastuzumab Emtansine by worst NCI CTCAE grade
- IRR with NCI CTCAE grade >=3
- Serious IRR
- Serious IRR related to Trastuzumab Emtansine

5.14.4 Death

A summary table will be provided on SAF by first regimen received and overall, and will present:

- Number of patients who died with the corresponding cause of death
- Number of patients who died within 28 days from last day of study drug administration and the corresponding cause of death.

Listing of deaths, dates and cause of deaths will be provided.

5.14.5 Laboratory Data

Laboratory parameters include:

- Hematology: hemoglobin, hematocrit, red blood cells [RBC], platelet count, white blood cells [WBC] with differential [including neutrophils, lymphocytes, monocytes, eosinophils and basophils]
- Biochemistry: glucose, blood urea nitrogen [BUN], creatinine, sodium, potassium, bicarbonate, phosphorus, chloride, calcium, uric acid, total protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, lactate dehydrogenase [LDH], AST, ALT, gamma-glutamyl-transferase [GGT].
- Coagulation (as clinically indicated): INR and aPTT.
- Urinalysis: pH, specific gravity, glucose, protein, ketones, blood, bilirubin and microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria

Clinical laboratory values will be expressed using conventional SI units.

All laboratory values will be listed. Separate listings will be generated to include all abnormal laboratory values, urinalysis and serology.

5.14.6 Vital Signs

Vital sign parameters include:

- Temperature (C)
- Pulse rate (beats/min)
- Respiratory rate (breaths/min)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Weight (kg)
- Oxygen saturation (%)

All vital signs data will be listed.

5.14.7 ECOG PS

All ECOG PS will be listed.

5.14.8 Left Ventricular Ejection Fraction (LVEF)

Actual value (as continuous and categorical variable) and change from baseline for LVEF (%) will be summarized by first regimen received and overall, for each visit using descriptive statistics.

Worst on treatment value (as categorical variable with categories >45%, 40-45% and <10% drop from baseline, 40-45% and >=10% drop from baseline, <40%) will also be described by first regimen received and overall.

All LVEF data will be listed.

A boxplot figure describing the LVEF percentage over time will be provided. The figure will present boxplots of LVEF values at each visit from screening to the last visit with at least 5 non missing LVEF values.

5.14.9 Electrocardiogram

All ECG data will be listed.

5.15 BIOMARKER ANALYSIS

A descriptive analysis of HER2 status will be performed.

HER2 status and proportion of positively stained tumor cells, in categories, by immunohistochemistry (IHC), will be summarized overall, by cohort and for both cohorts combined. This analysis will be performed on the SAF population.

HER2 IHC status and proportion of positively stained tumor cells will also be summarized, in correlation with the presence of gene amplification (gene protein assay). This analysis will be performed on the SCR population.

In addition, all data related to HER2 biomarker will be listed.

5.16 MISSING DATA

Imputation of partial/missing death date will be done as follows:

- If the date is completely missing, then the day of “Last known to be alive” +1 will be used
- If only day is missing and year and month are same as “Last known to be alive”, then the day of “Last known to be alive”+1 will be used otherwise the 1st day of the month will be used
- If day and month are missing and year is same as “Last known to be alive”, then the “Last known to be alive”+1 will be used, otherwise 1st of January will be used

Partially missing dates for adverse events (AEs) will be imputed as follows. Of note, imputation of missing/partial AE date will be done only to identify treatment emergent AEs.

AE onset dates

- Partially missing onset dates will be imputed as follows
 - When only Day is missing :
 - If Month & Year of the onset date are the same as Month & Year of first day of treatment, the imputed onset date will be imputed as the minimum of first day of treatment and the AE resolution date (imputed if needed).
 - Otherwise, the missing day will be replaced by “1”.
 - When Day & Month are missing:
 - If Year of the onset date is the same as Year of first day of treatment, the imputed onset date will be imputed as the minimum of first day of treatment and the AE resolution date (imputed if needed).
 - Otherwise, the missing Day & Month will be replaced by “01JAN”.
- Complete missing onset dates for AEs will be imputed by first day of treatment and the AE will be considered as treatment emergent, unless the end date of the AE (imputed if needed) or the end year of the AE (if day and month are missing) is entered and is before the year of the first day of treatment.

AE resolution dates

- Incomplete resolution dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case the date of death will be used to impute the incomplete resolution date.
- In all other cases the incomplete resolution date will not be imputed.

Partially missing dates for medications and procedures will be imputed as follows. Of note, imputation of missing/partial medications/procedures date will be done only to identify concomitant medications/procedures.

- If the start date of the medication/procedure is unknown (i.e. complete missing date) and there is no end date, the worst-case scenario will be assumed. The medication/procedure will be considered as both a prior medication/procedure and a concomitant medication/procedure for both treatment periods. In case there is an unknown start date but the end date is known and is prior to the first

day of treatment, then the medication/procedure will not be considered as concomitant for the first treatment period/post-progression treatment period.

- If the month and the day of the start date of the medication/procedure are missing and there is no end date, the month and the day will be imputed to January, 1st of the year specified. In case the month and the day of the start date are unknown but the end date is known and is prior to the first day of treatment, then the medication/procedure will not be considered as concomitant for the first treatment period /post-progression treatment period.
- If the day of the start date of the medication/procedure is missing and there is no end date, the day will be imputed to the first day of the month specified. In case the day of the start date is unknown but the end date is known and is prior to the first day of treatment, then the medication/procedure will not be considered as concomitant for the first treatment period/post-progression treatment period.
- If the end date is unknown (i.e. missing), the date will be kept as missing however the medication/procedure will be considered concomitant.
- If the month and the day of the end date of the medication/procedure are missing, the month and the day will be imputed to December, 31st of the year specified.
- If the day of the end date of the medication/procedure is missing, the day will be imputed to the last day of the month specified.

No other dates will be imputed, unless otherwise specified. The original incomplete or missing dates will be presented in the listings, not the imputed dates.

5.17 INTERIM ANALYSES

The first 6 patients of each cohort will be analyzed on an ongoing and per patient basis – i.e. based on the tolerability criteria (as defined in the iDMC charter) and in consultation with the SC and iDMC if needed. Further, there will be an analysis of the safety data after the first 6 patients of a cohort have completed 2 cycles of Regimen A. The results will be made available to the IDMC in order for them to make the decision as to whether to continue with Regimen A or to switch to Regimen B.

There will be analysis of the ORR results for the first 13 patients of each cohort (12 weeks after the 13th patient has been enrolled) in the selected treatment regimen. This will be done in order to decide whether to stop the study or not (as outlined in Section 3).

5.17.1 Optional Interim Analysis

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct additional interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by Sponsor study team personnel, who will have full access to the data.

6. REFERENCES

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Appendix 1 Protocol Synopsis

Objectives and Endpoints

This study will evaluate the efficacy, safety and pharmacokinetics of trastuzumab emtansine in patients with *locally advanced (unresectable and not treatable with curative intent)* or metastatic urothelial bladder cancer (UBC) or *locally advanced (unresectable and not treatable with curative intent)* or metastatic pancreatic cancer/cholangiocarcinoma. Specific objectives and corresponding endpoints for the study are outlined below.

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of trastuzumab emtansine	• Best overall response rate (BOR) as determined by the investigator (using RECIST 1.1). BOR is defined as the best response recorded from the first day of study treatment until disease progression/recurrence or death. Responders, as assessed every 6 weeks, will be defined based on tumor assessment status as partial responder (PR) or complete responder (CR) at these time points. To be assigned a status of PR or CR (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder.

Secondary Efficacy Objective:	
• To evaluate the efficacy of trastuzumab emtansine	<ul style="list-style-type: none"> • Progression-free survival (PFS), defined as the time from beginning of treatment to the first occurrence of disease progression, as determined by the investigator (using RECIST 1.1), or death from any cause, whichever occurs first. • Overall survival (OS), defined as the time from beginning of treatment to death from any cause.
Safety Objective:	
• To evaluate the safety of trastuzumab emtansine	<ul style="list-style-type: none"> • Incidence, type and severity of all adverse events (AEs) and serious adverse events (SAEs) based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03). • Incidence and type of AEs leading to discontinuation, modification, or delay of trastuzumab emtansine dose. • Changes in vital signs, physical examination findings, and clinical laboratory results during and following trastuzumab emtansine administration. • Death and cause of death. • Cases of drug-induced liver injury meeting Hy's Law criteria. • Pneumonitis of all grades. • Change in left ventricular ejection fraction (LVEF) over the course of the study as measured by echocardiogram (ECHO) or multiple-gated acquisition scan (MUGA). • Incidence of congestive heart failure (CHF).
Pharmacokinetic Objective:	
• <i>To characterize the pharmacokinetics of trastuzumab emtansine</i>	• <i>Concentrations of trastuzumab emtansine in plasma/serum to determine exposure.</i>

(Exploratory) Immunogenicity Objective:	
• To evaluate the immune response to trastuzumab emtansine	<ul style="list-style-type: none"> Incidence of anti-therapeutic antibodies (ATAs) during the study relative to the prevalence of ATAs at baseline. Exploratory assessment of immune checkpoints and infiltrating lymphocytes in the tumor before and after treatment by the assessment of immune-related biomarkers such as PDL1 and CD8.
Exploratory Biomarker Objective:	
• To identify biomarkers that are predictive of response, can provide evidence of trastuzumab emtansine activity, or can increase the knowledge and understanding of disease biology	<ul style="list-style-type: none"> <i>To further evaluate the HER2 status by other exploratory testing methods such as a novel gene-protein assay (GPA), e.g. immunohistochemistry (IHC) and in situ hybridization (ISH) combined in one assay on samples of all consenting screened patients.</i> Correlate levels of HER2 protein expression, HER2 gene amplification and circulating HER2 extracellular domain (HER2 ECD) to trastuzumab emtansine efficacy. To evaluate biomarkers that may be associated with response and/or safety on the protein, RNA and DNA level (e.g. by molecular subtyping and gene mutation analysis).

Study Design

Description of Study

This is an exploratory, multicenter, non-randomized, Phase II, single agent cohort study designed to evaluate the efficacy of trastuzumab emtansine in patients with *locally advanced (unresectable and not treatable with curative intent) or metastatic urothelial bladder cancer (UBC) or locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancer/cholangiocarcinoma.*

Number of Patients

In total, 32-38 patients will be enrolled per cohort; 64-76 patients in total.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Histologically centrally confirmed HER2-positive (IHC3+ in $\geq 30\%$ of tumor cells): locally advanced (*unresectable and not treatable with curative intent*) or metastatic urothelial bladder cancer or *locally advanced (unresectable and not treatable with curative intent) or metastatic pancreatic cancer/cholangiocarcinoma.*

HER2 status may be pre-screened at the participating site. However, HER2 determination at the referral center is not accepted to determine study eligibility. HER2 positivity needs to be prospectively confirmed with central laboratory HER2 testing before patient enrollment.

- There must be no standard treatment options available for patients with the above HER2 overexpressing tumors and they must have undergone at least one prior platinum-based treatment for *locally advanced (unresectable and not treatable with curative intent) or metastatic tumor.* (Note: for *pancreatic cancer/cholangiocarcinoma*, prior treatments are NOT required to be platinum-based.)
- The patient must have evaluable disease fulfilling all of the following imaging criteria:

- a. On diagnostic computed tomography scan/magnetic resonance imaging: lesion should be measurable according to RECIST 1.1.
- b. Target lesion(s) should not have been previously irradiated.
- At least one formalin-fixed paraffin-embedded biopsy of the primary tumor and/or from a metastatic site is required.
- Age \geq 18 years.
- Eastern Cooperative Oncology Group performance status of 0-2.
- No significant cardiac history and a current LVEF \geq 50%. LVEF should be determined within 28 days before the start of trastuzumab emtansine treatment.
- Adequate organ function, evidenced by the following laboratory results (performed within 7 days prior to commencement of dosing):
 - a. Absolute neutrophil count $>$ 1,500 cells/mm³.
 - b. Platelet count $>$ 100,000 cells/mm³.
 - c. Hemoglobin $>$ 9 g/dL.
 - d. Aspartate aminotransferase and alanine aminotransferase $<$ 2.5 \times upper limit of normal (ULN).
 - e. Total bilirubin \leq 1.5 \times ULN unless the patient has documented Gilbert's syndrome, in which case direct (conjugated) bilirubin level needs to be within normal limits.
 - f. Serum alkaline phosphatase \leq 2.5 \times ULN. Patients with bone metastases: alkaline phosphatase \leq 5 \times ULN.
 - g. Serum creatinine $<$ 2.0 mg/dL or $<$ 177 μ mol/L.
 - h. International normalized ratio and activated partial thromboplastin time or partial thromboplastin time $<$ 1.5 ULN.
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the study.
- Negative serum pregnancy test for women of childbearing potential (including pre-menopausal women who have had a tubal ligation) and for all women not meeting the definition of postmenopausal (\geq 12 months of amenorrhea), and who have not undergone surgical sterilization with a hysterectomy and/or bilateral oophorectomy. For all other women, documentation must be present in medical history confirming that the patient is not of childbearing potential.

For women of childbearing potential and men with partners of childbearing potential, agreement by the patient and/or partner to use a highly effective non-hormonal form of contraception such as surgical sterilization or two effective forms of non-hormonal contraception until 7 months after the last dose of trastuzumab emtansine.

Methods of birth control are considered highly effective forms of contraception in case they result in a low failure rate (i.e., $<$ 1% per year) when used consistently and correctly. The use of the following non-hormonal methods of contraception is acceptable:

- a. True abstinence, when this is the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, and symptothermal post ovulation methods) and withdrawal are not acceptable methods of contraception.
- b. Male sterilization (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomized male partner should be the sole partner.

Alternatively, use of two of the following effective forms of contraception is acceptable:

- a. Placement of intrauterine device or intrauterine system. Consideration should be given to the type of device being used, as there are higher failure rates for certain types (e.g., steel or copper wire).
- b. Condom with spermicidal foam/gel/film/cream/suppository.

- c. Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.

The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted: Failure rates indicate that, when used alone, the diaphragm and condom are not highly effective forms of contraception. Therefore, the use of additional spermicides does confer additional theoretical contraceptive protection.

However, spermicides alone are ineffective at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and should not be used alone.

- Signed written informed consent approved by Ethics Committee and obtained prior to any study procedure.
- Life expectancy of at least 12 weeks.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Patients with previous exposure to HER2-targeted therapies in any setting.
- Patients showing histologically confirmed focal HER2-expression, i.e., < 30% of positively stained tumor cells.
- Patients with brain metastasis as the sole site of metastatic disease and are symptomatic or require therapy to control symptoms.
NB: Brain metastases are allowed provided they are asymptomatic and/or controlled by previous radiotherapy.
- Current uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg).
- Current unstable angina pectoris.
- History of symptomatic CHF of any New York Heart Association criteria or ventricular arrhythmia that requires treatment.
- History of myocardial infarction within the last 6 months.
- Peripheral neuropathy, Grade ≥ 3 .
- Current dyspnea at rest due to complications of advanced malignancy, or other diseases that require continuous oxygen therapy.
- Current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures).
- History of other malignancy within the last 5 years, except for appropriately treated carcinoma in situ of the cervix, non-melanoma skin carcinoma, stage I uterine cancer, or other cancers with a similar outcome as those previously mentioned.
- For female patients, current pregnancy and lactation.
- Concurrent, serious, uncontrolled infections or current known infection with human immunodeficiency virus, active hepatitis B and/or hepatitis C.
- Known prior severe hypersensitivity to trastuzumab and trastuzumab emtansine or the excipients of the investigational medicinal product (IMP).
- Clinically significant bleeding within 30 days before enrollment
- Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment
- Concurrent participation in any other therapeutic clinical trial.

End of Study

Each cohort will close 18 months after the last patient was recruited or once all patients have died or withdrawn from study, whatever happens first.

End of study for a cohort will be declared at the last patient last visit (LPLV) as per definition is the last data collection point, which can be a clinic visit or a laboratory sample.

Length of Study

The total length of the study for an individual cohort, from screening of the first patient to the end of the study, is expected to be approximately 3 years (18 months of recruitment, *an expected 6 months of treatment and a further 12 months of follow-up*).

Patients will receive study medication until unacceptable toxicity, withdrawal of consent, disease progression, or death, whichever occurs first.

The data cutoff for the primary analysis of BOR will take place 12 weeks after the last patient of an individual cohort has been recruited (following a tumor assessment after 6 weeks [2 cycles] with a confirmation of BOR *performed no less than 4 weeks after the criteria for response are first met*).

The data cutoff for the final analysis for each cohort of all primary and secondary efficacy measures will take place 18 months after the last patient of a cohort was recruited, or once all patients have reported a progression event, whichever occurs earlier.

Investigational Medicinal Products

Test Product (Investigational Drug)

The IMP for this study is trastuzumab emtansine (Kadcyla).

Trastuzumab emtansine will be administered by intravenous infusion

- Regimen A: trastuzumab emtansine 2.4 mg/kg, weekly
- Regimen B: trastuzumab emtansine 3.6 mg/kg every 3 weeks.

In a safety run-in, the first 6 patients of each cohort will enter Regimen A and receive 2.4 mg/kg weekly trastuzumab emtansine. These first 6 patients will be assessed on an ongoing and patient per patient basis – i.e. based on the tolerability criteria (as defined in the Independent Data Monitoring Committee [IDMC] charter) and in consultation with the Steering Committee (SC) and iIDMC if needed. Recruitment for the respective cohort will be suspended until all 6 of these patients have completed the 2nd cycle (6 weeks) and the 'regimen decision point' has been reached. Based on tolerability and safety aspects, the iIDMC will decide for each cohort if the study is to continue on Regimen A (2.4 mg/kg qw), extending recruitment to a total of 32 patients (additional 26 patients) per cohort, or if the dose switches to Regimen B (3.6 mg/kg q3w). If the regimen is changed to Regimen B, 32 additional patients will be included per cohort; if the regimen remains unchanged (i.e., Regimen A), only 26 additional patients will be recruited.

Statistical Methods

The first 6 patients of each cohort will be analyzed on an ongoing and patient per patient basis – i.e. based on the tolerability criteria (as defined in the iIDMC charter) and in consultation with the SC and iIDMC if needed.

Primary Analysis

The primary efficacy endpoint BOR will be analyzed as follows:

Responders as assessed every 6 weeks will be defined based on tumor assessment status of PR or CR at these time points. Only patients with measurable disease at baseline will be included in the analysis of the response rate. Patients without a post-baseline tumor assessment will be considered to be non-responders. BOR is defined as the best response recorded from the first day of study treatment until disease progression/recurrence or death. To be assigned a status of PR or CR (i.e., a responder), changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder. The primary analysis will be based on the BOR result after 12 weeks (an assessment after 6 weeks [2 cycles] with a confirmation of BOR *performed no less than 4 weeks after the criteria for response are first met*).

The null hypothesis (H_0) is that the best response rate is 5% or less, which would yield a low activity profile. The alternative hypothesis (H_1) is that the best response rate is greater than or equal to 20%, which would yield an encouraging activity profile:

H_0 : best response rate $\leq 5\%$ vs H_1 : best response rate $\geq 20\%$

A Simon's two-stage design (Simon 1989) will be used to allow the study to stop early if there is no evidence of efficacy. The null hypothesis that the true response rate (BOR) is $\leq 5\%$ will be

tested against a one-sided alternative. In the first stage, 13 patients in each cohort will be accrued. If there are 0 responses (CR or PR) in these 13 patients, the study will be stopped for the respective cohort. Otherwise, 14 additional patients will be accrued per cohort for a total of 27. Recruitment may be suspended after the 13th patient in a cohort has been enrolled in the selected treatment regimen. This suspension will occur if there are no responses observed in the previous 12 patients (since the decision will be made to stop the study only if there are no responses in the first 13 patients).

In the primary analysis of efficacy the null hypothesis will be rejected if 4 or more responses are observed in 27 patients. This design yields a type I error rate of 0.05 and power of 80% when the true response rate is $\geq 20\%$.

It is planned to recruit more than the required 27 patients per cohort to allow for drop-outs. If there are no drop-outs amongst the 32 enrolled patients in a certain cohort then the decision rule will be revised as necessary to retain the same alpha and power. For example, if 32 patients have evaluable efficacy data, then if 5 or more responders are observed then we will reject H_0 and accept H_1 – i.e., accept that the best response rate $\geq 20\%$. If 4 or fewer responders are observed then we will accept H_0 .

A response rate of less than 5% will be considered of no clinical interest. A response rate of more than 20% will be considered of interest to potentially start a further study, which will not be part of this protocol.

Determination of Sample Size

The sample size estimation is based on the method of A'Hern (2001) and Simon (1989) and corresponding Statistical Analysis System programs.

To test the null hypothesis (H_0) that the best BOR is 5% or less (which would yield a low activity profile) against the alternative hypothesis (H_1) that the BOR is greater than or equal to 20% (which would yield an encouraging activity profile), 27 patients per cohort would be required to perform the test with 80% power, at the one-sided alpha=0.05 level. To allow for drop-outs (10-15%) and to ensure that at least 27 patients will have efficacy data available, 32 patients will be recruited per cohort on the respective treatment regimen.

Assuming a preferable BOR of 20% is observed, then with 27 patients, the 95% confidence limits would range from 7.2% to 39.8% (Clopper-Pearson exact confidence intervals).

Appendix 2 Schedule of Assessments

Schedule of Activities: *Regimen A (Trastuzumab emtansine, 2.4 mg/kg weekly)*

	Screening	Cycle 1 (day)			Cycle 2 (day)			Cycle 3 (day)			Cycle 4+ (day)			Study Drug Completion Visit ^a	Survival Follow-Up ^a
	-28 to 0	1	8	15	1	8	15	1	8	15	1	8	15		
Informed Consent ^a	x				(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)	(-1,+3)		
Assignment of patient numbers through the IwRS	x														
Tumor tissue for HER2 status testing ^b	x														
Medical history and demographics	x														
AEs	x ^c	ongoing ^c												x ^c	x ^c
Concomitant medications ^c	x ^f	ongoing ^f												x ^f	x ^f
Complete physical examination	x														
Limited physical examination ^g		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Height	x														
Weight	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs ^h	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECOG PS	x														
Hematology ^{i, j, k}	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum chemistry ^{i, k, m}	x ^m	x ^m	x ⁿ	x ⁿ	x ^m	x ⁿ	x ⁿ	x ^m	x ⁿ	x ⁿ	x ^m	x ⁿ	x ^m	x ^m	
INR and aPTT	x	As clinically indicated (e.g. for patients on anticoagulation therapy)												x	
Pregnancy test ⁱ	x ⁱ							x ⁱ					x ⁱ	x ⁱ	
Laboratory urinalysis ^o	x	As clinically indicated													
Blood sample for exploratory biomarker research	x												every 3 months		
Blood sample for PK ^p	x	x	x	x	x							x			
Blood sample HER2 ECD	x				x							x			
Blood sample for retrospective genotyping ^q	x														
ATA ^r	x									x		x		x	
Hepatitis B/C serology, HIV	x														
12-lead ECG ^s	x	As clinically indicated													
LVEF by ECHO (or MUGA) ^t	x ^t		x ^t					x ^t			every 3 rd cycle	x ^t		x ^t	
Tumor tissue for exploratory biomarker research ^u	x												x ^t	x ^t	
Tumor assessment ^{2, 3, 5}	x ^{2, 3, 5}	every 6 weeks ^{2, 3, 5}												x ^{2, 3, 5}	x ^{2, 3, 5}
Bone scan ^{4, 6}	x ^{4, 6}	As clinically indicated													
Trastuzumab emtansine administration/distribution ⁶		x(A)	x(A)	x(A)	x(A)	x(A)	x(A)	x(A)	x(A)	x(A)	x(A)	x(A)	x(A)		

^a Informed Consent must be obtained prior to performance of any study related procedure unless the assessments were performed as standard of care prior to obtaining informed consent and within 2 weeks prior to study entry.

^b HER2 status (IHC3+) should be completed within 28 days prior to baseline, however a maximum of 2 years is accepted unless otherwise stated.

^c After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs will be reported until 28 days after the last dose of study drug. After this period, the Sponsor should be notified in the investigator becomes aware of any SAE that is believed to be related to prior study drug treatment (see Section 5.6).

^d Performed 30 days (+/- 7 days) after the last dose of study treatment. Patients who discontinue study treatment will be asked to return to the clinic 4-6 weeks after the last dose of study drug for study drug completion visit. If the reason for study drug discontinuation is other than PD, tumor

assessments should be continued to be performed every 6 weeks from the first dose of study drug until PD or death

^e After completion of treatment, patients will be followed up for survival in a 3-monthly schedule until 18 months after LPI.

^f Record all concomitant therapy (non-investigational products), which includes prescription medication, over-the-counter preparation, herbal therapy, or radiotherapy used by a patient between the 28 days preceding date of first dose of study drug and the study drug completion/early termination visit.

^g Limited symptom-directed physical examination focusing on organ systems related to potential AEs based on patient's interim medical history and/or existing AE profiles of the study drug.

^h Systolic and diastolic blood pressure, pulse rate, oxygen saturation, respiratory rate, temperature should all be collected at screening, pre-dose, every 15 (+/- 5) minutes during the first trastuzumab emtansine infusion and 60 (+/-10) minutes after the infusion. In subsequent cycles, vital signs should be recorded within 60 minutes pre- and post-infusion. Abnormal or significant changes to vital signs from baseline should be recorded as an AE.

ⁱ Includes hemoglobin, hematocrit, platelet count, RBCs, WBCs; differentials including neutrophils, lymphocytes, monocytes, eosinophils and basophils.

^j Assessments should be performed at screening, on Day 1 of all cycles, and weekly following any hematologic AE. Local laboratory assessments should be performed within 72 hours preceding trastuzumab emtansine administration unless otherwise specified. Results of these local laboratory assessments must be reviewed and the review documented prior to trastuzumab emtansine administration.

^k For AEs associated with abnormal laboratory values, assessments should be performed at a minimum weekly until recovery to Grade \leq 2. Additional assessments may be done as clinically indicated.

^l For women of childbearing potential (including premenopausal women who have had a tubal ligation) and for women not considered post-menopausal, a serum b-HCG pregnancy test must be performed at a local laboratory within 7 days prior to the first administration of study drug (Day 1, Cycle 1). Urine pregnancy tests will be performed at specified subsequent visits (every 3 cycles, study completion visit, at 3 and 6 months (+/- 2 weeks) after last dose of study drug) within 7 days prior to receiving further study drug. All positive urine pregnancy tests must be confirmed by a serum b-HCG test.

^m Glucose, blood urea nitrogen (BUN)/urea, creatinine, sodium, potassium, bicarbonate, phosphorus, chloride, calcium, uric acid, total protein, albumin, total and direct bilirubin, alkaline phosphatase, LDH, ALT, AST, and GGT.

ⁿ AST, ALT, GGT, and total bilirubin only.

^o includes specific gravity, pH, protein, glucose, blood, ketones, bilirubin and microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria.

^p Six sampling timepoints in Cycle 1 (Day 1, Day 8, and Day 15, each predose and 15-30 minutes postdose), one sampling timepoint in Cycle 2 (Day 1, predose), and two sampling timepoints in Cycle 4 (Day 1, predose and 15 30 minutes postdose).

^q To be taken at baseline (Cycle 1, Day 1)

^r Samples for ATA assessment will be collected before dosing in Cycles 1 and 4, at the study drug completion visit, and 3 months after the last trastuzumab emtansine dose.

^s ECGs for each patient should be obtained from the same machine whenever possible. One set of all ECG tracings should be printed and kept with the patient's record.

^t Cardiac monitoring (ECHO/MUGA) will be performed in all patients enrolled in the study. Assessments will occur during the screening period, between Days 15 and 21 in Cycles 1 and 3, and between Days 15 and 21 of every 3rd cycle thereafter (Cycle 6, 9 etc). ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed \geq 28 days after last study treatment administration or if no post-treatment evaluation was performed. The LVEF follows the actual treatment cycle. Dose modification of study drug will follow the algorithm/process described in [Table 2](#).

¹ An optional tissue biopsy is taken at discontinuation of trastuzumab emtansine, either due to PD, unacceptable toxicity of systemic treatment or any other reason.

² Every 6 weeks from the start date of the study drug, regardless of dose delay or early discontinuation, until PD or study termination. Tumor assessments obtained within 28 days of Cycle 1, Day 1 may be used for screening purposes. Tumor assessments with CT or MRI scans of the chest, abdomen, and pelvis are to be performed every 6 weeks (+/- 3 business days). Response must be assessed through physical examination and imaged-based evaluation,

using RECIST 1.1. Assessments should include an evaluation of all known or suspected sites of disease whenever possible. The same radiographic procedure used to define measurable disease sites at baseline must be used throughout the study.

³ If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessments, unless signs of clinical progression are present. In cases where there is suspicion of clinical progression before the next scheduled assessment, an unscheduled assessment should be performed.

⁴ A CT or MRI of the brain and an isotope bone scan will be performed at screening. The bone scan and/or X-ray should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions.

⁵ At the investigator's discretion, CT scans, MRI scans, and/or bone scans may be obtained at any time when clinically indicated or if PD is suspected.

⁶ A = Regimen A (trastuzumab emtansine weekly, 2.4 mg/kg). Trastuzumab emtansine should be given over 90 minutes for the first dose and, in the absence of infusion-related AEs, over 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

Regimen B (Trastuzumab emtansine 3.6 mg/kg 3-weekly)

	Screening	Cycle 1 (day)			Cycle 2 (day)			Cycle 3 (day)			Cycle 4+ (day)			Study Drug Completion Visit ^d	Survival Follow-Up ^e
	-28 to 0	1	8	15	1	8	15	1	8	15	1	8	15		
Informed Consent ^a	x														
Assignment of patient numbers through the IwRS	x														
Tumor tissue for HER2 status testing ^b	x														
Medical history and demographics	x														
AEs	x ^c													x ^c	x ^c
Concomitant medications ^f	x ^f													x ^f	x ^f
Complete physical examination	x														
Limited physical examination ^g		x			x			x		x		x		x	x
Height	x														
Weight	x	x			x			x		x		x			
Vital signs ^h	x	x			x			x		x		x		x	
ECOG PS	x	x			x			x		x		x		x	
Hematology ^{i, j, k}	x	x			x			x		x		x		x	
Serum chemistry ^{j, k, m}	x ^m	x ^m			x ^m			x ^m		x ^m		x ^m			
INR and aPTT	x											x			
Pregnancy test ^l	x ^l							x ^l				x ^l		x ^l	
Laboratory urinalysis ⁿ		x													
Blood sample for exploratory biomarker research	x				x			x				every 3 months			
Blood sample for PK ^o	x				x						x				
Blood sample HER2 ECD	x				x						x				
Blood sample for retrospective genotyping ^p	x														
ATA ^q	x								x		x		x	x	
Hepatitis B/C serology, HIV	x														
12-lead ECG ^r	x														
LVEF by ECHO (or MUGA) ^s	x ^s				x ^s					x ^s		x ^s			
Tumor tissue for exploratory biomarker research ^t	x											x ^t			
Tumor assessment ^{2, 3, 5}	x ^{2, 3, 5}											x ^{2, 3, 5}		x ^{2, 3, 5}	
Bone scan ^{4, 6}	x ^{4, 6}														
Trastuzumab emtansine administration/distribution ⁶		x(B)			x(B)			x(B)		x(B)					

^a Informed Consent must be obtained prior to performance of any study related procedure unless the assessments were performed as standard of care prior to obtaining informed consent and within 2 weeks prior to study entry.

^b HER2 status (IHC3+) should be completed within 28 days prior to baseline, however a maximum of 2 years is accepted unless otherwise stated.

^c After informed consent has been obtained but prior to initiation of study drug, only SAEs caused by a protocol-mandated intervention should be reported. After initiation of study drug, all AEs will be reported until 28 days after the last dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any SAE that is believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each AE until the event has

resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

^d Performed 30 days (+/- 7 days) after the last dose of study treatment. Patients who discontinue study treatment will be asked to return to the clinic 4-6 weeks after the last dose of study drug for study drug completion visit. If the reason for study drug discontinuation is other than PD, tumor assessments should be continued to be performed every 6 weeks from the first dose of study drug until PD or death.

^e After completion of treatment, patients will be followed up for survival in a 3-monthly schedule until 18 months after LPI.

^f Record all concomitant therapy (non-investigational products), which includes prescription medication, over-the-counter preparation, herbal therapy, or radiotherapy used by a patient between the 28 days preceding date of first dose of study drug and the study drug completion/early termination visit.

^g Limited symptom-directed physical examination focusing on organ systems related to potential AEs based on patient's interim medical history and/or existing AE profiles of the study drug.

^h Systolic and diastolic blood pressure, pulse rate, oxygen saturation, respiratory rate, temperature should all be collected at screening, pre-dose, every 15 (+/- 5) minutes during the first trastuzumab emtansine infusion and 60 (+/-10) minutes after the infusion. In subsequent cycles, vital signs should be recorded within 60 minutes pre- and post-infusion. Abnormal or significant changes to vital signs from baseline should be recorded as an AE.

ⁱ Includes hemoglobin, hematocrit, platelet count, RBCs, WBCs; differentials including neutrophils, lymphocytes, monocytes, eosinophils and basophils. For Regimen B, laboratory assessments need only be performed in conjunction with a clinical visit, i.e. every 3 weeks on Day 1 of each cycle.

^j Assessments should be performed at screening, on Day 1 of all cycles, and weekly following any hematologic AE. Local laboratory assessments should be performed within 72 hours preceding trastuzumab emtansine administration unless otherwise specified. Results of these local laboratory assessments must be reviewed and the review documented prior to trastuzumab emtansine administration.

^k For AEs associated with abnormal laboratory values, assessments should be performed at a minimum weekly until recovery to Grade \leq 2. Additional assessments may be done as clinically indicated.

^l For women of childbearing potential (including premenopausal women who have had a tubal ligation) and for women not considered post-menopausal, a serum b-HCG pregnancy test must be performed at a local laboratory within 7 days prior to the first administration of study drug (Day 1, Cycle 1). Urine pregnancy tests will be performed at specified subsequent visits (every 3 cycles, study completion visit, at 3 and 6 months (+/- 2 weeks) after last dose of study drug) within 7 days prior to receiving further study drug. All positive urine pregnancy tests must be confirmed by a serum b-HCG test.

^m Glucose, blood urea nitrogen (BUN)/urea, creatinine, sodium, potassium, bicarbonate, phosphorus, chloride, calcium, uric acid, total protein, albumin, total and direct bilirubin, alkaline phosphatase, LDH, ALT, AST, and GGT.

ⁿ Includes specific gravity, pH, protein, glucose, blood, ketones, bilirubin and microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria.

^o Two sampling timepoints in Cycle 1 (Day 1 predose and 15-30 minutes postdose), one sampling timepoint in Cycle 2 (Day 1, predose), and two sampling timepoints in Cycle 4 (Day 1, predose and 15-30 minutes postdose).

^p To be taken at baseline (Cycle 1, Day 1).

^q Samples for ATA assessment will be collected before dosing in Cycles 1 and 4, at the study drug completion visit, and 3 months after the last trastuzumab emtansine dose.

^r ECGs for each patient should be obtained from the same machine whenever possible. One set of all ECG tracings should be printed and kept with the patient's record.

^s Cardiac monitoring (ECHO/MUGA) will be performed in all patients enrolled in the study. Assessments will occur during the screening period, between Days 15 and 21 in Cycles 1 and 3, and between Days 15 and 21 of every 3rd cycle thereafter (Cycle 6, 9 etc). ECHO or MUGA will be performed following study treatment discontinuation only if the most recent follow-up ECHO/MUGA was performed \geq 28 days after last study treatment administration or if no post-treatment evaluation was performed. The LVEF follows the actual treatment cycle. Dose modification of study drug will follow the algorithm/process described in Table 2.

¹ An optional tissue biopsy is taken at discontinuation of trastuzumab emtansine, either due to PD, unacceptable toxicity of systemic treatment or any other reason.

² Every 6 weeks from the start date of the study drug, regardless of dose delay or early discontinuation, until PD or study termination. Tumor assessments obtained within 30 days of Cycle 1, Day 1 may be used for screening purposes. Tumor assessments with CT or MRI scans of the chest, abdomen, and pelvis are to be performed every 6 weeks (+/- 3 business days). Response must be assessed through physical examination and imaged-based evaluation, using RECIST 1.1. Assessments should include an evaluation of all known or suspected sites of disease whenever possible. The same radiographic procedure used to define measurable disease sites at baseline must be used throughout the study.

³ If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessments, unless signs of clinical progression are present. In cases where there is suspicion of clinical progression before the next scheduled assessment, an unscheduled assessment should be performed.

⁴ A CT or MRI of the brain and an isotope bone scan will be performed at screening. The bone scan and/or X-ray should be repeated in the event of clinical suspicion of progression of existing bone lesions and/or the development of new bone lesions.

⁵ At the investigator's discretion, CT scans, MRI scans, and/or bone scans may be obtained at any time when clinically indicated or if PD is suspected.

⁶ B = Regimen B (trastuzumab emtansine 3-weekly, 3.6 mg/kg). Trastuzumab emtansine should be given over 90 minutes for the first dose and, in the absence of infusion-related AEs, over 30 minutes in subsequent doses. Vital signs should be taken before and after the trastuzumab emtansine infusion. Patients will be monitored for any untoward effects for at least 90 minutes after completion of the first trastuzumab emtansine infusion and, in the absence of infusion-related events, for a minimum of 30 minutes at subsequent infusions.

Appendix 3 List of Outputs

Outputs Number	Output Title	Population	Topline outputs for SREP
TABLES			
14.1.1.1.x	Patient Disposition	SAF	X
14.1.1.2.x	Patient Discontinuation and Early Termination	SAF	X
14.1.2.x	Enrolment by Country and Site	SAF	
14.1.3.x	Median Follow-up Duration	SAF	
14.1.4.x	Protocol Deviations	SAF	X
Demographics and Baseline Characteristics			
14.1.5.x	Summary of Baseline and Demographic Characteristics	SAF	X
14.1.6.a	Summary of Metastatic Urothelial Bladder Cancer History	SAF	X
14.1.6.b	Summary of Pancreas/Cholangio Cancer History	SAF	X
14.1.7.x	Summary of Prior Anti-Cancer Treatment/Procedures	SAF	X
14.1.8.x	Prior Anti-Cancer Therapies	SAF	
Exposure			
14.1.9.x	Summary of Drug Exposure	SAF	X
14.1.10.x	Summary of Infusion Interrupted or Delayed	SAF	
14.1.11.x	Summary of Infusion Rate Reduction	SAF	
Efficacy			
Overall Response Rate			
14.2.1.1.x	Summary of Overall Response Rate and Duration of Response as per Investigator	SAF	X
14.2.1.2.x	Summary of Overall Response Rate as per Investigator, by Cell Heterogeneity	SAF	X
Progression Free Survival			
14.2.2.x	Summary of Progression Free Survival as per Investigator	SAF	X
Overall Survival			
14.2.3.x	Summary of Overall Survival	SAF	X
Safety			

Outputs Number	Output Title	Population	Topline outputs for SREP
	AEs		
14.3.1.1.x	Overview of Treatment Emergent Adverse Events	SAF	X
14.3.1.2.x	Treatment-Emergent Adverse Events by SOC and PT and by Worst Intensity	SAF	
14.3.1.3.x	Treatment-Emergent Adverse Events Related to Trastuzumab Emtansine by SOC and PT and by Worst Intensity	SAF	
14.3.1.4.x	Selected Treatment-Emergent Adverse Events by Grouped Term and by Worst Intensity	SAF	X
14.3.1.5.x	Treatment Emergent Adverse Events of Grade 3 or More by SOC and PT	SAF	X
14.3.1.6.x	Serious Treatment Emergent Adverse Events by SOC and PT	SAF	X
14.3.1.7.x	Serious Treatment Emergent Adverse Events Related to Trastuzumab Emtansine by SOC and PT	SAF	
14.3.1.8.x	Treatment Emergent Adverse Events Leading to Discontinuation of Trastuzumab Emtansine by SOC and PT	SAF	X
14.3.1.9.x	Treatment Emergent Adverse Events Leading to Modification of Trastuzumab Emtansine by SOC and PT	SAF	
14.3.1.10.x	Treatment Emergent Adverse Events with Fatal Outcome by SOC and PT	SAF	X
14.3.1.11.x	Treatment-Emergent Adverse Event of Special Interest (AESI) Based on the eCRF Categories by SOC and PT	SAF	X
14.3.1.12.x	Serious Treatment-Emergent Adverse Event of Special Interest (AESI) Based on the eCRF Categories by SOC and PT	SAF	
14.3.1.13.x	Serious Treatment-Emergent Adverse Events - EudraCT Disclosure Requirements Data	SAF	
14.3.1.14.x	Non-Serious Treatment-Emergent Adverse Events Reported in $\geq 5\%$ of Subjects - EudraCT Disclosure Requirements Data	SAF	
14.3.1.15.x	Overview of Infusion-Related Reactions	SAF	
14.3.1.16.x	Infusion-Related Reactions_by SOC and PT and by Worst Intensity	SAF	
14.3.1.17.x	Infusion-Related Reactions_Related to Trastuzumab Emtansine by SOC and PT and by Worst Intensity	SAF	
14.3.1.18.x	Infusion-Related Reactions_of Grade 3 or More by SOC and PT	SAF	
14.3.1.19.x	Serious Infusion-Related Reactions_by SOC and PT	SAF	
14.3.1.20.x	Serious Infusion-Related Reactions Related to Trastuzumab Emtansine by SOC and PT	SAF	
14.3.1.21.x	Deaths and Reason for Death	SAF	X

Outputs Number	Output Title	Population	Topline outputs for SREP
	Other Safety Assessments		
14.3.7.1.x	Left Ventricular Ejection Fraction Over Time	SAF	
14.3.7.2.x	Left Ventricular Ejection Fraction Worst on Treatment Value	SAF	
	Biomarkers		
14.3.8.1	Summary of HER2 Status - Immunohistochemistry (IHC)	SAF	
14.3.8.2	Summary of HER2 Status - Gene Protein Assay by Immunohistochemistry (IHC)	SCR	
	Figures		
	Efficacy		
14.2.2.x	Kaplan Meier Plot for Progression Free Survival as per Investigator	SAF	
14.2.3.x	Kaplan Meier Plot for Overall Survival	SAF	
	Safety		
14.3.7.1.x	Boxplot of LVEF Over Time	SAF	
	LISTINGS		
	Patient Disposition		
16.2.1.x	Subject Disposition and Study Termination Information	SAF	
16.2.2.x	Protocol Deviations	SAF	
16.2.3.x	Analysis Populations	SAF	
	Demographics and Baseline Characteristics		
16.2.4.1.x	Demographics and Baseline Characteristics	SAF	
16.2.4.2.a	Metastatic Urothelial Bladder Cancer History	SAF	
16.2.4.2.b	Pancreas/Cholangio Cancer History	SAF	
16.2.4.3.x	Medical History	SAF	
16.2.4.4.a	Prior Surgery other than for Metastatic Urothelial Bladder Cancer	SAF	
16.2.4.4.b	Prior Surgery History other than for Pancreas/Cholangio Cancer	SAF	
16.2.4.5.a	Prior Metastatic Urothelial Bladder Cancer Surgery	SAF	
16.2.4.5.b	Prior Pancreas/Cholangio Cancer Surgery	SAF	
16.2.4.6.x	Prior Systemic Cancer Therapy	SAF	
16.2.4.7.x	Prior Cancer Radiotherapy	SAF	
16.2.4.8.x	On-Study Cancer Surgery	SAF	

Outputs Number	Output Title	Population	Topline outputs for SREP
16.2.4.9.x	On-Study Cancer Radiotherapy	SAF	
16.2.4.10.x	Prior and Concomitant Medications	SAF	
16.2.4.11.x	Subsequent Anti-Cancer Therapy	SAF	
	Drug Administration		
16.2.5.1.x	Trastuzumab Emtansine Administration	SAF	
16.2.5.2.x	Drug Exposure	SAF	
	Efficacy		
16.2.6.1.x	Individual Tumor Assessment and Overall Response as per Investigator	SAF	
16.2.6.2.x	Best Overall Response and duration of response	SAF	
16.2.6.3.x	Progression-Free Survival as per Investigator	SAF	
16.2.6.4.x	Overall Survival	SAF	
	Safety		
16.2.7.1.x	Adverse Events	SAF	
16.2.7.1.1.x	Adverse Events with Missing or Partial Start Date	SAF	
16.2.7.2.x	Adverse Events of Grade 3 or More	SAF	
16.2.7.3.x	Serious Adverse Events	SAF	
16.2.7.4.x	Adverse Events Leading to Treatment Discontinuation	SAF	
16.2.7.5.x	Adverse Events of Special Interest	SAF	
16.2.7.6.x	Selected Adverse Events	SAF	
16.2.7.7.x	Infusion Related Reactions	SAF	
16.2.7.8.x	Deaths	SAF	
16.2.8.1.x	Laboratory Values: Hematology	SAF	
16.2.8.2.x	Laboratory Values: Biochemistry	SAF	
16.2.8.3.x	Laboratory Values: Coagulation	SAF	
16.2.8.4.x	Laboratory Abnormalities: Hematology	SAF	
16.2.8.5.x	Laboratory Abnormalities: Biochemistry	SAF	
16.2.8.6.x	Laboratory Abnormalities: Coagulation	SAF	
16.2.8.7.x	Laboratory Values: Urinalysis	SAF	
16.2.8.8.x	Serology	SAF	
16.2.8.9.x	Pregnancy Test	SAF	
16.2.9.1.x	Vital Signs	SAF	
16.2.9.2.x	ECOG Performance Status	SAF	

Outputs Number	Output Title	Population	Topline outputs for SREP
16.2.9.3.x	Left Ventricular Ejection Fraction	SAF	
16.2.9.4.x	Electrocardiograms	SAF	
Biomarker			
16.2.10.1.x	Biomarker: HER2 IHC	SAF	
16.2.10.2	Biomarker: HER2 IHC and Gene Protein Assay	SCR	