Merus

# MCLA-128-CL02

# Phase II study of MCLA-128-based combinations in metastatic breast cancer (MBC): MCLA-128/trastuzumab/chemotherapy in HER2-positive MBC and MCLA-128/endocrine therapy in estrogen receptor positive and low-HER2 expression MBC

# Statistical analysis plan (SAP)

| | |
|---|---|
| **PROJECT:** | **MCLA-128-CL02** |
| **VERSION:** | **Amendment 1** |
| **DATE:** | **07 December 2022** |

# 1 APPROVAL PAGE

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## 2 HISTORY OF CHANGES

| Date, author | Changes |
|---|---|
| 17-Sep-2020, Anne-Sophie Le Bescond (4Clinics) | Original version |
| 20-Aug-2021, Manon Andre (4Clinics) | Amendment 1<br><br>-To replace “Treated population” by “Safety Set” and “Evaluable for efficacy population” by “Per-protocol Efficacy Set” to be CDISC compliant<br><br>-To update the definition of on-treatment period<br><br>-To update the list of tables and figures<br><br>-To suppress randomization wording as no randomization done<br><br>-To add the grading for Corrected Calcium |
| 16-Dec-2021, Manon André (4Clinics) | Addition of derivation of emergence, relationship and severity for AEs with missing information<br>Update safety set definition |
| 25-Nov-2022, Tioka Rabeony (4Clinics) | Clarification on efficacy set, endpoints definition,<br>Other changes from original version:<br>• sensitivity analyses are rewritten for clarity;<br>• On-treatment period (Section 2.1) is redefined at from the date of first administration of study treatment to 30 days after last dose of study treatment including start and stop date, instead of 35 days after |

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# 4 ABBREVIATIONS

| | |
|---|---|
| ADCC | Antibody-Dependent Cell-Mediated Cytotoxicity |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ALT | Alanine Transaminase |
| ALP | Alkaline Phosphatase |
| AST | Aspartate Transaminase |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area Under The Curve |
| BMI | Body Mass Index |
| BOR | Best Overall Response |
| BSA | Body Surface Area |
| CBR | Clinical Benefit Rate |
| CI | Confidence Interval |
| CL | Clearance |
| $C_{max}$ | Maximum Drug Concentration |
| CR | Complete Response/Complete Remission |
| CSR | Clinical Study Report |
| CT | Computed Tomography |
| CTCAE | Common Terminology Criteria For Adverse Events |
| ctDNA | Circulating Tumor DNA |
| CTP | Clinical Trial Protocol |
| DI | Dose Intensity |
| DOR | Duration of Response |
| DSUR | Development Safety Update Report |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EOI | End of Infusion |
| EOT | End of Treatment |
| ER | Estrogen Receptor |
| FDA | Food and Drug Administration |
| FISH | Fluorescence In Situ Hybridization |
| HER | Human Epidermal Growth Factor Receptor |
| HGLT | High Level Group Term |
| HLT | High Level Term |
| HR | Heart Rate |
| HRG | Heregulin |
| IB | Investigator's Brochure |
| IDMC | Independent Data Monitoring Committee |
| IG | Immunogenicity |
| IHC | Immunohistochemistry |
| IRR | Infusion-Related Reaction |
| IV | Intravenous |
| LLOQ | Lower Limit Of Quantitation |
| LVEF | Left Ventricular Ejection Fraction |
| MBC | Metastatic Breast Cancer |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MUGA | Multiple Gated Acquisition |
| MRI | Magnetic Resonance Imaging |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| PD | Progressive Disease |

| | |
|---|---|
| PDI | Planned Dose Intensity |
| PFS | Progression-Free Survival |
| PK | Pharmacokinetic(s) |
| PO | Per Os |
| PR | Partial Response/Partial Remission |
| PT | Preferred Term |
| QD | Once Daily |
| q3w | Once Every 3 Weeks |
| QTcF | Corrected QT Interval by Fredericia |
| RDE | Recommended Dose for Expansion |
| RDI | Relative Dose Intensity |
| RECIST | Response Evaluation Criteria In Solid Tumors |
| RQ-PCR | Real-Time Quantitative Polymerase Chain Reaction |
| RT-PCR | Reverse Transcription Polymerase Chain Reaction |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SD | Stable Disease |
| SOC | System Organ Class |
| SMQ | Standardized MedDRA Queries |
| $t_{1/2}$ | Terminal half-Life |
| $T_{max}$ | Time to Maximum Plasma Concentration |
| TBL | Total Bilirubin |
| TFL | Tables, Figures, Listings |
| TTR | Time To Response |
| ULN | Upper Limit of Normal |
| UNK | Unknown |
| V | Apparent Volume Of Distribution |
| Vss | Volume Of Distribution At Steady State |
| WBC | White Blood Cell |
| WHO-DD | World Health Organization – Drug Dictionary |

# 5 INTRODUCTION

This document provides the statistical analysis plan (SAP) of the preplanned analysis for the Clinical Study Report (CSR) of study MCLA-128-CL02.

This SAP provides detailed statistical methodology for the analysis of data that will be presented in the CSR. This version of the SAP is based on the Protocol version 5.0 (11 April 2022).

The details for the methodology and conventions that will be used for the analysis of pharmacokinetics (PK) data of the study MCLA-128-CL02 are described in a separate PK analysis plan.

All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document without the need to amend.

The SAP may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., IB updates, development safety update report (DSUR), maximum tolerated dose/ recommended dose for expansion (MTD/RDE) declaration, abstracts, posters, presentations, manuscripts.

This SAP presents information relevant to the analyses that will be performed. Clinical background information is available in the clinical trial protocol (CTP).

## 5.1 Study design

This is a phase 2, open-label, multicenter international study to evaluate the efficacy of MCLA-128-based combinations in two metastatic breast cancer (MBC) populations, HER2-positive/amplified (Cohort 1) and estrogen receptor (ER)-positive/low HER2 expression (Cohort 2). Three combination treatments are being evaluated, two in Cohort 1 and one in Cohort 2, in 20-30 sites in 7 countries in Europe and the USA.

**Figure 1: Study design for Cohort 1 combination therapies (doublet and triplet)**

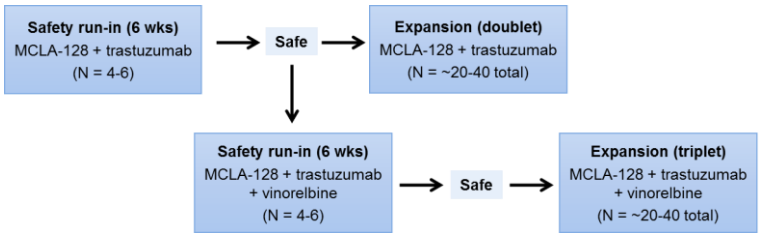
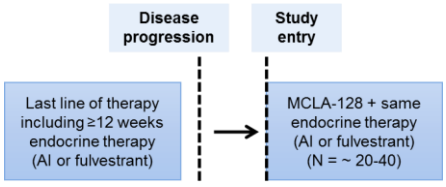


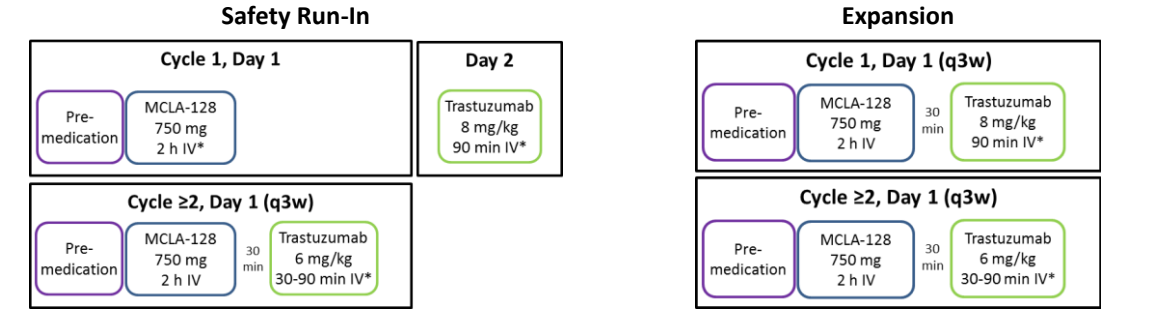

**Figure 2: Study design for Cohort 2 combination therapies**



An Independent Data Monitoring Committee (IDMC), composed of at least 2 physicians expert in the domain of early clinical development in MBC, reviews safety and efficacy throughout the study and decides on the addition of extra patients in the expansion parts, opening of the triple combination cohorts, and any *ad hoc* safety decisions.

For all combinations a cycle is considered 3 weeks (including Cohort 2 which may include q4w fulvestrant dosing).

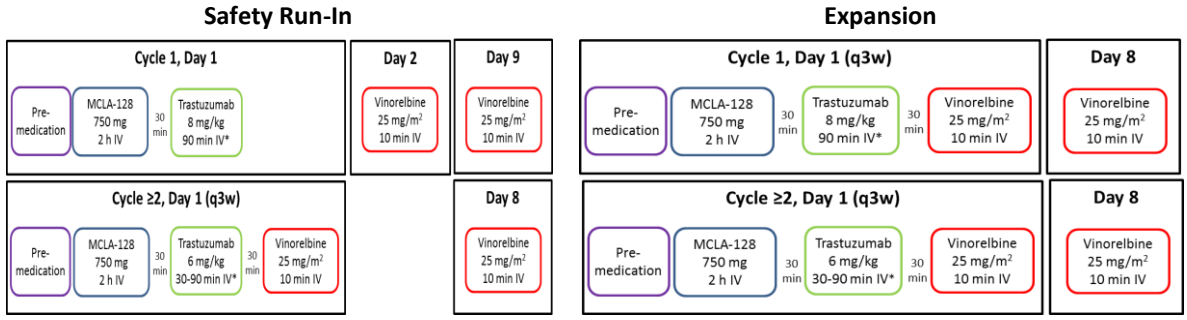
**Figure 3: Cohort 1 Doublet treatment administration**




* Followed by a 6-hour observation period from infusion start, for the initial administration and 2 hours for all subsequent administrations.
For Cycle 2, trastuzumab must be infused over 90 min

* Followed by a 6-hour observation period from infusion start, for the initial administration and 2 hours for all subsequent administrations.
For Cycle 2, trastuzumab must be infused over 90 min

**Figure 4: Cohort 1 Triplet treatment administration**

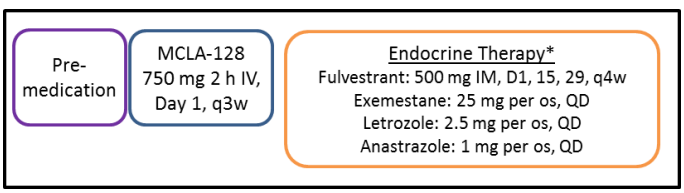



* Followed by a 6-hour observation period from infusion start, for the initial administration and 2 hours for all subsequent administrations.
For Cycle 2, trastuzumab must be infused over 90 min

* Followed by a 6-hour observation period from infusion start, for the initial administration and 2 hours for all subsequent administrations.
For Cycle 2, trastuzumab must be infused over 90 min

For both the doublet and the triplet combinations, if an individual patient does not tolerate all drugs on the same day, the safety run-in Cycle 1 dosing schedule is maintained for that patient.

**Figure 5: Treatment administration for Cohort 2 (all cycles)**




A 6-hour observation period will be implemented following infusion start for the initial MCLA-128 administration, and 2 hours for all subsequent administrations.

* Same endocrine therapy under which the patient progressed prior to study entry. Can be administered before, during, or immediately after the MCLA-128 infusion.

Study treatment is administered until confirmed progressive disease (as per RECIST 1.1), unacceptable toxicity, withdrawal of consent, patient non-compliance, investigator decision (e.g. clinical deterioration), treatment interruption > 6 consecutive weeks, withdrawal of any study drug. Patients will be followed up for safety for at least 35 ± 5 days following the last study drug administration and until recovery/stabilization of related toxicities, and for disease progression and survival status for 1 year and for LVEF assessments for 2 years.

No formal interim analysis is planned.

### 5.2 Study objectives and endpoints

**Cohort 1: MCLA-128 + Trastuzumab ± Vinorelbine in HER2-Positive/Amplified MBC**

Primary objective:

- Evaluate efficacy of MCLA-128 combined with trastuzumab ± vinorelbine in terms of clinical benefit rate (CBR) at 24 weeks based on RECIST 1.1 (per investigator review) in HER2-positive/amplified MBC patients who have progressed on prior HER2-directed therapy that included trastuzumab, pertuzumab, and an HER2 antibody drug conjugate (ADC) in any sequence and in any setting.

Secondary objectives:

- Evaluate CBR at 24 weeks based on RECIST 1.1 per central review
- Evaluate progression-free survival (PFS; per investigator and central review)
- Evaluate overall response rate (ORR) based on RECIST 1.1 (per investigator and central review)
- Evaluate duration of response (DOR) based on RECIST v1.1 (per investigator and central review)
- Evaluate overall survival (OS)
- Evaluate safety and tolerability of MCLA-128 in combination with trastuzumab ± vinorelbine
- Characterize pharmacokinetics (PK) of MCLA-128 in combination with trastuzumab ± vinorelbine
- Characterize immunogenicity of MCLA-128 in combination with trastuzumab

Exploratory objective:

- Evaluate potential correlations between biomarkers in tumor or blood samples and antitumor activity (including HER2, HER3, HER2:HER3 dimers, heregulin and other potential biomarkers)

**Cohort 2: MCLA-128 + Endocrine Therapy in Estrogen Receptor [ER]-Positive/Low HER2 Expression MBC**

Primary objective:

- Evaluate efficacy of MCLA-128 combined with endocrine therapy in terms of CBR at 24 weeks based on RECIST 1.1 (per investigator review) in ER-positive and low HER2 expression MBC patients who have previously progressed on the same endocrine therapy.

Secondary objectives:

- Evaluate CBR at 24 weeks based on RECIST 1.1 per central review

- Evaluate PFS (per investigator and central review)
- Evaluate ORR based on RECIST 1.1 (per investigator and central review)
- Evaluate DOR based on RECIST 1.1 (per investigator and central review)
- Evaluate OS
- Evaluate safety and tolerability of MCLA-128 combined with endocrine therapy
- Characterize PK of MCLA-128 combined with endocrine therapy
- Characterize immunogenicity of MCLA-128 combined with endocrine therapy

Exploratory objective:

- Evaluate potential correlations between biomarkers in tumor or blood samples and antitumor activity (including HER2, HER3, HER2:HER3 dimers, heregulin and other potential biomarkers)

**Endpoints**

Primary

*Cohorts 1 and 2:* CBR per investigator radiologic review at 24 weeks

Key secondary

*Cohort 1:* CBR at 24 weeks per central review, and ORR, PFS, and DOR per investigator and central review

*Cohort 2:* CBR at 24 weeks per central review, and PFS per investigator and central review

Other secondary (both cohorts):

*Safety:* Incidence, severity and relationship of AEs, laboratory abnormalities, SAEs, ECG and LVEF measurements and vital signs

*Tolerability:* discontinuations due to AEs, dose modifications due to AEs, immunogenicity, and cytokine assessments

*Other efficacy:* DOR (Cohort 2), PFS ratio (Cohort 2), ORR (Cohort 2), and OS (Cohorts 1 and 2)

*Pharmacokinetics:* $C_{max}$, $C_{0h}$, AUC, CL, $V_{ss}$, $t_{max}$ and $t_{1/2}$ for MCLA-128, and $C_{EOI}$ and $C_{0h}$ for trastuzumab.

### 5.3 Sample size

Cohort 1 safety run-in: 4 to 6 evaluable patients in the safety run-in will have power of 80 to 90% to detect an AE with a true incidence of 33%.

Cohort 1 efficacy expansion: 40 evaluable patients with observed CBR of > 45% will provide adequate precision to exclude 30% (lower limit of 90% CI > 30%). The threshold for the CBR rate at 24 weeks is defined based on the assumption that PFS follows an exponential distribution with a median of 5 months (clinically relevant) and 3.5 months (not clinically relevant).

Cohort 2: 40 evaluable patients with observed CBR of at least 45% will provide enough precision to exclude 30% (lower limit of 90% CI > 30%). The threshold for CBR at 24 weeks is defined based on the assumption that PFS follows an exponential distribution with a median of 5 months (clinically relevant) and 3.5 months (not clinically relevant).

The final number of patients will depend on the safety and efficacy outcomes during the study. Up to ~130 patients are anticipated, allowing for a total of 40 patients in each of the three planned combination regimens and a ~10% rate of non-evaluable patients

# 6 Data analysis and statistical methods

## 6.1 Data analysis general information

Study data will be analyzed by Merus and/or a designated CRO(s) using the most updated SAS® version.

The timing of the primary analysis is not specified in the protocol. The analysis of the primary endpoint will be conducted once all enrolled patients complete at least 24 weeks RECIST assessment or discontinue.

The final analysis will be conducted once all patients discontinue from the study and include additional data for patients continuing to receive study treatment past the data cutoff date of the primary CSR.

Data from participating centers in this study protocol will be combined (a center effect will not be assessed). The data will be summarized for demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

Data will be summarized by cohort and treatment, i.e. Cohort 1 Triplet, Cohort 1 Doublet, Cohort 2, unless specified otherwise.

**Date of first/last administration of study treatment**

The date of first (last) administration of study treatment is derived as the first (last) date when a dose of either MCLA-128 or any combination drug (trastuzumab, vinorelbine, endocrine therapy) was administered and recorded on the dosage administration record eCRF.

**Study day**

The study day, describes the day of the event or assessment date, relative to the reference start date.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1, if the event is on / after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date, if the event precedes the reference start date.

The reference start date for all assessments (safety, efficacy etc) is the start of study treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

**Time unit**

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

**Baseline**

For all evaluations including safety and efficacy, the last available assessment on or before the date of start of study treatment is taken as the “baseline” assessment. If both time of assessment and time of

treatment start are captured (e.g. pre-dose ECG), the last available assessment before the treatment start date/time is used for baseline.

For safety parameters where the study requires multiple replicates per time point (e.g. ECGs or vital signs), the average of these measurements would be calculated for baseline if not already available in the database.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: if values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or are collected for ECGs or vital signs, then the value closest to day 1 in the dataset should be considered as baseline.

If patients have no value as defined above, the baseline result will be missing.

**Study periods**

For each patient, the overall observation period will be divided into three mutually exclusive segments:

1. Pre-treatment period: from the day of patient's informed consent to the day before the first administration of study treatment
2. On-treatment period: from the date of first administration of study treatment to 30 days after last dose of study treatment including start and stop date
3. Post-treatment period: starting at day 31 after last administration of study treatment.

If incomplete dates prevent assignment to pre-, on-, or post-treatment periods, then the respective data will be assigned to the on-treatment period.

Safety summaries will include only data from the on-treatment period with the exception of baseline data which will be summarized where appropriate, e.g. change from baseline summaries. In addition, a separate summary for death, including on-treatment and post-treatment deaths will be provided. In particular, summary tables for AEs will summarize only on-treatment events with a start date during the on-treatment period, i.e. treatment-emergent AEs.

However, all safety data, including those from the pre- and post-treatment period, will be listed, and those collected during the pre- and post-treatment period will be flagged.

### 6.2 Analysis sets

**Safety Set**

Patients who receive at least one dose of MCLA-128.

**Efficacy Set**

Patients who receive at least 2 complete cycles (6 weeks) of treatment and have undergone baseline assessment and one on-study tumor assessment, or who discontinue early due to disease progression (including deaths due to study indication).

The table below provides the rules for exclusion of patients from the efficacy population. If a patient has both central and local non-missing result, central assessment supersedes local assessment; in case the central assessment result is not available, local result will be used instead.

Note: Patients will be enrolled based on their HER2 status, hormone receptor (HR) status (Cohort 2 only), and disease progression on the prior line of therapy, as reported in their medical records. Evaluability of patients for the primary endpoint will be confirmed by central review of their HER2 status, HR status (Cohort 2 only) after enrolment.

| Analysis set | Protocol deviations leading to exclusion | Non protocol deviation leading to exclusion |
|---|---|---|
| Safety Set | No written informed consent | No dose of study medication |
| Efficacy Set | No written informed consent | Patient received less than 2 complete cycles, or was not evaluated at baseline and at least once during study, unless progressive disease was documented<br>Cohort 1: patient is not HER2-positive/amplified (by central or local lab).<br>Cohort 2:<br>- patient is not low HER2 by IHC (by central or local lab),<br>- patient is not ER positive (by central or local lab)<br>- disease progression under the last line of therapy by imaging is not confirmed (by central or local imaging review). |

When a key central result is missing then all HER2 status, hormone receptor (HR) status (Cohort 2 only) eligibility should be assessed on local results.

**Withdrawal of Informed Consent**

Any data collected in the clinical database after a patient withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent will be recorded in the site file and is not captured in the eCRF.

Additional data which are collected in the clinical database and for which there is a separate informed consent (e.g. biomarker) will not be included in the analysis if that additional consent was not given by the patient.

### 6.3 Subgroups of interest

The following subgroups are defined:

Cohort 1:

- prior lines of therapy in metastatic setting: 0-2, >2
- history of brain metastases (current or antecedent): present, absent

Cohort 2:

- HER2 IHC: 1+, 2+
- visceral involvement: present, absent
- CDK4/6 inhibitor as last treatment: yes, no
- prior treatment: up to 4 months, over 4 months
- type of hormonal therapy: fulvestrant, aromatase inhibitors

### 6.4 Patient disposition, demographics and other baseline characteristics

The Safety Set will be used for all baseline and demographic summaries and listings unless otherwise specified.

**Analysis sets**

The number (%) of patients in each analysis set will be summarized by cohort and treatment (i.e., Cohort 1 doublet, Cohort 1 triplet and Cohort 2).

**Disposition**

The number (%) of treated patients included in the Safety Set will be presented overall and by cohort and treatment. The number (%) of screened and not-treated patients and the reasons for screening failure will also be displayed. The number (%) of patients in the Safety Set who are still on treatment at the cut-off, as well as those who discontinued the study phases and the reasons for discontinuation will be presented overall and by treatment group.

A table with the following summaries will be provided (with % based on the total number of patients in the Safety Set):

- Number (%) of patients who are still on-treatment (based on the 'End of Treatment' page not completed);
- Primary reason for study treatment discontinuation (based on the 'End of Treatment' page)
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment' or 'Follow-up' page).

**Protocol deviations**

The number (%) of patients in the Safety Set with any protocol deviations will be tabulated by deviation category (as specified in the study Protocol Deviations Document) overall and by cohort and treatment for the Safety Set.
Major protocol deviations leading to exclusion from analysis sets will be tabulated separately overall and by cohort and treatment. All protocol deviations will be listed.

**Basic demographic data**

All demographic and baseline disease characteristics data will be summarized and listed by cohort and treatment (i.e., Cohort 1 doublet, Cohort 1 triplet and Cohort 2). Categorical data (e.g. gender, age groups: <65 and ≥ 65 years, race, ethnicity, performance status) will be summarized by frequency counts and percentages; the number and percentage of patients with missing data will be provided. Continuous data (e.g. age, weight, height, body surface area, body mass index) will be summarized by descriptive statistics (N, mean, median, standard deviation, minimum and maximum).

BMI (kg/m2) will be calculated as weight[kg] / (height[m]2) using height at Baseline.

Body Surface Area (BSA) will be calculated using Gehan and George formula: BSA[m2]=234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000

**Diagnosis and extent of cancer**

Summary statistics will be tabulated for diagnosis, treatment and extent of cancer. This analysis will include the following, as appropriate:

- Primary site of cancer
- Histological type
- Hormonal status at diagnosis: Progesterone-receptor staining level (IHC), estrogen-receptor staining level (IHC)
- HER2/neu status at diagnosis (IHC, FISH)
- Stage at initial diagnosis
- Time from initial diagnosis to study entry
- Time from first metastatic disease to study entry
- Most recent hormonal status, local and central assessment
- Most recent HER2 status (IHC, FISH), local and central assessment
  - HER2 IHC score (0, 1, 2, 3)
  - HER2 H-score (quantitative)
  - HER2 status (positive, negative, unknown)
  - HER2 amplification. Amplification is not assessed in all patients and for statistical summaries needs to be considered by IHC score
  - HER2:HER3 dimer score
- NRG1 score
- Stage at time of study entry
- TNM stage at study entry
- Time from most recent relapse/progression to inclusion (in months)
- Non-measurable disease only
- Number and type of metastatic sites involved including visceral and no visceral involvement
- Tumor burden at study entry (mm).

Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page. Number of metastatic sites corresponds to the number of organs involved. Non-visceral sites include bones and soft tissue (e.g., lymph nodes, skin lesions).

**Prior antineoplastic therapy**

All prior anti-neoplastic medication, radiotherapy and surgery will be listed.

The number (%) of patients who received any prior anti-neoplastic medication, radiotherapy or surgery will be summarized.

The summary of prior anti-neoplastic medications will include

- Number of prior therapies including chemotherapy, anti-HER2 and hormonal therapy

- Number of prior therapies including chemotherapy and anti-HER2 in metastatic setting
- Number of prior chemotherapy regimens
- Number of prior anti-HER2 directed therapies
- Number of prior anti-HER2 directed therapies in metastatic setting
- Number of prior hormonal therapies
- Number of patients with prior anthracycline therapy
- Best response to last treatment (defined to be the best response during the last treatment regimens recorded),
- Reason for discontinuation of last treatment,
- Time (in months) from start of last treatment to progression.

Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term.

The summary of prior anti-neoplastic radiotherapy will include radiotherapy locations, (including all locations recorded for each patient), setting at last radiotherapy, and best response at last radiotherapy, as appropriate.

The summary of prior anti-neoplastic surgery will include procedure at last surgery.

**Medical history**

A listing and a summary by SOC and PT of medical history and current medical conditions will be provided, using the latest Medical Dictionary for Regulatory Activities (MedDRA) terminology available at the time of reporting.

### 6.5 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

Incomplete or missing start and end dates will be handled as described in 7.1.1, 7.1.2 and 7.1.3.

**Study treatment**

Duration of exposure, time to last infusion, total number of infusions received, total number of cycles received, cycle duration, actual cumulative dose, dose intensity (DI) and relative dose intensity (RDI) will be summarized by cohort and treatment, separately for each component of study treatment. The duration of exposure will also be presented for the study treatment combination (MCLA-128 and any combination drug (trastuzumab, vinorelbine, endocrine therapy)). Duration of exposure will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of patients in each interval.

The number (%) of patients who have dose reductions, interruptions, delays or permanent discontinuation, and the corresponding reasons, will be tabulated.

Patient listings of all doses administered on treatment along with dose change reasons will be produced.

The Safety Set will be used for all summaries and listings of study treatment.

**Duration of exposure to study treatment**

Duration of exposure to study treatment is considered by taking into account the duration of exposure to MCLA-128 and/or any combination drug (trastuzumab, vinorelbine, endocrine therapy), if applicable:

Duration of exposure to study treatment (days) = (last date of **exposure** to study treatment) – (date of first administration of study treatment) + 1.

The last date of exposure to study treatment is the latest of the last dates of exposure to MCLA-128 and/or any combination drug (trastuzumab, vinorelbine or endocrine therapy) (see table below).

Summary of duration of exposure of study treatment in appropriate time units will include categorical summaries (based on clinically meaningful time intervals) and continuous summaries.

| Scenario | Definition of last date of exposure of study drug | Example |
|---|---|---|
| Scenario 1: Study drug with a cyclic administration (half-life in days) | The last administration of study drug planned end date of the last cycle in which the last dose of the investigational drug was last administered.<br>Note: If the patient died or was lost to follow-up before the derived last date, the last date of exposure to investigational drug is the date of death or the date of last contact, respectively.<br>If the derived last date of exposure goes beyond the data cutoff date, it should be truncated to the date of data cutoff. | Example 1: In a once a week administration of an investigational drug, the last date of exposure is the date of administration in the last cycle + 6 days.<br>Example 2: In a 21-day cycle with one or several infusions in the beginning of the cycle, the last date of exposure is the date of first infusion in the last cycle + 20 days. |
| Scenario 2: Daily administration of the study drug (half-life <24 hours) | Date of last administration of a dose of the study drug. | Example 3: A patient had a permanent discontinuation of the study drug 06Jan2013 after being put on a temporary interruption since 01Jan2013. In this case the last date of exposure is 31Dec2012. |

**Time to last infusion**

For biologics with a prolonged half-life, the duration of exposure even after 1 dose can be weeks. Therefore, the time to last infusion can be used to describe when patients received their last dose of study treatment:

Time to last infusion (days) = (date of last **infusion**) – (date of first administration of study drug) + 1

Summary of time to last infusion should be expressed in the same units as duration of exposure and will include categorical summaries (based on clinically meaningful time intervals) and continuous summaries.

**Cumulative dose**

Cumulative dose of a study treatment is defined as the total dose given during the study treatment exposure and will be summarized for each study treatment component.

The planned cumulative dose for a study treatment component refers to the total planned dose as per the protocol up to the last date of study treatment administration.

The actual cumulative dose refers to the total actual dose administered, over the duration for which the patient is on the study treatment as documented in the Dose Administration eCRF.

When the actual dose administered is not collected in eCRF (for Vinorelbine at C1 D8/9), the intended dose will be used instead .
For patients who did not take any drug, the cumulative dose is by definition equal to zero.

For continuous dosing, the actual cumulative dose is the sum of the non-zero doses recorded over the dosing period and the planned cumulative dose is the planned starting dose summed over the same dosing period.

For intermittent dosing, the actual cumulative dose should be defined based on the days when the patient is assumed to have taken a non-zero dose during dosing periods.

**Dose intensity and relative dose intensity**

DI will be described for patients with dose and dates of administration available:

DI (dosing unit / unit of time) = Actual cumulative dose (dosing unit) / Duration of exposure to study treatment (unit of time).

If the dosing unit is mg and the unit of time is a day:

e.g., DI (mg/day) = Actual cumulative dose (mg) / Duration of exposure (day)

= 1200 (mg) / 18 (Day) = 66.7 (mg/day)

For patients who did not take any drug, the DI is by definition equal to zero.

Planned dose intensity (PDI) is defined as follows:

PDI (dosing unit / unit of time) = Planned cumulative dose (dosing unit) / Duration of exposure (unit of time).

Relative dose intensity (RDI) is defined as follows:

RDI = DI (dosing unit / unit of time) / PDI (dosing unit / unit of time).

DI and RDI will be summarized for combination studies separately for each study treatment component, using the duration of exposure of each component. DI will not be summarized for endocrine therapy in Cohort 2.

**Infusion and drug interruptions, dose reductions, delays or permanent discontinuations**

The table below provides definitions and sources of data for the key categories related to dose administration.

| Option | Description | 128-CL02 |
|---|---|---|
| Dose administration CRF name | CRF page name and dataset name | MCLA-128 treatment administration (EX1 and EX1C1)<br>Trastuzumab treatment administration (EX2 and EX2C1) |

| Option | Description | 128-CL02 |
|---|---|---|
| | | Vinorelbine treatment administration (EX3 and EX3C1)<br>Hormonal intake treatment (EX4) |
| Dose planned | Dose planned per protocol or prescribed for the visit | Y |
| Dose administered | Dose actually administered to a patient | Y |
| Infusion interrupted | Interruption of an infusion that may or may not resume | Y |
| Infusion re-start time | Start and stop time for re-started infusion after interruption | Y |
| Drug interrupted | The actual dose is 0 and the patient did not receive any drug at the intended visit | -- |
| Dose reduced | Planned dose is lower than previous planned dose or administered dose is lower than planned dose - can be derived programmatically | -- |
| Drug withdrawn | Permanent discontinuation of study drug | -- |
| Dose delay | The infusion is administered prior to the next scheduled administration but outside the protocol-defined window - to be derived programmatically | -- |
| Premedication | Information on premedication used | Entered on the same page as treatment administration |

**Dose reduction**: A dose change where the prescribed dose level is lower than the previous prescribed dose level or where the actual dose administered/total daily dose is lower than the calculated dose amount based on the prescribed dose. Therefore any dose change to correct a dosing error will not be considered a dose reduction. Only dose change is reported in the eCRF. The number of reductions will be derived programmatically.

**Compliance**

Compliance to the study treatment will be summarized in terms of the RDI according to predefined categories of < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients in each category will be presented, for each treatment type in cohort 1.

**Post treatment anti-cancer therapy**

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term, overall and by treatment group/cohort.

**Concomitant medications**

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures), other than the study treatment, administered to a patient during the study treatment period.

Concomitant medications will be coded using the WHO-DD(most recent version), ATC classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages.

Incomplete or missing start and end dates will be handled as described in Table 2.

Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term.

Concomitant medication summaries will include:

- Baseline concomitant medication: medications starting prior to start of study treatment and continuing after the start of study treatment.
- On-study concomitant medication: medications starting on or after the start of study treatment and up to 30 days after the start of the last dose of study treatment

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The Safety Set will be used for all concomitant medication tables and listings.

**Study drug premedication** is a concomitant medication administered to patients to prevent development of IRRs. The number (%) of patients who received study drug premedication will be summarized overall and by infusion, as well as type of premedication by ATC class and preferred term.

### 6.6 Analysis of the primary objective

Evaluation of antitumor activity will be based on investigator assessment according to RECIST v1.1.

The primary endpoint for Cohort 1 (doublet and triplet) and Cohort 2 is CBR at 24 weeks +/- 3 days *i.e.* from 165 to 171 days, per investigator assessment.

**Clinical benefit rate (CBR)**

CBR is the proportion of patients with confirmed CR or PR, or SD lasting 24 weeks – 3 days or longer *i.e.* 39 days or more, according to RECIST 1.1 criteria. SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD) . For the primary objective analysis, CBR will be calculated in the Efficacy Set based on the investigator assessments up to PD, death or the next anti-cancer therapy, whichever occurs earlier.

Patients with only non-measurable disease at baseline will be analyzed for best overall response (secondary objective) and CBR, and will be considered as a SD if their response is a 'Non-CR/Non-PD'.

Observed CBR in both cohorts will be presented with accompanying 90% exact binomial confidence interval.

Two sensitivity analyses of CBR will be performed:

- Sensitivity 1 on efficacy set but excluding patients from both cohorts with unavailable central assessment of HER2 status, hormone receptor (HR) status (Cohort 2 only) (keeping cohort 2 patients without central imaging)
- Sensitivity 2 on patients who received at least 2 complete cycles (6 weeks) of treatment and had undergone baseline assessment and one on-study tumor assessment, or who discontinued early due to disease progression (*i.e*. without confirmation of their eligibility on central assessment of HER2 status, hormone receptor (HR) status (Cohort 2 only))

### 6.7 Analysis of secondary efficacy objectives

The following variables will be used to evaluate antitumor activity in the Efficacy Set: CBR at 24 weeks +/- 3 days *i.e.* 165 to 171 days, per central assessment, BOR, ORR, DOR, PFS, and OS.

Two sensitivity analyses of BOR and ORR will be performed:

- Sensitivity 1 on efficacy set but excluding patients from both cohorts with unavailable central assessment of HER2 status, hormone receptor (HR) status (Cohort 2 only) (keeping cohort 2 patients without central imaging)
- Sensitivity 2 on patients who received at least 2 complete cycles (6 weeks) of treatment and had undergone baseline assessment and one on-study tumor assessment, or who discontinued early due to disease progression (*i.e*. without confirmation of their eligibility on central assessment of HER2 status, hormone receptor (HR) status (Cohort 2 only)))

Key secondary:

*Cohort 1:* CBR at 24 weeks per central review, and ORR, PFS, and DOR per investigator and central review

*Cohort 2:* CBR at 24 weeks per central review, and PFS per investigator and central review

Other secondary (both cohorts):

DOR (Cohort 2), PFS ratio (Cohort 2), ORR (Cohort 2), and OS (Cohorts 1 and 2)

**Best overall response (BOR)**

The BOR is the best response recorded from the start of the treatment until disease progression/recurrence.

The following categories are defined:

- Complete response (CR) - at least two determinations of CR at least 4 weeks apart before progression where confirmation is required or one determination of CR prior to progression where confirmation is not required.
- Partial response (PR) - at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation is required or one determination of PR prior to progression where confirmation is not required
- Stable disease (SD) - at least one SD assessment (or better) > 6 weeks +/- 3 days *i.e.* 39 days or more after start of treatment (and not qualifying for CR or PR).

- Progressive disease (PD) - progression after start of treatment (and not qualifying for CR, PR or SD).
- Not evaluable (NE) - all other cases (i.e. not qualifying for confirmed CR or PR, without SD after more than 6 weeks, or PD).

An **assessment of the concordance** between independent radiological review and local assessment of the BOR for each patient will be provided by cohort and treatment, overall across all treatments. The calculation will be based on the percent agreement (the proportion of response outcomes that match in the Independent Reviewer and Investigator Assessments): Percent Agreement = (Number of matched responders + Number of matched non-responders) / total number of patients assessed.

**Overall response rate (ORR)**

ORR is the proportion of patients with a BOR of CR or PR (RECIST v1.1).
Confirmed Objective response is defined as a CR or PR (RECIST 1.1) on two consecutive occasions ≥4 weeks apart.

**Disease control rate (DCR)**

DCR is the proportion of patients with a BOR of CR, PR, or SD (RECIST v1.1). Both confirmed and unconfirmed BOR will be analyses.

BOR, ORR, DCR and CBR will be summarized by cohort and treatment. For ORR accompanying 2-sided 90% exact binomial CIs will be provided (Clopper and Pearson, 1934). Waterfall plots will be provided by cohort and treatment showing best change in sum of diameters for RECIST v1.1. Individual lesion measurements and overall response assessments will be listed by patient and assessment.

Percent change from baseline over time in sum of diameters of target lesions will be presented graphically for patients with measurable disease. Swimmer plots with duration of exposure, DOR and indicator of clinical benefit at 24 weeks may be produced.

**Progression-free survival**

For assessment per RECIST v1.1, PFS is the time from the date of treatment start to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, PFS is censored at the date of last adequate tumor assessment. More details are provided in the table below based on the draft FDA guidance for industry on clinical trial endpoints for the approval of NSCLC drugs and biologics.

**Description of censoring and progression date rules**

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| No baseline tumor assessments | start of treatment | Censored |
| Progression documented between scheduled visits | Date of progression | Progressed |
| No progression | Date of last adequate assessment (not NE and not missing) | Censored |
| Treatment discontinuation for undocumented progression | Date of last adequate assessment (not NE and not missing) | Censored |
| Treatment discontinuation for toxicity or other reason | Date of last adequate assessment (not NE and not missing) | Censored |

| Situation | Date of Progression or Censoring | Outcome |
|---|---|---|
| New anticancer treatment started | Date of last adequate assessment (not NE and not missing) | Censored |
| Death before first progressive disease assessment | Date of death | Progressed |
| Death between adequate assessment visits | Date of death | Progressed |
| Death after 1 missed assessment | Date of death | Progressed |
| Progression after 1 missed assessment | Date of progression | Progressed |
| Death or progression after more than 1 missed assessment | Date of last adequate assessment (not NE and not missing) | Censored |

Concordance analysis of PFS will consist in a listing of PFS per central and local review by PFS event type (PD, death, censored).

**PFS ratio (Cohort 2 only)**

The ratio of PFS observed on the previous regimen to PFS recorded on study treatment.

For patients in Cohort 2, the number and proportion of any patients with a PFS ratio $\geqslant$ 1.3 (Von Hoff et al., 2010) will be tabulated together with 90% exact CI, along with descriptive data of the PFS ratio for each of these patients.

**Duration of response (DOR)**

DOR applies only to patients with a BOR of confirmed CR or PR (RECIST v1.1). For RECIST v1.1, DOR is defined as the time from the date of the first documented response (CR or PR) to the date of first documented progression, or death due to any cause. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

**Time to response (TTR)**

TTR applies only to patients with a BOR of confirmed CR or PR (RECIST v1.1). For RECIST v1.1 TTR is defined as the time from the date of the first dose to the first documented response (CR or PR).

DOR and TTR will be listed for all patients with a response.

**Overall survival (OS)**

OS is defined as the time from the date of the first dose to the date of death due to any cause. For any patients still alive at the cut-off date, OS will be censored at the date of last contact.

**Analysis of time to event endpoints**

PFS, DOR, TTR and OS will be listed for all patients. Kaplan-Meier plots for PFS will be presented by cohort and treatment. Median PFS, DOR, OS (in months) with corresponding [90%] CI (Brookmeyer and Crowley 1982) and Kaplan-Meier estimated probabilities (PFS, OS rate) with corresponding 90% CIs (Greenwood's formula, Kalbfleisch and Prentice 2002) at several time points (in months) will be presented. For PFS the number (%) of progressions, deaths and patients censored will also be summarized.

**Use of alternative cancer therapy**

For RECIST v1.1, if any alternative cancer therapy is taken, any subsequent assessments will be excluded from the analysis of endpoints based on tumor response assessments.

## 6.8 Other efficacy endpoints

**ECOG performance status**

The ECOG PS scale will be used to assess disease progression, how the disease affects the daily living abilities of the patient, and to determine appropriate treatment and prognosis.

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

Oken, M.M et al (JCO, 1982)

Listing of collected ECOG scores will be produced.

## 6.9 Safety analyses

All safety analyses will be based on the Safety Set.

### *6.9.1 Adverse events*

AE summaries will include all AEs occurring during the on-treatment period (i.e., TEAEs). All AEs collected on the AE eCRF page will be listed along with the information collected on those AEs, e.g. AE relationship to study drug, AE outcome etc. AEs with a start date outside of the on-treatment period will be flagged in the listings.

Grading of AEs will be done according to NCI-CTCAE version 4.03.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AEs with a missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries, the primary SOC will be presented alphabetically and the PTs will be sorted within primary SOC in descending frequency. Cohort 1 and Cohort 2 will be presented separately. In Cohort 1, the sort order for the PT will be based on their frequency in the triplet.

The following AE summaries will be produced by cohort and treatment:

- overview of AEs and deaths (number and % of patients who died, who had at least 1 AE, SAE, dose reductions/interruptions, AE leading to treatment discontinuation; for all AEs irrespective of relationship, severe (grade 3-4), and related AEs);
- AEs by SOC and PT, summarized by:

- relationship (all AEs and AEs related to study treatment),
- seriousness (SAEs and non-SAEs),
- leading to treatment discontinuation,
- leading to dose interruption/adjustment,
- requiring additional therapy and
- leading to a fatal outcome,
- infusion-related reactions (IRRs)*.

*Infusion-related reaction (IRR) is defined as an AE developed within 24 hours of the MCLA-128 or trastuzumab infusion reported as judged by the investigators as a sign or symptom of IRRs. It includes the preferred term of "infusion-related reaction" as well as any other PT marked as such on the AE CRF page (e.g. IRR, nausea, vomiting, abdominal pain, headache, hypotension, pyrexia, tremor and hypersensitivity).

Listing of SAEs, AEs leading to treatment discontinuation, and IRRs will also be produced.

A separate listing of patients with IRRs will include time and grade of IRR onset, infusion status (complete or incomplete), recurrence in subsequent cycles.

***Adverse events of special interest (AESI)***

An AESI is a grouping of AEs that are of scientific and medical concern specific to compound MCLA-128. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms).

AESIs for MCLA-128 combinations include:

- Infusion-related reactions (for any antibodies, known AESI for MCLA-128)
- Cardiotoxicity (anti-HER2 therapy)
- Diarrhea (anti-HER2 therapy)
- Myelosuppression (vinorelbine)

The final scope of AESI related to all components on the combinations will be provided from the case retrieval strategy document.

For each specified AESI, the number and percentage of patients with at least one event of the AESI occurring during the on-treatment period will be summarized by AESI, SOC and preferred term.

Summaries of these AESIs will be provided by cohort and group (specifying grade, SAE, relationship, leading to treatment discontinuation, leading to dose adjustment/interruption, hospitalization, death etc.). If a sufficient number of events occurred, analysis of time to first occurrence will be applied.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated. These listings should be included in section 16 of CSR.

### *6.9.2 Laboratory data*

In the laboratory data analysis, data from all sources (central and local laboratories, as applicable) will be combined. The summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date (see Section 6.5).

The following summaries will be produced for hematology and biochemistry laboratory data (by laboratory parameter and treatment):

- Worst post-baseline CTC grade (regardless of the baseline status). For each patient, only the worst grade observed post-baseline will be counted.
- Shift tables using CTC grades to compare baseline to the worst on-treatment value.
- For laboratory tests where CTC grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- Trends of lab parameter values over time (baseline and selected on-treatment timepoints) will be presented as tables and displayed as boxplots based on time windows for WBC, ANC, platelets, hemoglobin, bilirubin, AST, ALT, alkaline phosphatase.

The following listings will be produced for the laboratory data:

- Listings of all laboratory data, with CTC grades and classification relative to the laboratory normal range. Lab data collected during the post-treatment period will be flagged.
- Listing of all CTC grade 3 or 4 laboratory toxicities.

***Liver function parameters***

Liver function parameters of interest are total bilirubin (TBL), alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP). The number (%) of patients with worst post-baseline values will be summarized:

A table with the following summaries will be produced:

- ALT or AST > 3xULN
- ALT or AST > 5xULN
- ALT or AST > 8xULN
- ALT or AST > 10xULN
- ALT or AST > 20xULN
- TBL > 2xULN
- TBL > 3xULN
- ALT or AST > 3xULN & TBL > 2xULN
- ALT or AST > 3xULN & TBL > 2xULN & ALP < 2xULN (potential Hy's law)

Potential Hy's law events are defined as those patients with **concurrent** occurrence of AST or ALT > 3xULN and TBL > 2xULN and ALP < 2xULN in the same assessment sample during the on-treatment period. Further medical review of any identified patients will be conducted to assess potential confounding factor such as liver metastases, liver function at baseline etc.

### *6.9.3 ECG*

The number and percentage of patients with notable ECG values will be presented by treatment arm.

- QT, QTcF, or QTcB
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from Baseline of > 30 ms to ≤ 60 ms
  - Increase from Baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms
- QRS
  - Increase from baseline >25% and to a value > 120 ms

A listing of all ECG assessments will be produced by cohort and treatment and notable values will be flagged. A separate listing of only the patients with notable ECG values may also be produced. In the listing, the assessments collected during the post-treatment period will be flagged.

### *6.9.4 Left ventricular ejection fraction (LVEF)*

Number of patients with LVEF abnormalities on treatment will be summarized as shift tables with baseline vs worse post-baseline value according to CTCAE grade below:

Grade 0: LVEF > 50% and absolute change from baseline > -10%
Grade 2: LVEF in [40%, 50%] or absolute change from baseline in (-20%, -10%].
Grade 3: LVEF in [20%, 40%) or absolute change from baseline ≤ -20%.
Grade 4: LVEF < 20%.

Note that there is no grade 1.

A descriptive summary table will be produced for LVEF at baseline, worst post-baseline value and absolute change from baseline.

Worst post-baseline LVEF value is defined as the lowest value.

The number (%) of patients with dose delay or infusion interruption will be tabulated by presence/absence of LVEF abnormality (grade 2 or above) for patients with at least 1 post-baseline LVEF evaluation by ECHO or MUGA. The listing of LVEF will include dose administration information.

### *6.9.5 Vital signs*

Vital sign assessments are performed to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg).

Vital signs collected on treatment will be summarized. Values measured outside of on treatment period will be flagged in the listings.

For analysis of vital signs, clinically notable vital signs criteria are provided in Table 1 below.

**Table 1: Clinically notable changes in vital signs**

| Vital sign (units) | Above normal value | Below normal value |
|---|---|---|
| Weight (kg) | increase > 10% from Baseline | decrease > 10% from Baseline |
| Systolic blood pressure (mmHg) | >=160 with increase from baseline of >=20 | <=90 with decrease from baseline of >=20 |
| Diastolic blood pressure (mmHg) | >=105 with increase from baseline of >=15 | <=50 with decrease from baseline of >=15 |
| Pulse rate (bpm) | >=100 with increase from baseline of >25% | <=50 with decrease from baseline of > 25% |
| Body temperature | >= 39.1 | - |

The number and percentage of patients with notable vital sign values (high/low) will be presented by cohort and treatment.

Maximal changes in vital signs will be summarized in tabular form.

A listing of all vital sign assessments will be produced by cohort and treatment and notable values will be flagged.

### 6.10 Pharmacokinetic analysis

Serum concentrations of MCLA-128 will be determined by the bioanalytical lab LGC, UK. Serum concentrations of trastuzumab will be determined by the bioanalytical lab QPS, The Netherlands. The PK analysis and reporting will be performed by Venn Life Sciences, The Netherlands, using the serum concentrations of MCLA-128 and trastuzumab and the actual sampling times and dosing information obtained from the eCRF. A separate PK study analysis plan will be prepared by Venn Life Sciences and approved by Merus, detailing the data handling, analysis, statistics and reporting of the PK data (including the generation of tables, listings and graphs).

#### *6.10.1 Immunogenicity*

Serum samples will be processed by LGC, UK. Immunogenicity will be characterized by incidence of treatment emergent immunogenicity in IG evaluable patients as described in Shankar et al (2014). Among patients with treated emergent immunogenicity the number of patients with treatment-induced ADA and treatment-boosted ADA will be provided.

Evaluable subject: a subject with at least one immunogenicity sample taken after drug administration during the treatment period with reportable result.

ADA-positive subject: a subject with at least one treatment-induced or treatment-boosted ADA-positive sample during the treatment period.

ADA-negative subject: a subject without a treatment-induced or treatment-boosted ADA-positive sample during the treatment period.

Treatment-induced ADA: ADA developed de novo (seroconversion) following biologic drug administration (i.e., formation of ADA any time after the initial drug administration in a subject without pre-existing ADA).

Treatment-boosted ADA: pre-existing ADA that were boosted to a higher level following biologic drug administration.

Any anti-MCLA-128 antibody samples collected after 30 days of the last dose will not be used for summaries or derivations and will only be included in the listing.

A listing will be provided by patient with supporting information (i.e. ADA sample status at each timepoint (including titer for positive samples) and patient ADA status).

The impact of ADA on the occurrence of safety endpoints will be explored by summary tables for incidence of overall and each of the preferred terms of AESIs by subject ADA status, if the number of subjects is sufficient (e.g. number of subjects positive for ADA). Otherwise, individual subject's safety profile will be examined and described based on a listing.

Additional analyses of ADA vs. safety, efficacy, and PK, if conducted, will be defined in a separate SAP and the results reported separately from the CSR.

#### *6.10.2 Cytokines (Safety run-in only)*

A serum cytokine panel (TNFα, IFNγ, IL-1β, IL-6, IL-8, IL-10) will be assessed by LGC, UK.

For each cytokine descriptive statistics will be tabulated per each scheduled time point after MCLA-128 and trastuzumab infusions for measured cytokine concentration, absolute and percent change from baseline, and fold change from baseline.

Cytokine levels after MCLA-128 given alone (Cycle 1, Day 1) and trastuzumab given alone (Cycle 1, Day 2) will be compared graphically with those obtained after the combination of MCLA-128 and trastuzumab (Cycle 2, Day 1).

### 6.11 Biomarkers

The Safety set will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data. Assessment of associations between biomarker and safety data will be conducted using the safety set.

For exploratory markers, since the studies are not adequately powered to assess specific biomarker-related hypotheses, the goal of these exploratory statistical analyses should be considered as the generation of new scientific hypotheses. No adjustment for multiple comparisons is usually planned for exploratory analyses. Furthermore, additional post hoc exploratory assessments may be performed.

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue their analysis due to either practical or strategic reasons. Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

Additional analyses that may be performed after the completion of the end-of-study CSR will be documented in separate reports. The data analysis will be described in a stand-alone analysis plan.

The Cycle 1 Day 1 assessment (pre-dose) will be used as the baseline value. For assessments performed in tumor biopsies, fresh biopsy results will be used for baseline when both archived and fresh tumor samples are available. When more than one biomarker data value are available for a patient at any time point, the mean of the replicate values will be used for all statistical analyses.

**Derivation of change and percent change variables**

Absolute and relative change (percent change) and fold change from baseline may be calculated for each <patient> <and> </><or> <treatment group>.

Fold change is calculated as the ratio of biomarker value at ((visit i) / (Baseline biomarker value)), while percent change is computed as ((visit i – baseline) / baseline) * 100.

The average percent change from baseline is computed as the average expression level at each time point and then the percent change using the average values. The number of patients for the average of percent change from baseline might vary due to potential missing values at respective time points.

If both the baseline and post baseline values are below LLOQ, absolute change, percent change and fold change from baseline will not be imputed and reported as missing.

**Tumor markers**

For patients with measured tumor markers (CA15-3, CEA, and CA27-29) at baseline, descriptive statistics will be tabulated by time with observed, change and percent change from baseline following rules outlined above. These biomarkers may be summarized by subgroups, e.g. exposure of at least 4 cycles, CA15-3 positive/negative.

### 6.12 Exploratory analyses

The goal of these exploratory analyses is to evaluate potential correlations between biomarkers in tumor or blood samples and antitumor activity (including HER2, HER3, HER2:HER3 dimers, heregulin and other potential biomarkers measured at baseline only or at baseline and after start of treatment).
HER2 score, NRG1 score, HER2:HER3 dimer score will be summarized at baseline.

Correlation to “clinical response” plots (scatter plots) will be provided: HER2 score, H-score, NRG1 score, HER2:HER3 dimer score, sHeregulin level to cycle number, global resp. category, tumour size change from baseline.

Tables will be produced to investigate whether certain categorical parameter is enriched in certain patient category (responder/non-responder or other category).

### 6.13 Interim analysis

No formal interim analysis is planned.

# 7 Appendix

## 7.1 Imputation rules

### *7.1.1 Study drug*

The following rule should be used for the imputation of the dose end date for a given study treatment component:

**Scenario 1:** If the dose end date is completely missing and there is no EOT page and no death date, the patient is considered as ongoing:

The patient should be treated as ongoing and the cut-off date should be used as the dose end date.

**Scenario 2:** If the dose end date is completely or partially missing and the EOT page is available:

Case 1: The dose end date is completely missing, and the EOT completion date is complete, then this latter date should be used.

Case 2: Only Year(yyyy) of the dose end date is available and yyyy < the year of EOT date:

**Use Dec31yyyy**

Case 3: Only Year(yyyy) of the dose end date is available and yyyy = the year of EOT date:

**Use EOT date**

Case 4: Both Year(yyyy) and Month (mm) are available for dose end date, and yyyy = the year of EOT date and mm < the month of EOT date:

**Use last day of the Month (mm)**

All other cases should be considered as a data issue and the statistician should contact the data manager of the study.

After imputation, compare the imputed date with start date of treatment, if the imputed date is < start date of treatment:

**Use the treatment start date**

Patients with missing start dates are to be considered missing for all study treatment component related calculations and no imputation will be made. If start date is missing then end-date should not be imputed.

For exposure endpoints, the following rule should be used for the imputation of the start date for FULVESTRANT:

**Incomplete of start date**

Missing day is defaulted to the 15$^{th}$ of the month.

### *7.1.2 AE, Concomitant medication and safety assessment date imputation*

Rules for imputation of start dates for AEs, concomitant medications as well as for safety assessments are outlined in Table 2Table 2.

**Table 2: Imputation of start dates (AE, concomitant medications) and assessments (laboratory data, ECG, vital signs)**

| Missing Element | Rule |
|---|---|
| day, month, and year | No imputation will be done for completely missing dates |
| day, month | If available year = year of study treatment start date then<br>If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY<br>Else set start date = study treatment start date.<br>If available year > year of study treatment start date then 01JanYYYY<br>If available year < year of study treatment start date then 01JulYYYY |
| day | If available month and year = month and year of study treatment start date then<br>If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.<br>Else set start date = study treatment start date.<br>If available month and year > month and year of study treatment start date then 01MONYYYY<br>If available month and year < month year of study treatment start date then 15MONYYYY |

Any AEs and Concomitant Medications with partial/missing dates will be displayed as such in the data listings.

Any AEs and Concomitant Medications which are continuing as per the data cut-off will be shown as 'ongoing' rather than the end date provided.

**Table 3: Imputation of end dates (AE, concomitant medications)**

| Missing Element | Rule |
|---|---|
| day, month, and year | Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period* |
| day, month | If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period * |
| day | If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period* |
| *=last treatment date plus 30 days AND prior to min(death date, cut-off date, withdrawal of consent date) | |

Note : Imputation of AE end date will be done only for emergent AEs

### *7.1.3 Other imputation rules*

**Incomplete date of initial diagnosis of cancer and date of most recent recurrence**

Missing day is defaulted to the 15$^{th}$ of the month and missing month and day is defaulted to 01-Jan.

**Incomplete assessment dates for tumor assessment**

All investigation dates (e.g. MRI scan, CT scan) must be completed with day, month and year. If one or more assessment dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date and assessment date is

calculated as the latest of all investigation dates (e.g. MRI scan, CT scan) if the overall response at that assessment is CR/PR/SD/UNK. Otherwise – if overall response is progression – the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the 1st of the month is used. If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

**Applying the cut-off to tumor assessment**

For tumor related assessments, if an evaluation has some assessments done prior to cut-off date and others after the cut-off date, then the evaluation is considered post-cut-off date and will be excluded from analysis.

**Incomplete of death**

Missing day is defaulted to the 15th of the month. **Incomplete date follow-up treatment**

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 31-Dec, or death date if patient died before.

### *7.1.4 Assessment of disease response using RECIST 1.1*

Overall response is calculated for each assessment time point as per **Error! Reference source not found.**.

**Table 4: Overall response in patients with target (+/- non-target) disease**

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

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

The best overall response is determined once all data for a given patient are available and is defined as the best response recorded between the start and end of treatment, as described in **Error! Reference source not found.**.

**Table 5: Best overall response**

| Overall response First time point | Overall response Subsequent time points | Best overall response |
|---|---|---|
| CR | CR | CR |
| CR | PR | SD, PD or PR[1] |
| CR | SD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| CR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD provided minimum criteria for SD duration met, otherwise, PD |
| PR | NE | SD provided minimum criteria for SD duration met, otherwise NE |
| NE | NE | NE |

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

### *7.1.5 CTCAE grading of laboratory parameters*

Toxicity grading will be done for selected laboratory parameters according to CTCAE version 4.03.

For CTCAE grading of calcium, the corrected calcium derivation is based on total calcium and albumin level:

Imperial units: Corrected Calcium (mg/dL) = 0.8 * [4 - Albumin (g/dL)] + Calcium (mg/dL)

SI units: Corrected Calcium (mmol/L) = 0.2 * [4 - Albumin (g/dL)] + Calcium (mmol/L)

The grading for Corrected Calcium (mmol/L) is defined as :

*With LLN & ULN for Calcium

| | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| **Hypocalcemia** | Corrected serum calcium <LLN* - 2.0 | Corrected serum calcium <2.0 - 1.75 | Corrected serum calcium <1.75 - 1.5 | Corrected serum calcium <1.5 |
| **Hypercalcemia** | Corrected serum calcium of >ULN* - 2.9 | Corrected serum calcium of >2.9 - 3.1 | Corrected serum calcium of >3.1 - 3.4 | Corrected serum calcium of >3.4 |

## 8 References

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# 9 Appendix 1 - Planned CSR outputs

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