Phase 2 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

Published: 15-04-2019
Last updated: 09-04-2024

Cohort 1 (HER2-positive/amplified MBC): MCLA-128 + trastuzumab ± vinorelbine 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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Observational invasive

Summary

ID

NL-OMON48717

Source
ToetsingOnline

Brief title
MCLA-128-CL02

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Merus N.V.
Source(s) of monetary or material Support: Merus N.V.

Intervention

Keyword: Metastatic Breast cancer

Outcome measures

Primary outcome

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

Secondary outcome

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: Cmax, C0h, AUC, CL, Vss, tmax and t1/2 for MCLA-128, and CEOI

and C0h for trastuzumab.

Study description

Background summary

Preclinical Studies for MCLA-128 + Trastuzumab in HER2-Positive MBC
There is a strong rationale to combine trastuzumab with MCLA-128 for the treatment of MBC. Trastuzumab is effective in blocking constitutive ligand-independent signaling through the HER2:HER3 heterodimer in the context of HER2 overexpression. However, it has very poor growth inhibition activity in tumors and cell lines where HER2:HER3 signaling is driven by HER3 ligand dependency (Wehrman et al., 2006; Junttila et al., 2009). Preclinical and clinical evidence points to increased HER3 expression and/or HER3 ligand upregulation as the main drivers leading to trastuzumab resistance (Sergina et al., 2007; Ocana et al., 2013). The bispecific antibody MCLA-128 docks HER2 present on the cancer cells to subsequently lock HER3 in an inactive confirmation. This results in potent inhibition of the HRG ligand-induced HER2:HER3 dimer formation and may overcome the resistance mechanism observed with trastuzumab.
Preclinical studies showed that the combination of MCLA-128 and trastuzumab was more potent than single-agent MCLA-128 to block HRG-induced tumor proliferation, supporting the addition of MCLA-128 to a trastuzumab-containing regimen in the clinic. In addition, the bispecific anti-HER2xHER3 antibody MCLA-128 presents enhanced ADCC. The monovalent interaction of the antibody to HER2 results in a greater density of antibody per tumor cell. In turn, this will result in greater recruitment of immune effector cells and, combined with ADCC, superior tumor cell killing activity.
In light of the distinct mechanisms of action for MCLA-128 and trastuzumab, these preclinical data suggest that administration of MCLA-128 and trastuzumab in HER2-positive patients has the potential for additive or synergistic activity in this setting.
1.3.2 Preclinical Studies for MCLA-128 + Endocrine Therapy in Hormone Receptor-Positive/HER2-Negative MBC
Bidirectional crosstalk between ER and HER2/3 has been hypothesized to underlie ET resistance via their activation (Houston et al., 1999; Thrane et al., 2013). The HER2:HER3 heterodimer activates PI3K/AKT and MAPK downstream signaling cascades but can also induce ER phosphorylation independent of estrogen (Pietras et al., 1995; Curley et al., 2015) which may reduce the effectiveness of endocrine therapies (Arpino et al., 2008). On the other hand, HER2 may be preferentially upregulated by estrogen deprivation, while tamoxifen induces expression of EGFR and HER2 (García-Becerra et al., 2012). The nature of the

HER2/ERα cross-talk seems to be conditioned by the context of endocrine resistance; in a series of paired biopsies from patients relapsing on tamoxifen evaluated in an in vivo model, conversion from HER2-negative to HER2-positive was rare, however <20% of tamoxifen-resistant patients relapsed with adaptive upregulation in HER2 and either suppressed or enhanced ERα expression and signaling (Gutierrez et al., 2005).
Taken together, these data support a combined ER/HER2-targeted approach in patients with acquired ET resistance in ERα-positive/HER2-negative breast cancer. The EGF30008 trial comparing letrozole alone versus in combination with lapatinib in hormone receptor-positive MBC suggests this may be translated into the clinic, as although the addition of lapatinib did not confer benefit in the overall hormone receptor-positive/HER2-negative group, there was a trend toward a benefit in the endocrine-resistant hormone receptor-positive/HER2-negative subset (Johnston et al., 2009).
A recent preclinical study took this concept a step further, demonstrating direct cross-talk between HER2/HER3 and ER with phosphorylation of ER only observed in cells expressing both HER2 and ER* or HER3 and ER**(Collins et al., 2017). The authors used an in vivo mouse model of ER+/HER2-low (HER2 IHC 1+ or 2+ without gene amplification) human breast cancer to evaluate a triple therapy targeting HER2 (pertuzumab), HER3 (lumretuzumab) and the ER (fulvestrant), resulting in long-lasting tumor regression.
Preclinical studies support that adding MCLA-128 to hormonal treatment could delay or reverse resistance to therapy in ER+ HER2- (HER2 IHC 1+ or 2+ by HercepTest*) breast cancer. MCLA-128 with anti-ER drugs (tamoxifen and fulvestrant) combined with the AI letrozole was evaluated in two in vivo xenograft models of ER+ HER2-low breast cancer. All hormone therapies reduced tumor growth, while MCLA-128 single agent had no efficacy. However, when MCLA-128 was added to the hormone therapy regimen, it led to a further decreased in tumor growth. Mechanistically, HER2 expression was increased with fulvestrant and tamoxifen, which is supported by published studies (Osipo et al., 2007; García-Becerra et al., 2012). When MCLA-128 was added to anti-ER drugs, this increase in HER2 could be reversed. Most importantly, a proximity ligation assay showed that fulvestrant treatment upregulated the formation of HER2:HER3 dimers and enhanced activation of the Akt signaling pathway, which could be inhibited by adding MCLA-128. Together, these data show that the efficacy of hormonal therapies may be limited due to activation of the HER2/HER3 signaling axis, which could be reversed by MCLA-128.
While the in vivo tumor models tested responded to hormonal therapy, there is also evidence that in the context of ET-resistant tumors, the inhibition of HER3 by MCLA-128 could be therapeutically beneficial, as suggested by Collins et al. (2017). The MCF-7 cell line engineered to respond to AIs was initially sensitive to letrozole, but tumors subsequently became resistant (Curley et al., 2015). The addition of an anti-HER3 antibody at the start of treatment was more effective than hormone therapy alone, as observed for MCLA-128. Importantly, the combination of the anti-HER3 with hormone therapy after resistance restored antitumor activity. This was not the case when the anti-HER3 was given as single agent, demonstrating that hormone receptor and

HER3 inhibition work in synergy before and after the occurrence of HT resistance.
In patients with ER-positive/low HER2 expression MBC, based on this strong preclinical evidence, a rescue approach will be used to evaluate the effect of the addition of MCLA-128 on the natural history of the disease when treated with ET.

Study objective

Cohort 1 (HER2-positive/amplified MBC): MCLA-128 + trastuzumab ± vinorelbine
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 (estrogen receptor [ER]-positive/low HER2 expression MBC): MCLA-128 + endocrine therapy
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).

Study design

A phase 2, open-label, multicenter international study will be performed to evaluate the efficacy of MCLA-128-based combinations in two metastatic breast cancer (MBC) populations, HER2-positive/amplified (Cohort 1) and ER-positive/low HER2 expression (Cohort 2). Three combination treatments will be evaluated, two in Cohort 1 and one in Cohort 2, in 20-30 sites in 7 countries in Europe and the USA.
Cohort 1: Patients with HER2-positive/amplified MBC, having confirmed HER2 overexpression by immunohistochemistry (IHC) 3+ or IHC 2+ combined with positive fluorescence in situ hybridization (FISH), who have been treated with up to a maximum of 5 lines of HER2-directed therapy in the metastatic setting and have progressed on the most recent line as per RECIST v1.1, are eligible. Patients must have been treated previously with trastuzumab, pertuzumab and an HER2 ADC in any sequence and in any setting. For enrollment, HER2 status will be based on medical records, and eligibility will be confirmed subsequently as soon as possible, by central lab review. Patients found to be ineligible retrospectively will not be evaluable for the primary objective and may be replaced. Documented imaging proof of disease progression on the last prior line of therapy should be made available when possible.
Initially MCLA-128 will be administered with trastuzumab (doublet combination). Safety will be reviewed by an Independent Data Monitoring Committee (IDMC). After the safety of the doublet has been assessed, MCLA-128 + trastuzumab + vinorelbine (triplet combination) will be evaluated in parallel with the doublet combination (see figure below).
The doublet and triplet Cohort 1 combinations will both be evaluated in two steps with an initial safety run-in in 4 to 6 patients who will be reviewed by the IDMC, followed by a cohort efficacy expansion, as described below. The triplet combination go/no-go decision will be made by the IDMC after evaluation of the doublet safety run-in patients. If the triplet combination is considered safe, the expansion of the doublet and triplet combinations will be performed in parallel. Patients with be included with a 3:1 ratio for triplet or doublet respectively, favoring the triplet combination and taking into account previous exposure to vinorelbine.

Safety run-in: After 4-6 patients have received at least 2 complete cycles (6 weeks) of MCLA-128 + trastuzumab, a safety review will be performed by the IDMC. If the doublet combination is considered safe, the safety run-in for the triplet combination will be initiated in the next 4 to 6 successive eligible

patients. Safety of the triplet will be evaluated by the IDMC after these 4-6 patients have received at least 2 complete cycles (6 weeks) of MCLA-128 + trastuzumab + vinorelbine.
Based on the observed safety in the first 4-6 patients (adverse events [AEs], serious adverse events [SAEs], relationship to study drug, and other clinically relevant parameters [e.g. laboratory parameters], available PK, immunogenicity, and cytokine data) the IDMC, investigators and Sponsor will decide on a potential additional run-in period for each combination (i.e. doublet and triplet).
Expansion: After the safety run-in, each Cohort 1 combination therapy considered tolerable by the IDMC will be expanded to a total of up to 40 patients evaluable for efficacy.
If the doublet combination regimen is not tolerated, Cohort 1 will be closed.
If the triplet combination is not well tolerated but the doublet is acceptable, the doublet expansion will be continued.
Cohort 2: Patients with ER-positive and low HER2 expression MBC (IHC 1+, or IHC 2+ combined with negative FISH) who have radiologic or photographic evidence of disease progression on the last line of prior endocrine therapy (administered for at least 12 weeks) that included an aromatase inhibitor or fulvestrant. Patients who have received up to 3 prior endocrine therapies in the metastatic setting and have progressed on a cyclin-dependent kinase inhibitor (in any line) are eligible. For enrollment, HER2 and HR status and radiologic/photographic documentation of prior progression will be based on medical records. Eligibility will be confirmed as soon as possible for HER2/HR status by central lab review and for prior disease progression by central imaging review. Patients found to be ineligible retrospectively will not be evaluable for the primary objective and may be replaced.
MCLA-128 will be administered in combination with the same previous endocrine therapy on which progressive disease is radiologically/photographically documented. A total of up to 40 patients evaluable for efficacy will be included.

An Independent Data Monitoring Committee (IDMC), composed of at least 2 physicians expert in the domain of early clinical development in MBC, will review safety and efficacy throughout the study and decide on the addition of extra patients in the expansion parts, opening of the triple combination cohorts, and any ad hoc safety decisions. The principal investigators, the Sponsor*s medical expert(s) and other representatives may be called upon to assist as observers.

Study burden and risks

• MCLA-128 risks
MCLA-128 has been given to ~50 patients in an ongoing clinical study of different tumor types. The preliminary data from this clinical study shows that when MCLA-128 was administered alone (without other cancer therapies) it was relatively well tolerated at the same dose you will receive in this

clinical study.
The most frequent side effects observed at this dose include infusion-related reactions (allergic reaction, nausea, vomiting, and fever, which were reported 25% of patients), diarrhea (19% of patients) and fatigue (13% of patients). At other doses (lower or higher), some patients also experienced skin disorders such as rash (21% of patients), stomatitis (inflammation in the mouth mucosa, 14% of patients) and abdominal pain (7% of patients). When they occurred, these toxicities were mild or moderate and patients usually recovered completely from them before the next planned treatment. However, in one patient with associated cardiac disease, allergic reaction resulted in death.
• Trastuzumab risks
As trastuzumab is an approved drug for the treatment of breast cancer and has been administered to many patients worldwide, its tolerance is better known. The most common side effects (reported in > 10% of patients) are: infections, decreased number of blood cells (white blood cells, red blood cells, platelets), weight decrease, anorexia, insomnia, tremor, dizziness, headache, paresthesia (feeling of tingling or pricking), taste disturbance, conjunctivitis, modification of blood pressure (increase or decrease), palpitations, decrease of cardiac function, hot flush, wheezing, respiratory difficulties, cough, nose hemorrhage, rhinorrhea, diarrhea, vomiting, nausea, abdominal pain, digestion difficulties, constipation, stomatitis, skin eruption, hair loss, nails disorders, joint pain, muscles pain, fatigue, chest pain, chills, flu-like syndrome, infusion-related reactions, pain, fever (associated or not with low white blood cells), mucosal inflammation and peripheral edema.
• Vinorelbine risks
Vinorelbine is also an approved drug with a well-known safety profile which has been administered to many patients worldwide. The most common side effects (reported in > 10% of patients) are: decreased number of blood cells (white blood cells, platelets), neurologic disorders including loss of deep tendon reflexes, stomatitis, nausea, vomiting, constipation, transient elevation of liver tests without clinical symptoms, hair loss, reactions at injection site (erythema, burning pain).
• Hormone therapy risks
The side effects of the hormone therapy agent that you are receiving were already explained to you by your investigating doctor when the treatment was initiated.
However, any of these side effects for both drugs (MCLA-128 and hormone therapy agent) may occur with greater intensity, or other effects, not yet known, could occur given that this clinical study is the first time that these drugs have been administered together.
Your investigating doctor will assess you for these side effects regularly and inform you of their intensity or of any potential risk. You should be sure to inform your doctor if any side effects occur. If necessary, he or she will give you treatment to prevent or relieve symptoms.
Your study treatment (MCLA-128 and your hormone therapy) could be interrupted, delayed or even stopped altogether, if any side effects occur and are severe.

However, any of these side effects for all three drugs may occur with greater intensity, or other effects, not yet known, could occur given that this clinical study is the first time that these drugs have been administered together in the clinical setting.
Your investigating doctor will assess you for these side effects regularly and inform you of their intensity or of any potential risk. You should be sure to inform your doctor if any side effects occur. If necessary, he or she will give you treatment to prevent or relieve symptoms.
Your study treatment (MCLA-128, trastuzumab and vinorelbine) could be interrupted, delayed or even stopped altogether, if any side effects occur and are severe. In addition, the dose of vinorelbine can be reduced in the event of certain side effects.
• Pregnancy and reproductive risks
The potential risks of MCLA-128 on human reproductive function and on the human fetus have not yet been studied. You must not therefore become pregnant or breast-feed while you are taking part in the present clinical study. As a result, if you (or your sexual partner) are of child-bearing potential, you must use an effective method of contraception throughout the clinical study and for 7 months after the last dose of MCLA-128. Effective methods of contraception include: true abstinence, or a sole partner who is vasectomized, or a combination of two of the following: intrauterine device/system, a condom with spermicidal foam, gel, film, cream, or suppository, and an occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream or suppository. The use of hormonal methods of contraception is not considered effective enough for this clinical study. If you fall pregnant during the clinical study, you must inform your investigating doctor and you will no longer be able to take part in this clinical study.

As MCLA-128 is a new drug being developed, there may be other side effects that are not yet known especially since MCLA-128 has not previously been administered in combination with other anticancer drugs.
5. Other side effects associated with medical procedures used during the clinical study
Blood draws are standard practice in your illness and are not specific to this clinical study. However, there may be more blood draws than usual which may make you more susceptible to side effects (pain, bruising, inflammation and swelling of the vein, bleeding or even an infection at the puncture site).
Minimal risks and side effects are possible after tumor biopsies, such as pain, bleeding, bruising or infection.
CT scans, magnetic resonance imaging (MRI) and bone scans normally carried out to diagnose and assess your disease will not be different from routine practice in this clinical study.
A CT scan is a series of x-rays put together by a computer. CT scans will expose you to small amounts of radiation. Although repeated radiation may damage your body tissues and slightly increase your chances of having cancer, you should not expect an increased risk from the imaging being done for this clinical study.

Magnetic resonance imaging (MRI) is a technique that uses a magnetic field and radio waves to create detailed images of the organs and tissues within your body.

CT scans and MRI scans involve dyes (called *contrast medium*) being injected into one of your veins to help show up the organs in your body and your cancer. There is a risk that you may have an allergic reaction to the dye. This reaction may be mild (such as a skin rash or hives) or severe (such as breathing difficulties and shock. In rare instances severe or fatal allergic reactions have been reported.
A bone scan is a nuclear medicine test which helps find cancer that has started in or has spread to the bones. This means that the procedure uses a very small amount of a radioactive substance, called a tracer. The tracer is injected into a vein. A bone scan carries no greater risk than conventional X-rays. The tracers in the radioactive dye used in a bone scan produce very little radiation exposure. Even the risk of having an allergic reaction to the tracers is low.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Signed informed consent before initiation of any study procedures.
2. Women with histologically or cytologically confirmed breast cancer with evidence of metastatic or locally advanced disease not amenable to any local therapy with curative intent:
2.1 Cohort 1 (MCLA-128 + trastuzumab ± vinorelbine)
a. Documented HER2 overexpression/amplification, defined as immunohistochemistry (IHC) 3+ positive, or IHC 2+ combined with positive fluorescence in situ hybridization (FISH), based on local analysis on the most recent tumor biopsy (preferably metastatic, otherwise primary), either fresh or archival collected within 24 months before screening..
b. Documented disease progression (by investigator assessment) on up to a maximum of 5 lines of HER2-directed therapy administered in the metastatic setting, and have progressed on the most recent line. Trastuzumab, pertuzumab and an HER2 antibody drug conjugate (e.g. T-DM1) must have been previously administered in any sequence and in any setting.
2.2 Cohort 2 (MCLA-128 + endocrine therapy)
a. Documented hormone receptor positive status (estrogen receptor positive [ER+] and/or progesterone receptor positive [PR+]), defined as >= 1% positive stained cells by local standards, based on local analysis on the most recent tumor biopsy
b. Documented low-level HER2 expression, defined as IHC HER2 1+, or IHC HER2 2+ combined with negative FISH, based on local testing on a fresh tumor biopsy or an archival biopsy collected within 24 months before screening (preferably metastatic otherwise primary).
c. No more than 3 lines of prior endocrine therapy (aromatase inhibitor or fulvestrant) for metastatic disease, with radiologically documented disease progression on the last line, after at least 12 weeks of therapy.
d. Progression on a cyclin-dependent kinase inhibitor.
e. No more than two previous chemotherapy regimen for advanced/metastatic disease.
Note: Pre/peri-menopausal women can be enrolled if amenable to be treated with the LHRH agonist goserelin. Such patients must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to study entry, and patients who received an alternative LHRH agonist prior to study entry must switch to goserelin for the duration of the trial.
3. In Cohort 1, patients must have at least one lesion with measurable disease as defined by RECIST version 1.1. In Cohort 2, patients must have at least one

lesion with measurable disease as defined by RECIST version 1.1. Patients with bone-only disease are eligible, even in the absence of measurable disease. Patients with bone-only disease must have lytic or mixed lesions (lytic + sclerotic). For Cohort 2, imaging documenting progression on the last line of hormone therapy must be available for central review..
4. Age >= 18 years at signature of informed consent.
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Life expectancy of >= 12 weeks, as per investigator.
7. Left ventricular ejection fraction (LVEF) >= 50% by echocardiogram (ECHO) or multiple gated acquisition scan (MUGA).
8. Adequate organ function:
a. Absolute neutrophil count (ANC) >= 1.5 X 109/L
b. Hemoglobin >= 9 g/dL
c. Platelets >= 100 x 109/L
d. Serum calcium within normal ranges (or corrected with supplements)
e. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) <= 2.5 x upper limit of normal (ULN) and total bilirubin <= 1.5 x ULN (in cases of liver involvement, ALT/AST <= 5 x ULN and total bilirubin within normal ranges will be allowed)
f. Serum creatinine <= 1.5 x ULN or creatinine clearance >= 60 mL/min calculated according to the Cockroft and Gault formula or MDRD formula for patients aged > 65 years (Appendix 19.2)
g. Serum albumin > 3.0 g/dL

Exclusion criteria

1. Central nervous system metastases that are untreated or symptomatic, or require radiation, surgery, or continued steroid therapy to control symptoms within 14 days of study entry.
2. Known leptomeningeal involvement.
3. Advanced/metastatic, symptomatic, visceral spread, with a risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement).
4. Participation in another interventional clinical trial or treatment with any investigational drug within 4 weeks prior to study entry.
5. Any systemic anticancer therapy within 3 weeks of the first dose of study treatment. For cytotoxic agents that have major delayed toxicity, e.g. mitomycin C and nitrosoureas, or anticancer immunotherapies, a washout period of 6 weeks is required. For patients in Cohort 2, this does not apply to the most recently received hormone therapy.
6. Major surgery or radiotherapy within 3 weeks of the first dose of study treatment. Patients who received prior radiotherapy to >= 25% of bone marrow are not eligible, irrespective of when it was received.
7. Persistent grade > 1 clinically significant toxicities related to prior

antineoplastic therapies (except for alopecia); stable sensory neuropathy <= grade 1 NCI-CTCAE v. 4.0 is allowed.
8. History of hypersensitivity reaction or any toxicity attributed to trastuzumab, murine proteins or any of the excipients that warranted permanent cessation of these agents (applicable for Cohort 1 only).
9. Previous exposure to vinorelbine (applicable for Cohort 1 triplet combination only)
10. Exposure to the following cumulative anthracycline doses:
a. Doxorubicin or liposomal doxorubicin > 360 mg/m²
b. Epirubicin > 720 mg/m²
c. Mitoxantrone > 120 mg/m² and idarubicin > 90 mg/m²
d. Other anthracycline at a dose equivalent to > 360 mg/m² doxorubicin
e. For patients having received > 1 anthracycline, the cumulative dose must not exceed the equivalent of 360 mg/m² doxorubicin
11. Chronic use of high-dose oral corticosteroid therapy (>10 mg of prednisone equivalent a day).
12. Uncontrolled hypertension (systolic > 150 mmHg and/or diastolic > 100 mmHg) or unstable angina.
13. History of congestive heart failure of Class II-IV New York Heart Association (NYHA) criteria, or serious cardiac arrhythmia requiring treatment (except atrial fibrillation, paroxysmal supraventricular tachycardia).
14. History of myocardial infarction within 6 months of study entry.
15. History of prior or concomitant malignancies (other than excised non-melanoma skin cancer or cured in situ cervical carcinoma) within 3 years of study entry.
16. Current dyspnea at rest of any origin, or other diseases requiring continuous oxygen therapy.
17. Current serious illness or medical conditions including, but not limited to uncontrolled active infection, clinically significant pulmonary, metabolic or psychiatric disorders.
18. Known HIV, HBV, or HCV infection.
19. Pregnant or lactating women; women of childbearing potential must use effective contraception methods (patient and/or partner, e.g., surgical sterilization, a reliable barrier method) prior to study entry, for the duration of study participation, and for 7 months after the last dose of MCLA-128/trastuzumab. See Section 8.10.
20. Patients with only non-measurable lesions other than bone metastasis (e.g. pleural effusion, ascites or other visceral locations).
21. Patients with bone-only disease with blastic-only metastasis.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-07-2019
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	MCLA-128
Generic name:	MCLA-128

Ethics review

Approved WMO Date:	15-04-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-06-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	30-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-08-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-02-2022
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-002821-39-NL
ClinicalTrials.gov	NCT03321981
CCMO	NL66656.031.19