A Phase I/II Study of MCLA-128, a full length IgG1 Bispecific Antibody Targeting HER2 and HER3, in Patients with Solid Tumors (eNRGy)

Published: 01-12-2014
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This study has been transitioned to CTIS with ID 2024-512358-78-00 check the CTIS register for the current data. Part 1 of the trial (already completed):The primary objective of the research concerned the determination of the Maximum Tolerated Dose...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54685

Source
ToetsingOnline

Brief title
MCLA-128-CL01

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
metastatic epithelial tumours, solid tumours

Research involving
Human

Sponsors and support

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

Intervention

Keyword: first in man, full length IgG1 antibody, HER2 & HER3-targeted therapy, Phase I, solid tumours

Outcome measures

Primary outcome

Part 2 of the study:

The determination of the safety and tolerability of MCLA-128 by the frequency

and nature of the adverse events and to explore the anti-tumour activity of

MCLA128 and disease related biomarkers.

Secondary outcome

Part 2 of the study:

PK profile - total exposure, maximum concentration, clearance, volume

distribution, half-life and AUC of MCLA-128.

Immunogenicity - incidence and serumtiters of anti-drug antibodies against

MCLA-128.

Evaluation of PFS and overall survival, duration of response

Exploratory - Assessment of other relevant tumor biomarkers and markers of

MCLA-128 activity in archival and/or fresh tumor sample/biopsy material and

blood. (see protocol for details).

Study description

Background summary

MCLA-128 is a humanized full length IgG1 bispecific antibody with an enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) that simultaneously targets the transmembrane tyrosine kinase receptors HER2 and HER3.
HER2 and HER3 receptors, which are part of the growth factor family, are present on a variaty of epithelial tumourcells.
MCLA-128 binds to the HER2 and HER3 and in this way prevents these receptors to function. Because of this the cancercell no longer receives the singals which it needs to grow.

There are approved antibodies vor therapeutic use, which target the HER2 receptors. Many patients do not have a proper response to this treatment (refractory), or their disease will return after a certain period of proper response to the treatment (relaps).
Interaction between HER2- and HER3-receptors could be the cause of this refractory respons or relaps.

MCLA-128 is developed to overcome the HER3-mediated resistence and relaps to anti-HER2 therapy. An amplified presence of HER3 is often observed in epithelial tumours like breast-, stomach-, colorectal-, ovarycancer, etc. and HER2 amplified presence is often observed in a certain percentage of different forms of epithelial tumours, like breast-, colorectal-, ovary-, stomachcancer, etc.

Besides that, MCLA-128 is developed with the purpose to enhance the immunesystem of the patients to target the cancer (so called antibody-dependent cell-mediated cytotoxicity (ADCC)).

Study objective

This study has been transitioned to CTIS with ID 2024-512358-78-00 check the CTIS register for the current data.

Part 1 of the trial (already completed):
The primary objective of the research concerned the determination of the Maximum Tolerated Dose (MTD) and/or Maximum Recommended Dose (MRD) of MCLA-128. Which was set to 750mg.
The secundary objective of the research concerned the characterisation of the safety and tolerability, the PK profile, the immunogenicity and the evaluation of the anti-tumour response, the clinical benefit and the clinical benefit rate of MCLA-128.

An exploratory objective of the research concerned the presence of biomarkers

and pharmacodynamic responses to MCLA-128.

Part 2 of the trial:
Group A-E
The primary objective of this research is to characterize the safety and tolerability of MCLA-128.
The relationship between anti-tumor activity and disease related biomarkers will be explored.

Group F, G, H
To assess magnitude of anti-tumor activity of MCLA-128 in patients with NRG1 fusion as assessed locally
To assess durability of anti-tumor activity of MCLA-128 in patients with NRG1 fusions as assessed locally

The key secundary objective of this research for Group A- E is:
- PK profile of MCLA-128
- Immunogenicity of MCLA-128
- evaluation of PFS and overall survival, duration of response

Group F, G, H (NRG1 fusion)
To assess the magnitude of anti-tumor activity of MCLA-128 in patients with NRG1 fusions as assessed centrally
- To assess the clinical benefit rate (CBR) of MCLA-128 in patients with NRG1 fusions as assessed locally and centrally
- To assess durability of anti-tumor activity of MCLA-128 in patients with NRG1 fusions as assessed centrally
- To assess time to onset of response in patients with NRG1 fusions as assessed locally and centrally
- To characterize the safety and tolerability of MCLA-128
- PK profile of MCLA-128
- Immunogenicity of MCLA-128
- Evaluation of progression-free survival and overall survival

Study design

This is a pase I/II, open label, dose escalation study to evaluate the safety, torelability, PK pharmacodynamics and immunogenicity of MCLA-128. The anti-tumour activity of MCLA-128 will also be evaluated.

The study is designed in 2 parts: a phase I study (already completed) to evaluate the dose escalation (part 1) to identify a recommended dose of MCLA-128. This was set to 750mg

Part 2 is a phase I/II study in which a the safety and tolerability of the selected dose level of MCLA-128 is further explored.
Besides that, the anti-tumour activity will be evaluated in patients with

metastastatic breast cancer (group A), - ovarian cancer (group C), - gastric or gastroesophageal junction cancer (Group D), - endometrial cancer (Group E) and - non small cell lung cancer with NRG1 fusion (Group F), pancreatic cancer with NRG1 fusion (Group G) , and other solid tumors with NRG1 fusion (group H)

The Inclusion of patients in the colorectal cancer group (group B) has been closed per amendment 3.0 (19Jan17), because is anticipated that patients are less likely to benefit from single agent therapy with MCLA-128.

Group A (breast cancer) has been closed per 30May2017, because "proof of concept" was reached.
And Group C (ovarium cancer) has been closed per 16Nov17 because 30 patiënts were already included. The sponsor thinks enough data has been collected. Group D & E have been closed as well and group F will only continue for patients with documented NRG1 fusion.

Intervention

For part 2:

For protocol v3.0 the maximum tolerated dose was determined to be 750mg.
IV MCLA-128 (infusion time 120 minutes) will be dispensed to the patients on the first day of every cycle.
Every cycle lasts 3 weeks.

Protocol v4.0: the dosing schedule has been adjusted to a four week schedule:
For C1 and C2: C1D1 800mg, and furthermore a dose of 400mg per week (for the next 7 weeks)
For C3 and further: 400 mg per week, during 3 weeks and 1 week off.

Protocol v5.0: For new patients in group F,G, and H a four week schedule apply:
Biweekly: 750 mg every 2 weeks

Study burden and risks

The patients who are asked for participation in this study are relapsed or refractory to at least 1 prior regimen of available standard therapy and for whom no curative therapy is available and MCLA-128 is a reasonable treatment option.

The following adverse events have been noted in subjects treated with MCLA-128 in Part 1 of the study:
• Gastrointestinal problems such as nausea, vomiting, abdominal pain, diarrhoea and inflammation of the mouth and lips (stomatitis)
• Infusion related reactions/hypersensitivity, such as fever, chills, allergic reactions, hypotension, headache, nausea, vomiting, abdominal pain, involuntary

muscle contraction (tremor)
• Weakness or asthenia
• Tiredness or fatigue
• Allergic reactions were observed, mostly mild in nature however, one case resulted in death

MCLA-128 targets the receptors HER2 and HER3 which also are present on the surface of a variety of normal body tissues, such as heart tissue, but in low to very low amounts. Accordingly, in all drugs targeting those receptors, close monitoring of patients* safety is essential.
• Common known side effects (>=1/100 to <1/10 patients), seen with approved therapeutic antibodies targeting HER2 receptor only (such as Herceptin/trastuzumab/ Roche), might also be expected with usage of MCLA-128. However, it is unknown if these side effects will be necessarily experienced with MCLA-128, or if observed would be milder or more serious.
• Amongst the most serious and/or common adverse reactions reported in Herceptin usage to date are infusion-related reactions, haematotoxicity (in particular decrease of white blood cells, infections cardiac dysfunction and pulmonary adverse reactions.
• However, most adverse events reported with Herceptin, have been from clinical trials in combination use with chemotherapy agents.
• Infusion related reactions (IRRs), such as infusion site pain and irritation, fever, chills, respiratory distress. Most IRRs were reported with Herceptin to be experienced in the first or second cycle.
• Infectious disorders due to immune system impairment.
• Haematology disorders such as neutropenia (diminution of neutrophils count, neutrophils being blood cells which have anti-microbial function) or thrombocytopenia (diminution of platelets count, platelets being blood cells which have wound repair function).
• Cardiac dysfunction has been reported with Herceptin monotherapy up to 9 % of patients. Most cases has been reversible, however fatal outcomes have also been reported.
• Decrease liver or kidney function Hepatic or renal disorders.
• Pulmonary disturbance such as shortness of breath and edema of the lungs with rare fatal outcomes are reported.

Protocol v3.0: The patients will be exposed to the following study related procedures (based on completion of screening, cycle 1, end of treatment visit and final study visit):
- physical examination (screening, cycle 1 day 1, 8 and 15, end of treatment visit and final study visit);
- vital signs (screening, cycle 1 day 1, 8 and 15, end of treatment visit and final study visit);
- urine/blood pregnancy test, if applicable (screening, cycle 1 day 1, end of treatment visit);
- urine analysis (screening, cycle 1 day 1, end of treatment visit and final

study visit);
- blooddraw clinical chemistry and hematology (screening, cycle 1 day 1, 8 and 15, end of treatment visit and final study visit);
- blooddraw hemostasis (screening, cycle 1 day 1, end of treatment visit and final study visit);
- blooddraw PK (cycle 1 day 1 before infustion, end of infusion and 1, 2, 4, 8 and 24 hours after infusion, day 4, day 8 and day 15);
- tumour serum markers, when applicable and at screening elevated, than also at the end of each cycle.
- biomarker/PD blooddraws (C1D1 and end of treatment visit);
- biomarker/PD biopsy mandatory at screening and optional at end C4 and optional at end of treatment visit);
- radiological tumour assessment (screening, end of every 2nd cycle, final study visit and long-term f-up);
- MCLA-128 IV dispensing (cycle 1 day 1).
- MUGA scan: Screening, end of C4 and EoT visit

Protocol v4.0:
- physical examination (screening, cycle 1 day 1, 8 and 15, C2 and further Day1, end of treatment visit and final study visit);
- vital signs (screening, cycle x day 1, end of treatment visit and final study visit);
- urine/blood pregnancy test, if applicable (screening, cycle x day 1, end of treatment visit);
- urine analysis (screening, cyclus x day 1, end of treatment visite en final study visite);
- blooddraw clinical chemistry and hematology (screening, cyclus 1&2 day 1, 8, 15 and 22, C2 and further: day 1 and 15, end of treatment visit and final study visit);
- blooddraw hemostasis (screening, cyclus x day 1, end of treatment visit and final study visit);
- blooddraw PK (cyclus 1 day 1 before infusion, EOI and 2, 4 and 24 uur EOI, pre-dose on day 8 and day 15, and pre-dose + EOI on day 22. In cycle 2&3: pre-dose + EOI on day 15; cycle 4: pre-dose on day 1 and pre-dose + EOI on day 15. Afterwards every 2 cycles pre dose on day 15.)
- tumour serum markers, when applicable and at screening elevated, than also at the end of each cycle;
- biomarker/PD blooddraw (screening and end of treatment visit);
- biomarker/PD biopsy (mandatory at screening and optional at C5 and optional at end of treatment visit);
- radiological tumour assessment (screening, every 6 weeks, final study visit and long-term f-up);
- MUGA scan: screening, C5 en EoT.

The venapunctures and biopsies can be painfull and can lead to bleeding or bruising.
The size of the tumour(s) will be measured by use of a CT- and/or MRI scan. The

contrastfluid used can lead to an allergic reaction (e.g. rash, respiratory distress or shock. When a CT-scan is made a small amount of radiation is released, which has very little effect on the patient's health.

When taking a MUGA-scan of the heart a radioactive fluid will be injected in a vein, which will attach itself to red blood cells. The radioactive fluid will disappear from the body after a short while.

Contacts

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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. Age 18 years or older;
2. At least one measurable lesion according to RECIST v1.1 OR evaluable disease for a limited number of patients (up to 15) in Group H;

3. Performance status of ECOG 0, 1 or 2;
4. Estimated life expectancy of at least 12 weeks;
5. Toxicities incurred as a result of previous anti-cancer therapy resolved to <=Grade 1 (as defined by NCI CTCAE v4.03) except for alopecia, Grade 2 sensory neurotoxicity, or any other toxicity that in the opinion of the investigator does not affect the assessment of adverse events related to the study drug;
6. Treatment with anti-cancer medication or investigational drugs within the following intervals before the first dose of MCLA-128:
a. >14 days or >5 half-lives prior to study entry, whichever is shorter.
b. >14 days for radiotherapy. Note: A less than 1-week wash-out period is permitted only for palliative radiation to non-CNS disease with Sponsor approval.
7. Patient has recovered from prior surgery or other procedure or complication to <= Grade 2 or to baseline condition that in opinion of the investigator does not affect the assessment of adverse events related to the study drug;
8. Laboratory values at Screening:
a. Absolute neutrophil count >=1.5 x 109/L without colony stimulating factor support for at least 7 days prior to screening;
b. Platelets >=75 x 109/L without transfusion support for at least 7 days prior to screening;
c. Hemoglobin >=8 g/dL or >=5 mmol/L;
d. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) <=3 x upper limit of normal (ULN) and total bilirubin <=1.5 x ULN; in cases of metastatic liver involvement, ALT/AST <=5 x ULN and total bilirubin <=2 x ULN will be allowed; isolated elevation of AST or ALT > 3x ULN in the absence of underlying liver disease may be considered for enrollment upon Sponsor review and approval; in cases of antecedents of Gilbert*s syndrome when total bilirubin <=3.0 x ULN or direct bilirubin <=1.5 x ULN will be allowed;
e. Estimated glomerular filtration rate (GFR) of >30 mL/min based on the Cockroft-Gault formula;
9. Able to provide at baseline a mandatory tumor biopsy sample (FFPE), preferably a block. If safe/feasible, a fresh FFPE biopsy sample is preferred; archival tissue is acceptable (preferably not more than 2 years old);
NOTE1: For patients who received afatinib or other HER-targeting agents, a biopsy collected after the last line of treatment is strongly preferred to assess for mechanisms of acquired resistance.
NOTE2:For patients with a locally confirmed NRG1 gene fusion, when archival tissue is not available and collection of a fresh biopsy is not safe or feasible during the screening period, these patients will be allowed to enroll in the MCLA-128-CL01 trial provided they meet all other inclusion/exclusion criteria.
10. Negative pregnancy test during Screening and within 7 days of Cycle 1;
NOTE: Women with amenorrhea associated with prior treatment with antineoplastic medications are still considered as being of child-bearing potential.
11. Sexually active male and female patients of childbearing potential must agree to use one of the highly effective methods of birth control during the entire duration of the study and for 6 months after final administration of

MCLA-128.
12. Ability to give written, informed consent prior to any study-specific Screening procedures, with the understanding that the consent may be withdrawn by the patient at any time without prejudice;
13. Capable of understanding the mandated and optional protocol requirements, is willing and able to comply with the study protocol procedures and has signed the main informed consent document. For any optional biopsy sampling (tissue and/or blood) and long-term sample storage, additional consent is required;
14. Patients must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate standard of care therapy or no satisfactory alternative treatment options are available;
15. Locally-advanced unresectable or metastatic solid tumor malignancy with documented NRG1 gene fusion, identified through molecular assays such as PCR, next generation sequencing-based assays [DNA or RNA], or FISH as routinely performed at CLIA or other similarly-certified laboratories.The following tumor types are included:
- Group F: NSCLC
- Group G: pancreatic adenocarcinoma
- Group H: any other solid tumor
NOTE: Patients harboring fusions that are predicted to be non-functional, i.e. lack of EGF-domain, will not be included in the study. For equivocal cases, including those with NRG1 as the upstream partner, the sponsor will manually review genomic results and may request collateral testing, approve, or deny the case.

Exclusion criteria

1. Pregnant or lactating;
2. Presence of an active uncontrolled infection or an unexplained fever greater than 38.5°C during Screening up to the first scheduled day of dosing. At the discretion of the Investigator, patients with tumor fever or a clinically insignificant minor infection may be enrolled (i.e. mild upper respiratory infection);
3. Known hypersensitivity to any of the components of MCLA-128 or history of severe hypersensitivity reactions to human or humanized monoclonal antibodies, including therapeutic antibodies;
4. Patients with the following infectious diseases are excluded:
a. known HIV
b. active Hepatitis B infection (HBsAg positive) without receiving antiviral treatment
Note:
• Patients with active hepatitis B (HBsAg positive) must receive antiviral treatment with lamivudine, tenofovir, entecavir, or other antiviral agents,

starting at least >= 7 days before the initiation of the study treatment.
• Patients with antecedents of Hepatitis B (anti-HBc positive, HBsAg and HBV-DNA negative) are eligible.
c. positive test for Hepatitis C ribonucleic acid (HCV RNA)
Note: Patients in whom HCV infection resolved spontaneously (positive HCV antibodies without detectable HCV-RNA) or those that achieved a sustained response after antiviral treatment and show absence of detectable HCV RNA >= 6 months (with the use of IFN-free regimens) or
>= 12 months (with the use of IFN-based regimens) after cessation of antiviral treatment are eligible; NOTE: Patients without known or suspected HIV, Hepatitis B or Hepatitis C infection do not require specific viral testing during the screening period.
5. Known symptomatic or unstable brain metastases. Patients with asymptomatic brain metastases are eligible to participate if the metastases have been radiographically and clinically stable for at least one month. If on steroids for this indication, the patient must be on a stable dose for at least one month.
6. Patients with leptomeningeal metastases;
7. Previous or concurrent malignancy, excluding non-basal cell carcinoma of skin or carcinoma in situ of the uterine cervix unless the tumor was treated with curative or palliative intent and in the opinion of the investigator, with sponsor agreement, the previous or concurrent malignancy condition doesn*t affect the assessment of safety and efficacy of the study drug;
9. Presence of LVEF <50% on the screening echocardiogram; or history or presence of any significant cardiovascular disease, including unstable angina or myocardial infarction within 12 months prior to screening, congestive heart failure (NYHA Class III or IV), or ventricular arrhythmia requiring medication;
10. Presence of any other medical or psychological condition deemed by the Investigator to be likely to interfere with a patient's ability to sign informed consent, cooperate or participate in the study, or interfere with the interpretation of the results.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-03-2015
Enrollment:	34
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	full length IgG1 bispecific antibody

Ethics review

Approved WMO Date:	01-12-2014
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	09-03-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-02-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	12-08-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-02-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-03-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-04-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	20-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	30-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-08-2020
Application type:	Amendment
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Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-11-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	20-01-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-04-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-05-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-08-2023
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
EU-CTR	CTIS2024-512358-78-00
EudraCT	EUCTR2014-003277-42-NL
ClinicalTrials.gov	NCT02912949
CCMO	NL51045.031.14