MCLA-128 is a bispecific, humanized, full-length IgG1 antibody with enhanced antibody-dependent cell-mediated cytotoxic (ADCC) activity that potently inhibits Functional NRG1 fusions result in expression of the EGF-like domain of NRG1, which binds to extracellular HER3, leading to HER2/HER3 heterodimerization. This in turn causes increased downstream PI3K/AKT/mTOR signaling and tumor growth. NRG1 gene fusions are emerging as clinically actionable genomic targets. MCLA-128 is a bispecific, humanized, full-length IgG1 antibody with enhanced antibody-dependent cell-mediated cytotoxic (ADCC) activity that potently inhibits HER3 signaling pathway.

FIGURE 1: DOCK & BLOCK® action of MCLA-128 in HER2/3 signaling
A) NRG1 fusion proteins function as ligands for HER3 (similar to NRG1) and bind to HER3 with high affinity to promote HER2/HER3 dimerization and downstream signaling. B) MCLA-128 inhibits the HER3/HER3 interaction via its DOCK & BLOCK® mechanism, whereby one arm of the antibody binds to the HER3 receptor, optimally positioning the anti-HER3 arm to block the ligand/receptor interaction and prevent HER3/HER3 dimerization.

Potent in vitro/vivo activity was observed with MCLA-128 in NRG1-fusion positive models (MDA-MB-175 [breast], OVCAR3 [ovarian], OV-10-0050 [ovarian]). In the clinic, MCLA-128 has shown promising single-agent activity in the first-in-human study across several tumor types. Clinical proof-of-concept has been achieved in metastatic breast cancer and gastric cancer in heavily pretreated patients progressing on multiple anti-HER2 therapies. MCLA-128 has a very well tolerated safety profile with grade 3-4 events reported in <5% of patients, and an absence of clinical cardiotoxicity and severe gastrointestinal events. MCLA-128 is now being investigated in patients with NRG1-fusion-positive tumors in the ongoing Phase 2 part of the study.

Key Eligibility Criteria
- Locally-advanced unresectable or metastatic solid tumor with documented NRG1 gene fusion, identified by a molecular assay such as PCR, NGS (RNA or DNA) or FISH
- At least 18 years-old
- At least one measurable lesion by RECIST v1.1 (evaluable non-measurable is permitted for up to 10 patients)
- Failure or non-suitability of standard therapy
- Availability of a fresh or archived FFPE tumor biopsy sample

FIGURE 2: NRG1 fusion cohorts
NRG1 fusion pancreas
NRG1 fusion NSCLC
NRG1 fusion other solid tumors

FIGURE 3: Global distribution of recruiting centers

FIGURE 4: Treatment and follow-up plan
Pre-screening
Screening
Treatment
Follow-up
Micile pancreate & NSCLC-NA
MicroRNA panel
NRG1 fusion cohorts: 1. Pancreas 2. NSCLC 3. Other
Cycle 1
Cycle 2
Cycle 3-4
Cycle 5-8
Thermalization +
750 mg MCLA-128, IV 2-4h

Phase 2 Study Objectives
Primary objectives:
- To explore antitumor activity of MCLA-128 according to RECIST v1.1, per local investigator assessment, in terms of overall response rate and duration of response
- To characterize safety/tolerability of MCLA-128

Secondary objectives:
- To evaluate progression-free and overall survival
- To characterize the pharmacokinetic profile and immunogenicity

Exploratory objectives:
- To identify potential biomarkers and their relationship with anti-tumor activity
- To evaluate best overall response according to PET response criteria

Treatment
- Patients with NRG1-fusion positive tumors receive a regimen of 750 mg MCLA-128, IV over 2 hours, every other week, in 4-week cycles.
- After treatment discontinuation, patients are followed-up for 3 months to 2 years.

References

STUDY STATUS / CURRENT SITES
Recruitment into all three NRG1 cohorts was opened in September 2019. The study is actively accruing NRG1 fusion patients in Europe, North America, and Asia. There are currently 23 sites open, and another 12 are planned to be opened by Q4 2020. (List below.)

Sponsor / funding: Merus N.V.

Corresponding author:
Pi: Alison Schram schramfa@merus.nl

Clinical trial enrollment:
Ernesto Wasserman ewasserman@merus.nl; Jim Ford jford@merus.nl

AM Schram1, AR Drilon2, T Macarulla Mercade3, EM O’Reilly, J Rodon3, BM Wolpin4, S-HI Ou5, D-W Kim6, JCH Yang7, JYC Lam8, A Varga9, AJ de Langen10, P Witteveen11, V Boni12, G Cerea13, M Duruisseaux14, SV Liu15, E Wasserman16, DM Hyman1, J Taberner2

1) Memorial Sloan Kettering/Weill Cornell Medical College, NY, USA; 2) Vall d’Hebron University Hospital/VHID, Barcelona, Spain; 3) MD Anderson Cancer Center, TX, USA; 4) Dana-Farber Cancer Institute, MA, USA; 5) University of California Irvine, CA, USA; 6) Seoul National University Hospital, Seoul, Republic of Korea; 7) National Taiwan University Cancer Center/Hospital, Taipei, Taiwan; 8) National Cancer Centre Singapore, Singapore; 9) Gustave Roussy Cancer Campus, Villejuif, France; 10) Netherlands Cancer Institute, Amsterdam, Netherlands; 11) UMC Utrecht Cancer Center, Utrecht, Netherlands; 12) START Madrid-CIOCC/University Hospital San Carlos, Madrid, Spain; 13) Niguarda Cancer Center, Ospedale Niguarda/Università degli Studi di Milano, Italy; 14) Hôpital Louis Pradel-Hospices Civils de Lyon, France; 15) Lombardi Cancer Center Georgetown University, Washington, USA; 16) Merus N.V., Utrecht, Netherlands

Background & rationale
NRG1gene fusions, which encode chimeric NRG1 fusion proteins, are oncogenic drivers found in various cancers including pancreatic and lung adenocarcinomas.

NRG1 gene fusions result in expression of the EGF-like domain of NRG1, which binds to extracellular HER3, leading to HER2/HER3 heterodimerization. This in turn causes increased downstream PI3K/AKT/mTOR signaling and tumor growth. NRG1 gene fusions are emerging as clinically actionable genomic targets.

MCLA-128 is a bispecific, humanized, full-length IgG1 antibody with enhanced antibody-dependent cell-mediated cytotoxic (ADCC) activity that potently inhibits HER3 signaling pathway.

Study Design
FIGURE 2: NRG1 fusion cohorts
GLOBAL STUDY OBJECTIVES
Phase 2
- Single-agent MCLA-128

Phase 2 Study Objectives
Primary objectives:
- To explore antitumor activity of MCLA-128 according to RECIST v1.1, per local investigator assessment, in terms of overall response rate and duration of response
- To characterize safety/tolerability of MCLA-128

Secondary objectives:
- To evaluate progression-free and overall survival
- To characterize the pharmacokinetic profile and immunogenicity

Exploratory objectives:
- To identify potential biomarkers and their relationship with anti-tumor activity
- To evaluate best overall response according to PET response criteria

Treatment
- Patients with NRG1-fusion positive tumors receive a regimen of 750 mg MCLA-128, IV over 2 hours, every other week, in 4-week cycles.
- After treatment discontinuation, patients are followed-up for 3 months to 2 years.