First-in-human phase 1/2 study of MCLA-128, a full length IgG1 bispecific antibody targeting HER2 and HER3; final phase 1 data and preliminary activity in HER2+ metastatic breast cancer (MBC)

Maria Alsina[1], Valentina Boni[2], Aurelia de Vries Schultink[3], Victor Moreno[4], Kees Bol[5], Martine Westendorp[5], L. Andres Sirulnik[5], Josep Tabernero[1], Emiliano Calvo[2]

1) Vall d'Hebron University Hospital and Institute of Oncology (VHIO), Barcelona, Spain; 2) START Madrid CIOCC, Hospital HM Universitario Sanchinarro, Madrid, Spain; 3) The Netherlands Cancer Institute, Amsterdam, The Netherlands; 4) START Madrid – FJD, Hospital Fundación Jimenez Diaz, Madrid, Spain; 5) Merus N.V., Utrecht, The Netherlands.

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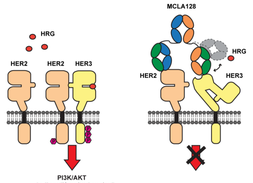
Background

- MCLA-128 is a bispecific humanized full-length IgG1 antibody that binds the transmembrane receptor tyrosine kinases human epidermal growth factor receptors 2 and 3 (HER2 and HER3).
- MCLA-128 was developed to inhibit HER2:HER3-driven cell growth and to overcome HER3-mediated resistance (primary or acquired) and/or relapse under HER2- or EGFR-targeted therapies, a phenomenon frequently observed in epithelial tumors.
- It acts via two independent mechanisms of action: 1) inhibition of HER2:HER3 signaling and 2) elimination of tumor cells via enhanced antibody-dependent cell-mediated cytotoxicity (ADCC).
- MCLA-128 employs a 'dock and block' mechanism. Based on X-ray crystal structure, MCLA-128 docks to the HER2 domain I which orientates the HER3 binding arm to block the HER3 domain III (putative HRG domain), thus blocking oncogenic signaling via the HER2:HER3 heterodimer [Maussang et al. 2017 AACR].



- Potent *in vitro* and *in vivo* antitumor activity has been shown, including stronger inhibition of proliferation of HER2-amplified cells at high HRG concentrations compared to other anti-HER2 and anti-HER3 antibodies [Geuijen et al. 2015 AACR, Maussang et al. 2017 AACR].
- We report final phase 1 data from a first-in-human study and results from the ongoing phase 2 part of the study, with a focus on antitumor activity in metastatic breast cancer (MBC) patients.

Objectives & Design

- **Primary objectives:**
  - ✓ Phase 1: to determine the MTD of single agent MCLA-128
  - ✓ Phase 2: to characterize safety and antitumor activity
- **Secondary objectives:** to characterize the pharmacokinetics (PK) and immunogenicity profiles, and evaluate antitumor activity
- **Exploratory objectives:** to evaluate potential biomarkers

Phase 1: Dose-finding

- MCLA-128 dose escalation at a starting dose of 40 mg (flat dose), 1-2 hours IV, every 3 weeks (q3w)
- Initial accelerated escalation then classic 3+3 design
- RP2D defined

Population

- Advanced/metastatic epithelial solid tumors
- Relapsed/refractory to ≥ 2 prior therapies or no curative option

Phase 2: Expansion cohorts

- Treatment at the RP2D of 750 mg, 2 hours IV, q3w
- Mandatory premedication with antipyretics, antihistamines and corticosteroids

Population

- Selected metastatic indications
  - ✓ Breast HER2-amplified
  - ✓ Gastric/GEJ HER2-amplified
  - ✓ Ovarian
  - ✓ Endometrial
  - ✓ NSCLC HER2-expressing

Study Assessments

- Adverse events: as per CTCAE v 4
- Antitumor activity: as per RECIST 1.1, and clinical benefit rate (CBR) defined as CR + PR + SD ≥ 12 weeks
- PK: Serum MCLA-128 concentrations
- Blood cytokine panel: TNFα, IFNγ, IL-1β, IL-2, IL-6, IL-8, IL-10
- Immunogenicity: anti-MCLA-128 antibodies
- Biomarkers: HER2 status (presented), HER3, HER2:HER3 dimers, heregulin, pHER2, pHER3, pAKT, pERK1/2 (ongoing)

Patient Demographics & Treatment

Phase 1: Dose escalation has been completed, with 9 dose levels evaluated (40 to 900 mg) in 28 epithelial solid tumor patients who received a median of 2 cycles (range 1-28) [Calvo et al. 2016 AACR].
Phase 2: As of 15 Feb 2017, 19 patients were enrolled in the phase 2 part (750 mg q3w), 16 of whom were treated. A median of 3 cycles (range 1-12) had been administered, with the 9 treated MBC patients receiving a median of 5 cycles (range 2-12).

Phase 2 RP2D expansion (enrolled)	mBC (N=10)	Other[1] (N=9)	Total (N=19)
Age (years), Median (Min;Max)	52 (37;70)	57 (33;74)	54 (33;74)
Gender (male), N (%)	0	6 (67%)	6 (32%)
ECOG PS (0/1), N	2 / 8	1 / 8	3 / 16
N Metastatic Sites, Median (Min;Max)	3 (1;3)	2 (1;4)	2.5 (1;4)
N Prior Therapies, Median (Min;Max)	6 (4;18)	3 (2;8)	5.5 (2;18)
N Prior HER Therapies, Median (Min;Max)	3 (3;4)	1 (0;2)	3 (0;4)

1. Metastatic gastric/gastroesophageal (6 patients), ovarian (2 patients), and colorectal (1 patient; cohort closed prematurely)

Safety

- No DLTs were observed during dose escalation, and 750 mg q3w was selected as the recommended phase 2 dose (RP2D), based on safety and PK model simulations [Calvo et al. 2016 AACR].

All related AEs, Phase 1 treated patients (N=28)

AE Preferred Term	G1-4[1]	G3-4
Infusion related reaction	10 (36%)	1 (4%)
Nausea	8 (29%)	0
Vomiting	7 (25%)	0
Diarrhea	5 (18%)	0
Stomatitis	4 (14%)	0
Asthenia	4 (14%)	0
Abdominal pain	2 (7%)	0
Fatigue	2 (7%)	0

1. Related AEs in 1 patient each: bilirubin increase, dyspnea, gastroesophageal reflux, headache, hypotension, mucosal inflammation, neutropenia, pyrexia, tremor, sinus tachycardia, dermatitis acneiform, rash erythematous, rash macular, rash maculo-papular, skin fissures, onychomadesis.

All related AEs, Phase 2 treated patients (N=16)

AE Preferred Term	G1-4	G3-4
Infusion related reaction	4 (25%)	0
Diarrhea	3 (19%)	0
Fatigue	2 (13%)	0
Hypersensitivity	1 (6%)	1 (6%)[2]
Anxiety	1 (6%)	0
Constipation	1 (6%)	0
Decreased appetite	1 (6%)	0
Myalgia	1 (6%)	0
Nausea	1 (6%)	0
Rash papular	1 (6%)	0
Stomatitis	1 (6%)	0
Transaminases increased	1 (6%)	0

2. A 71-year-old gastric carcinoma patient had a grade 4 hypersensitivity reaction on Day 1 Cycle 1 followed by cardiorespiratory arrest. The patient's baseline cardiac condition (severe aortic stenosis) contributed to the fatal outcome.

Safety

Adverse Events of Special Interest

- No suspected cardiac clinical AEs or clinically significant LVEF declines occurred; overall, 5/27 (19%) evaluable patients had grade 2 LVEF decreases, none symptomatic or clinically significant (defined as LVEF decline >10% from baseline and to a value of <50%).
- No severe (grade 3-4) diarrhea or diarrhea requiring treatment discontinuation was observed.
- Infusion-related reactions (IRR) were analyzed according to all preferred terms reported by the investigator as manifestations of IRRs (e.g. IRR, hypersensitivity, nausea, vomiting, pyrexia, etc.). As per this definition, 14 phase 1 patients (50%) and 5 phase 2 patients (31%) had IRRs. All but 2 IRRs were grade 1-2 and resolved completely with symptomatic treatment.

Antitumor Activity

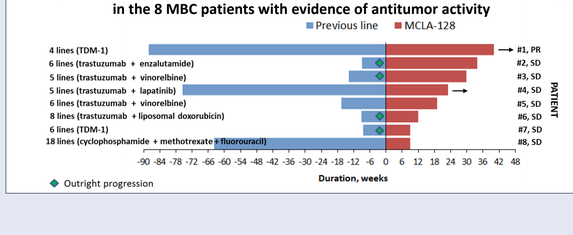
- **Phase 1**: among the 28 evaluable patients, 1 NSCLC patient had a confirmed PR (360 mg, 18.0 months) and 3 patients had SD >3 months (breast, 3.6 months; colorectal, 7.3 months; gastroesophageal junction, 13.4+ months).
- **Phase 2**: 16 evaluable patients (ongoing enrollment), 9 MBC and 7 other tumors. Antitumor activity was seen in 6 MBC patients (1 PR and 5 SD), and 2 other tumor types (2 SD including a gastric patient with 7+ cycles).
- **MBC cohort activity** (11 patients; 9 at 750 mg, 2 at 480 mg)
  - ✓ 1 MBC patient had PR and 7 had SD (4 lasting ≥ 5 months)
  - ✓ The clinical benefit rate in MBC patients was 64% (7/11 patients)
  - ✓ Patients were heavily pretreated, all with 2-5 anti-HER therapy lines

Characteristics of the HER2-positive MBC patient cohort (750 and 480 mg)

Patient ID	Metastatic sites	N prior lines	N HER2 therapies	Dose (mg)	N cycles	Best response	Response duration (weeks)[1]
#1	Bone, lung	4	4	750	14	PR	34.4+
#2	Bone, lymph nodes	6	3	750	12	SD	37.0
#3	Skin, lymph nodes	5	3	750	11	SD	34.0
#4	Bone, brain	5	3	750	8	SD	23.3+
#5	Lung	6	5	480	7	SD	21.4
#6	Bone, skin	8	3	750	5	SD	14.9
#7	Brain, liver, peritoneum	6	2	480	4	SD	12.0
#8	Skin	18	4	750	4	SD	11.7
#9	Bone, lymph nodes, skin	5	3	750	2	PD	-
#10	Lung, lymph nodes, skin	8	2	750	2	PD	-
#11	Pleura, lymph nodes, skin	5	3	750	2	PD	-

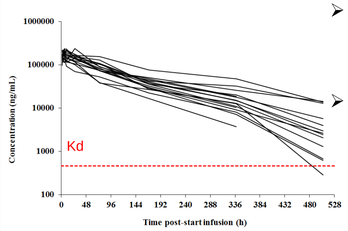
1. RECIST response duration calculated until 10 May 2017

Comparison of treatment duration with MCLA-128 versus last line of prior therapy in the 8 MBC patients with evidence of antitumor activity



PK, Cytokines & Immunogenicity

Individual serum MCLA-128 concentrations and mean PK parameters in patients treated at 750 mg (Phase 1 and 2, N=16)



- C_{max} was 194 µg/mL; $AUC_{0-\infty}$ was 22500 µg·h/mL; V_{ss} was 4.5 L; CL was 37 mL/h ; t½ was 101 h.
- After 21 days median trough levels were 2.6 µg/mL, well above the MCLA-128 concentration that results in 50% receptor occupancy *in vitro* (Kd).
- Only 1 patient (160 mg MCLA-128) of 34 had a positive anti-drug-antibody (ADA) titer at Day 36, with no apparent effect on PK. All other patients were ADA-negative throughout treatment.
- At the RP2D, modest and transient cytokine elevations from baseline were observed 2 hours after the end of the infusion, mainly in IFNγ (0.4-3.4 fold), IL-8 (0.7-8.4 fold) and TNFα (0.8-11.6 fold).

Conclusions

- Single agent MCLA-128 administered at the RP2D is very well tolerated, with a low incidence of grade 3-4 related toxicity (2 of 22 patients treated at 750 mg q3w).
- Promising evidence of activity has been shown in HER2-positive MBC in heavily pretreated patients progressing on multiple HER2 therapies.
- Pharmacokinetic data support MCLA-128 dosing at 750 mg q3w.
- MCLA-128 shows a low risk for immunogenicity.
- The demonstrated single agent activity in MBC prompted further phase 2 development of MCLA-128-based combinations in two MBC populations.

HER2+ MBC failing 2-4 prior HER2 therapies (including T-DM1)

- **Doublet**: MCLA-128 + trastuzumab
- **Triplet**: MCLA-128 + trastuzumab + vinorelbine

HR+/HER2-low expression MBC failing ≥1 prior endocrine therapy + CDK4-6 inhibitor

- MCLA-128 + endocrine therapy

References

- Calvo et al. (2016). A phase I/II study of MCLA-128, a full length IgG1 bispecific antibody targeting HER2/HER3, in patients with solid tumors. Cancer Res 76 (14 Supp)
- Geuijen et al. (2015). Mechanism of action of MCLA-128, a humanized bispecific IgG1 antibody targeting the HER2:HER3 heterodimer. Cancer Res 75, Abstract LB-261
- Maussang et al. (2017). The binding mode of the bispecific anti-HER2xHER3 antibody MCLA-128 is responsible for its potent inhibition of HRG-driven tumorigenesis. Proc AACR. Vol 58

Contact

- Enquiries@Merus.nl

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