**Background**

MCLA-128 is a bispecific humanized full-length IgG1 antibody that binds the transmembrane tyrosine kinase 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 HER2-mediated resistance (primary or acquired) and/or release under HER2- or ERβ-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 orients the HER3 binding arm to block the HER3 domain III (putative HRG domain), thus blocking signaling through the HER2:HER3 heterodimer (Maussang et al. 2017; JACC).

**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

**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 + clinical benefit.
- **PK:** Serum MCLA-128 concentrations
- **Immunogenicity:** anti-MCLA-128 antibodies

**Patient Demographics & Treatment**

**Phase 1:** Dose escalation has been completed, with 9 dose levels evaluated (40 mg to 900 mg) in 28 epithelial solid tumor patients who received the 50 mg dose level. Three dose levels (100, 200, and 400 mg) were escalated, thus allowing the evaluation of 93 evaluable patients receiving a median of 3 cycles (range 1-10).

**Phase 2:** At the end of the phase 1 part of the study, 9 dose levels (100, 200, and 400 mg) were escalated, thus allowing the evaluation of 93 evaluable patients receiving a median of 3 cycles (range 1-10).

**Patient Characteristics**

- **N Prior Therapies, Median (Min;Max) 6 (4;18)**
- **N Metastatic Sites, Median (Min;Max) 3 (1;3)**

**Biomarkers:** HER2 status (present), HER3, HER2:HER3 dimers, heregulin, EGF, HER2, pHER2, pHER3, pAKT, pERK1/2 (ongoing)

**Safety**

- **Adverse Events of Special Interest**
  - No Drug-Related Deaths
  - No Pneumonitis
  - No severe (grade 3-4) diarrhea or diarrea requiring treatment discontinuation was observed.

**PK, Cytokines & Immunogenicity**

Individual serum MCLA-128 concentrations and mean PK parameters in patients treated at 750 mg (Phase 1 and 2, N=12)

**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 12 patients at 750 mg). Patients were heavily pretreated, all with 1-2 anti-HER2 therapy lines.

- Promising evidence of activity has been shown in HER2-positive MBC in heavily pretreated patients progressing on multiple HER2 therapies.

- Pharmacodynamic studies support MCLA-128 disintegrating at 750 mg qw.

- 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.

**Contact**

- Maussang et al. (2017). The binding mode of the bispecific anti-HER2/HER3 antibody MCLA-128 is responsible for its potent inhibition of HRG-driven tumorigenesis. Proc AACR 60, 651-652