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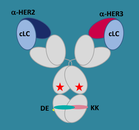
# Clinical activity of MCLA-128 (zenocutuzumab), trastuzumab and vinorelbine in HER2-amplified metastatic breast cancer patients (MBC) who had progressed on anti-HER2 antibody drug conjugates (ADCs)

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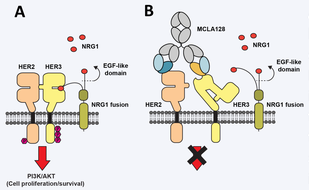
## BACKGROUND

MCLA-128 (zenocutuzumab) is a bispecific humanized full-length IgG1 antibody that binds the transmembrane receptor tyrosine kinase human epidermal growth factor receptors 2 and 3 (HER2 and HER3).
MCLA-128 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).

**Figure 1. DOCK & BLOCK® mechanism action**




**A)** Ligands (such as NRG1) bind to HER3 with high affinity and promote HER2/HER3 dimerization and downstream signaling.
**B)** MCLA-128 inhibits the HER3-ligand interaction; one arm of the antibody binds the HER2 receptor, and at a different epitope to trastuzumab. This optimally positions the anti-HER3 arm to block the ligand/receptor interaction, preventing HER2/HER3 dimerization and PI3K/AKT/ mTOR pathway activation.[1]

HER3 overexpression and/or HER3 ligand upregulation are important drivers in breast cancer progression associated with trastuzumab resistance.[2]

MCLA-128 inhibited proliferation in HER2-amplified breast cancer cell lines *in vitro* and *in vivo*, and showed synergy with trastuzumab.[1] In the first-in-human phase 1/2 study, consistent antitumor activity was observed with single agent MCLA-128 in heavily pretreated HER2-amplified breast cancer patients progressing on anti-HER2 therapies.[3]

The current open-label phase 2 study was designed to explore the efficacy of the triplet combination of MCLA-128 plus trastuzumab and vinorelbine in MBC.

## STUDY DESIGN

**Population**

- Metastatic or locally advanced breast cancer with HER2 overexpression by IHC 3+ or IHC 2+ with FISH amplification.
- Up to 5 lines of anti-HER2 therapy (metastatic setting with progression on the most recent line, per RECIST v1.1).
- Prior trastuzumab, pertuzumab and an HER2 ADC.

**Prior treatment**

*Trastuzumab
*Pertuzumab
*HER2 ADC
*Any sequence

→ PD

**Study treatment**

MCLA-128 + trastuzumab + vinorelbine
**Safety run-in**
**SAFE**
**Cohort expansion**

**Day 1 (3-week cycles)**

Pre-medication → MCLA-128 750 mg 2 h IV → 30 min → Trastuzumab 8 mg/kg, 90 min IV (Cy 1) 6 mg/kg, 30-90 min (Cy ≥2) → 30 min → Vinorelbine 25 mg/m² 10 min IV

**Day 8**

Vinorelbine 25 mg/m² 10 min IV

An Independent Data Monitoring Committee (IDMC) evaluated 2 consecutive safety run-in cohorts (5 patients each for 2 cycles), initially for an MCLA-128 + trastuzumab doublet, then the MCLA-128 triplet combination.
The IDMC approved expansion of the triplet cohort up to 40 patients evaluable for efficacy in total.

**Assessments**

- CT/MRI tumor assessment every 6 weeks
- AEs (CTCAE v4.03); LVEF every 3 months
- PK analyses for serum MCLA-128

**Endpoints**

- Primary: Clinical benefit rate (CBR) at 24 weeks, RECIST 1.1 per investigator
- Secondary: Overall response rate, duration of response, safety/tolerability, PK

## PATIENT POPULATION

A total of 39 patients were treated with the MCLA-128 triplet combination, and 12 of them were ongoing at the time of the efficacy cut-off of 31 March 2020.
The 39 treated patients had received a median of 5 cycles [range 1-22].

**Table 1. Demographics and disease characteristics**

| | N=39 |
|---|---|
| **Age** (years), median [range] | 57 [29-84] |
| **ECOG PS (0/1)**, N (%) | 21 (54%) / 18 (46%) |
| **Prior therapies** | |
| **N therapies** (chemotherapy, anti-HER2, hormonal), median [range] | 5 [2-8] |
| **N anti-HER2 lines** (metastatic setting), median [range] | 3 [1-5] |
| **Prior pertuzumab**, N (%) | 39 (100%) |
| **Prior T-DM1**, N (%) | 39 (100%) |
| **N metastatic sites***, median [range] | 3 [1-5] |
| Lymph nodes | 22 (56%) |
| Bone | 21 (54%) |
| Lung | 20 (51%) |
| Liver | 13 (33%) |
| Breast | 12 (31%) |
| Brain | 8 (21%) |

* Sites present in >20% of the cohort.

## SAFETY

At the safety data cut-off of 14 November 2019, the 28 patients treated with the triplet regimen had received a median of 5 cycles [range 1-17].

**Table 2. Treatment- related AEs in >5% patients and all grade ≥3 events (N=28)**

| | All grades | Grade 3-4 |
|---|---|---|
| **N patients ≥1 related AE** | 25 (89%) | 15 (54%) |
| Diarrhea | 17 (61%) | 1 (4%) |
| Neutropenia | 17 (61%) | 13 (46%) |
| Asthenia | 9 (32%) | 0 |
| Nausea | 8 (29%) | 0 |
| Fatigue | 4 (14%) | 0 |
| Abdominal pain | 3 (11%) | 0 |
| Constipation | 3 (11%) | 0 |
| Vomiting | 3 (11%) | 0 |
| Dysgeusia | 2 (7%) | 0 |
| Dyspnoea | 2 (7%) | 0 |
| Mucosal inflammation | 2 (7%) | 0 |
| Myalgia | 2 (7%) | 0 |
| Pyrexia | 2 (7%) | 0 |
| Febrile neutropenia | 1 (4%) | 1 (4%) |
| Peripheral motor neuropathy | 1 (4%) | 1 (4%) |

- All grade 3-4 neutropenia (46% of patients) was related to vinorelbine.
- 3 of 15 evaluable patients had transient grade 2 LVEF decrease, 1 was clinically significant but was asymptomatic.
- Infusion-related reactions (grouped term for AEs associated with infusion) were reported in 18% of patients.
- 2 patients discontinued treatment due to AEs related to vinorelbine, including 1 patient who developed fatal sepsis*.
- MCLA-128 dose interruptions occurred in 14% of patients.

*This 46-yo patient with bone, brain, liver, lung and LN metastases, progressed on 5 lines of therapy, and had elevated WBC/ANC at baseline. She developed sepsis and G4 neutropenia (related to vinorelbine) on day 13, and died 3 days later.

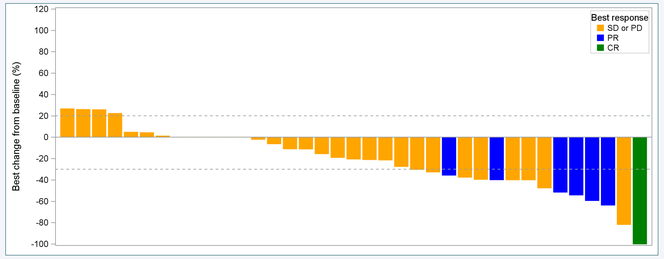
## ANTITUMOR ACTIVITY

- Antitumor activity (RECIST v1.1) was evaluated in 37 evaluable patients with locally confirmed HER2 amplification (3+ IHC or 2+ IHC confirmed by FISH), at the efficacy cut-off of 31 March 2020.
- The CBR (CR + PR + [SD at 24 weeks]) was 35.1% [90%CI 22.2-50.0].
- 1 patient had a CR lasting 19.3 weeks, 6 patients had PR (lasting from 5.3+ to 12.3+ weeks, and 22 had SD (lasting from 5.9+ to 59.1+ weeks; Table 3, Fig. 2 and 3). Among patients with best response of SD, 5 patients had unconfirmed PR, 2 of which are ongoing.

**Table 3. CBR, ORR, and BOR, Investigator assessed (RECIST v1.1)**

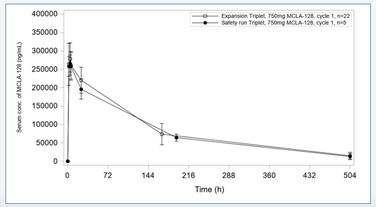
| | N=37 |
|---|---|
| **Clinical benefit rate at 24 weeks, N (%) [90%CI]** | 13 (35.1%) [22.2-50.0] |
| Overall response rate, N (%) [90%CI] | 7 (18.9%) [9.2-32.6] |
| Best overall response (confirmed) | |
| Complete response | 1 (2.7%) |
| Partial response | 6 (16.2%) |
| Stable disease | 22 (59.5%) |
| Disease progression | 8 (21.6%) |

**Figure 3: Waterfall plot of best percent change from baseline in target lesions in patients with measurable disease (N=37)**



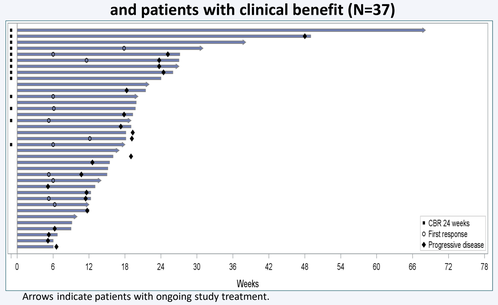

## PHARMACOKINETICS

**Figure 4: Concentration vs time curve of MCLA-128 in cycle 1**




- PK data from 27 evaluable patients were assessed by non-compartmental analysis.
- Mean $C_{max}$ was 294 µg/mL; $AUC_{\infty}$ was 49980 µg·h/mL; Vss was 2.6 L; CL was 16.1 mL/h ; t½ was 117 h.
- At the mean trough level (16 µg/mL), predicted receptor occupancies for HER2 and HER3 are >90%, suggesting relevant pharmacological activity for the entire 3-week dosing interval.
- MCLA-128 PK was similar to single agent PK analyses.[4]

**Figure 2: Plot of duration of exposure (weeks), onset of response, and patients with clinical benefit (N=37)**




Arrows indicate patients with ongoing study treatment.

## CONCLUSIONS

- **The MCLA-128 (zenocutuzumab) triplet combination is active in heavily pretreated HER2+/amplified MBC patients who have progressed on T-DM1, with 35% of patients achieving clinically meaningful benefit at 6 months.**
- **The most common severe AE reported with the triplet therapy was neutropenia considered related to vinorelbine, with few patients discontinuing due to AEs.**
- **The PK profile of MCLA-128 administered in combination with trastuzumab and vinorelbine was similar to that of single agent MCLA-128.**

**References**

1. Geuijen et al. *Cancer Cell.* 2018; 33(5):922-36
2. Lyu et al. *Acta Pharm Sin B.* 2018; 8(4):503-10
3. Alsina et al. *J Clin Onc.* ASCO 2017; 35 (15 Suppl): 2522
4. De Vries Schultink et al. *Clinical Pharmacokinet*. 2020; doi: 10.1007/s40262-020-00858-2

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Due to the COVID-19 pandemic, not all data were source verified.