# Updated analysis of MCLA-128 (zenocutuzumab), trastuzumab, and vinorelbine in patients with HER2 positive/amplified (HER2+) metastatic breast cancer who progressed on previous anti-HER2 ADCs

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## INTRODUCTION

Zenocutuzumab (Zeno; MCLA-128) is a bispecific Biclonics® humanized full-length IgG1 antibody with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC).

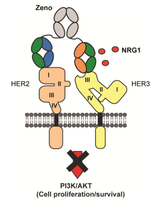



**Figure 1 | Dock and Block Mechanism of Zeno**

Zeno inhibits HER3 from interacting with its ligands (e.g., NRG1). One arm of the antibody docks onto the transmembrane receptor tyrosine kinase human epidermal growth factor receptor 2 (HER2), at HER2 domain I. This optimally positions the anti-HER3 arm to block the ligand/receptor interaction, thereby preventing HER2/HER3 dimerization and downstream PI3K/AKT/mTOR pathway activation.[1]

HER3 overexpression and/or HER3 ligand upregulation are key drivers in breast cancer progression associated with trastuzumab resistance.[2] Zeno inhibited proliferation in HER2-amplified breast cancer cell lines *in vitro* and *in vivo.* Zeno in combination with herceptin, which binds HER2 domain IV,[3] resulted in stronger inhibition compared to Zeno alone (data on file). In a first-in-human phase 1/2 study with single agent Zeno (NCT02912949), preliminary antitumor activity was observed in heavily pretreated HER2-amplified breast cancer patients who progressed on anti-HER2 therapies.[4]

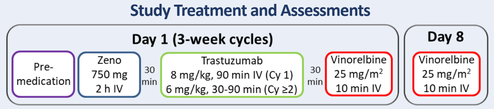
We present here an open-label, multicenter phase 2 study designed to explore the efficacy of a triplet combination of Zeno plus trastuzumab and vinorelbine in metastatic breast cancer patients (NCT03321981). Preliminary results for patients treated with the triplet regimen were presented at ASCO 2020. The combination was deemed safe in the run-in cohort and the cohort was expanded.[5] Updated results from the cohort expansion are presented here.

## STUDY DESIGN

**Patient Population**

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

**Study Treatment and Assessments**




- CT/MRI tumor assessment every 6 weeks
- AEs (CTCAE v4.03) throughout; LVEF every 3 months
- PK analyses of serum Zeno at baseline and during treatment
- Baseline analysis of tumor biomarkers by functional proteomics reverse-phase protein array (RPPA; fresh biopsy preferred or archival <2 years)

**Statistical Hypothesis, Endpoints, and Analysis Population**

A sample size of 40 patients with a clinical benefit rate (CBR) at 24 weeks of 45% provides adequate precision to exclude 30% (lower limit of 90% CI > 30%). The CBR threshold was based on the assumption that progression-free survival (PFS) follows an exponential distribution, with a median of 5 months considered clinically relevant and 3.5 months considered not clinically relevant.

**Primary endpoint:** CBR at 24 weeks, RECIST v1.1 per investigator

**Secondary endpoints:** CBR at 24 weeks (per central), overall response rate (ORR), duration of response, PFS, overall survival (OS), safety, PK parameters, and biomarkers

**Evaluable for efficacy population:** patients who receive ≥2 complete treatment cycles (6 weeks) with a baseline tumor assessment and ≥1 on-study tumor assessment

## STUDY POPULATION

At the efficacy data cut-off (31 March 2021), 39 patients had received the Zeno-based triplet combination, 4 of whom were ongoing. All patients had completed at least 6 months of treatment or discontinued.

**Table 1 | Patient Demographics and Disease Characteristics (N=39)**

| | |
|---|---|
| Age (years), median [range] | 57 [29-84] |
| ECOG PS (0/1), N (%) | 21 (54%) / 18 (46%) |
| Prior therapy | |
| N therapies (chemotherapy, anti-HER2, hormonal), median [range] | 5 [2-8] |
| N anti-HER2 lines (metastatic), median [range] | 3 [2-5] |
| Pertuzumab, N (%) | 39 (100%) |
| T-DM1, N (%) | 39 (100%) |
| N metastatic sites*, median [range] | 3 [1-5] |
| Bone | 19 (49%) |
| Lung | 19 (49%) |
| Liver | 13 (33%) |
| Brain | 8 (21%) |

* In >20% of patients

## SAFETY

At the safety data cut-off (12 January 2021), the 39 patients had received a median of 6 cycles [range 1-23] of the triplet regimen.

**Table 2 | Treatment-Related AEs in ≥7.5% Patients and Grade ≥3 AEs in ≥5% Patients (N=39)**

| | All Grades | Grade 3-4 |
|---|---|---|
| N pts with ≥1 AE | 36 (92%) | 20 (51%) |
| Diarrhea | 25 (64%) | 1 (3%) |
| Neutropenia | 18 (46%) | 12 (31%) |
| Nausea | 13 (33%) | 0 |
| Asthenia | 12 (31%) | 1 (3%) |
| Fatigue | 8 (21%) | 0 |
| Neutrophil count decr. | 7 (18%) | 5 (13%) |
| Constipation | 6 (15%) | 1 (3%) |
| Abdominal pain | 5 (13%) | 0 |
| Alopecia | 4 (10%) | 0 |
| Anemia | 4 (10%) | 1 (3%) |
| Dysgeusia | 4 (10%) | 1 (3%) |
| Dyspnea | 4 (10%) | 0 |
| Myalgia | 4 (10%) | 0 |
| Stomatitis | 4 (10%) | 0 |
| Decreased appetite | 3 (8%) | 1 (3%) |
| Ejection fraction decr. | 3 (8%) | 0 |
| Headache | 3 (8%) | 1 (3%) |
| Pyrexia | 3 (8%) | 0 |
| Vomiting | 3 (8%) | 0 |
| Peripheral motor neuropathy | 2 (5%) | 1 (3%) |

- Diarrhea was the most frequent treatment-related AE.
- All grade 3-4 neutropenia or neutrophil count decreases were related to vinorelbine.
- 6/29 (21%) evaluable patients had grade 2-3 LVEF decrease, 3 reported as a grade 2 AE.
- 2 patients discontinued treatment due to AEs related to vinorelbine.

## ANTITUMOR ACTIVITY

In total, 37 patients with locally confirmed HER2 overexpression (IHC 3+, or IHC 2+/FISH-positive) were evaluable for antitumor activity.

- The CBR (complete response + partial response + stable disease ≥24 weeks) per investigator assessment was 49% (18/37 patients; 90% CI 34 - 63) (**Table 3, Figure 2**).
- CBR was consistent across investigator and central independent radiological review, as well as across local and central laboratory determination of HER2 overexpression/ amplification detection.
- Confirmed responses (per investigator) were reported in 10 patients, including 2 patients with complete response lasting 4.2 and 7.2+ months, and 8 patients with partial responses lasting from 2.6 to 12.4 months (**Figures 2 and 3**).
- Median duration of response was 4.2 months (90% CI 2.8 - 12.4).
- Median PFS was 5.5 months (90% CI 4.1 - 5.6); 7 patients (19%) were censored. Estimated OS rates at 12 and 24 months were 73% and 61%, respectively.
- Analysis of baseline expression of ERBB pathway proteins and phospho-proteins, including neuregulin, HER2, and HER3, did not show clear correlations with clinical outcome. Further analyses are ongoing.

**Table 3 | Efficacy Outcomes (RECIST v1.1) (N=37)**

| | |
|---|---|
| Clinical benefit rate at 24 weeks, % (90% CI) | |
| RECIST investigator/HER2 local (N=37) | 49 (34-63) |
| RECIST investigator/HER2 central (N=29) | 55 (38-71) |
| RECIST central/HER2 local (N=36) | 44 (30-59) |
| RECIST central/HER2 central (N=28) | 50 (33-67) |
| Best overall response (confirmed; per investigator), N (%) | |
| Complete response | 2 (5.4%) |
| Partial response | 8 (21.6%) |
| Stable disease | 19 (51.4%) |
| Disease progression | 8 (21.6%) |
| Overall response rate (confirmed; per investigator), % (90% CI) | 27 (15-42) |

## PHARMACOKINETICS

Serum PK data for 35 evaluable patients assessed by non-compartmental analysis are consistent with data previously reported at ASCO 2020.[5] Predicted HER2 and HER3 receptor occupancy supports relevant pharmacological activity throughout the dosing interval. PK of Zeno administered with trastuzumab and vinorelbine is similar to that of single agent Zeno (data on file).

**Figure 2 | Duration of Exposure, Onset of Response, and Clinical Benefit (N=37)**

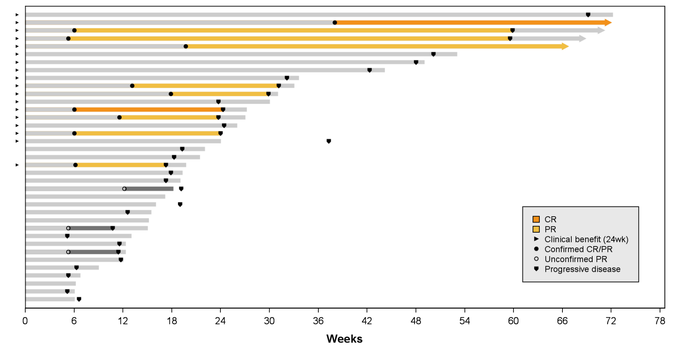
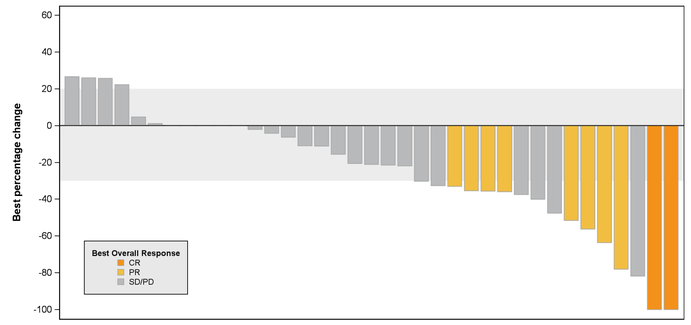



**Figure 3 | Waterfall Plot of Best Percent Change from Baseline in Target Lesions in Patients with Measurable Disease (N=37)**




## CONCLUSIONS

- In this updated analysis with all enrolled patients who had at least 6 months of follow-up, the prespecified criterion for success was met for the primary endpoint of CBR at 24 weeks with the triplet combination of zenocutuzumab, trastuzumab and vinorelbine.
- The zenocutuzumab-based triplet combination showed clinically relevant efficacy after 3 lines of anti-HER2 therapies including T-DM1.
- The combination was safe and well tolerated, with AEs primarily related to chemotherapy.

**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. Cho** et al, Nature 421 (2003): 756-60. **4. Alsina** et al. J Clin Oncol. 2017; 35 (15_Suppl):Abstract 2522; **5. Hamilton** et al. J Clin Oncol. 2020; 38 (15_suppl):Abstract 3093/Poster, ASCO Annual Conference 29 May-02 June, 2020.

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