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 (Zenocutus; MCLA-128) is a bispecific biotechnology humanized full-length IgG1 antibody with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC). This combination was deemed safe and well tolerated, with AEs deemed clinically relevant efficacy after 3 lines of anti-HER2 therapy. The combination was deemed safe and well tolerated, with AEs deemed clinically relevant efficacy after 3 lines of anti-HER2 therapy.

In this updated analysis with all enrolled patients who had at least 6 months of follow-up, the prespecified criterion for success was the primary endpoint of CBR at 24 weeks with the triplet combination of zenzocutuzumab, trastuzumab and vinorelbine. The combination was deemed safe and well tolerated, with AEs deemed clinically relevant to chemotherapy.

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

PHARMACOKINETICS

Clinical benefit rate at 24 weeks, % (90% CI)
RECIST investigator/HER2 local (N=37) 49 (34-63)
RECIST investigator/HER2 central (N=29) 55 (37-81)
RECIST central/HER2 local (N=36) 44 (30-59)
RECIST central/HER2 local (N=26) 50 (33-67)

Stable disease
19 (41.4)

Disease progression
21 (6.2)

Overall response rate (confirmed; per investigator), % (90% CI)
27 (15-42)

Complete response
2 (5.4)

Partial response
8 (21.6)

Stable disease
19 (41.4)

Disease progression
21 (6.2)

Overall response rate (confirmed; per investigator), % (90% CI)

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 DESIGN

Study Treatment and Assessments

Day 1 (3-week cycle) Day 2

CT/MRI tumor assessment every 4 weeks (N=35), CTCAE v4.0B, throughout; UBT every 3 months.
PK analysis of serum Zen in baseline and during treatment.
Baseline analysis of tumor biomarkers by functional proteomics reverse-phase protein array (90h), fresh blood colonies and xenograft mice.

Day 3

CT/MRI tumor assessment every 4 weeks (N=35), CTCAE v4.0B, throughout; UBT every 3 months.
PK analysis of serum Zen in baseline and during treatment.
Baseline analysis of tumor biomarkers by functional proteomics reverse-phase protein array (90h), fresh blood colonies and xenograft mice.

Statistical Hypothesis, Endpoints, and Analysis Population

A sample size of 40 patients with a clinical benefit rate (CBR) at 24 weeks of 49% 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 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), QoL, 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

SAFETY

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

In total, 37 patients with locally confirmed HER2 overexpression (HER 1+, or 2+ (FISH-positive) were evaluable for antitumor activity.

CBR (complete response + partial response + stable disease 224 weeks) per investigator assessment was 49% (18/37 patients; 90% CI: 34 - 64) (Table 3, Figure 2).

CBR was deemed safe and well tolerated, with AEs associated with clinical benefit rate at 24 weeks, % (90% CI)

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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

References