Clinical activity of MCLA-128 (zenocutuzumab) in combination with endocrine therapy (ET) in ER+/HER2-low, non-amplified metastatic breast cancer patients with ET-resistant disease who had progressed on a cyclin-dependent kinase (CDK) 4/6 inhibitor


BACKGROUND

MCLA-128 (zenocutuzumab) is a bispacific humanized full-length IgG1 antibody that binds the transmembrane receptor tyrosine kinase human epidermal growth factor receptors 2 and 3 (HER2 and HER3) that binds the transmembrane receptor tyrosine kinase human epidermal growth factor receptors 2 and 3 (HER2 and HER3), resulting in HER2/HER3 signaling and 2) elimination of tumor cells via enhanced antibody-dependent cell-mediated cytotoxicity (ADCC).

SAFETY

At the safety data cut-off date of 14 November 2019, the 48 treated patients had received a median of 3 cycles (range 1-17).

Table 2. Treatment related AEs in ≥5% of patients and all grade ≥3 events (N=48)

Determinant of HER2/3 signaling are the receptors’ intracellular domains which interact; one arm of the antibody binds the HER2 receptor. This optimally positions the anti-HER3 arm to block the ligand/receptor interaction, preventing HER2/HER3 dimerization and PI3K/AKT/mTOR pathway activation.

Bi-directional crosstalk between the estrogen receptor and HER2/3 may contribute to ET resistance, increasing expression of HER2 and HER3, promoting dimerization, and downstream signaling.

In HER2-low breast cancer xenografts, MCLA-128 combined with endocrine therapy outperformed single-agent endocrine treatments. Consistent antitumor activity was observed with single-agent MCLA-128 in heavily pretreated HER2-amplified breast cancer patients in the first-line setting.

The current open-label, phase 2 study was designed to explore the efficacy of MCLA-128 to rescue patients with ET-resistant metastatic breast cancer who have progressed on a CDK4/6 inhibitor.

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ünstantivity (RECIST v1.1) was evaluated in 48 evaluable patients with locally confirmed hormone receptor positive, HER2-low disease, at the efficacy cut-off of 31 March 2020.

CONCLUSIONS

In metastatic breast cancer patients who are endocrine-resistant and have progressed on a CDK4/6 inhibitor, addition of MCLA-128 (zenocutuzumab) to the same most recent hormone therapy resulted in clinical response in 17% of patients, with clinically meaningful benefit for at least 6 months.

The combination of MCLA-128 with endocrine therapy is safe and well tolerated.