**Background**

- Targeting human epidermal growth factor receptor-2 (HER2) is the cornerstone of HER2+ breast cancer (BC) treatment.1
- Trastuzumab causes lysis of tumor cells among others via antibody-dependent cellular cytotoxicity (ADCC) through NK cells.2
- NK- and CD8+ T-cell activity is inhibited by binding of the inhibitory receptor NKG2A to HLA-E expressed on tumor cells.3
- Monalizumab targets NKG2A, thereby blocking the NKG2A-HLA-E interaction. Phase II study has shown efficacy for monalizumab in head and neck cancer when combined with cetuximab.4
- We hypothesize that monalizumab improves trastuzumab-mediated ADCC and thereby helps to overcome trastuzumab-resistance and can promote anti-tumor immunity by unleashing NK cells and CD8+ T cells in HER2+ breast cancer.

**Aim**

The primary objective is to determine activity (as measured by objective response rate (ORR) by RECIST 1.1) of monalizumab and trastuzumab in patients with metastatic HER2+ breast cancer.

**Trial design**

The MIMOSA-trial is an explorative, phase II trial in which patients are treated biweekly with trastuzumab and monalizumab (figure 1). Patients are assigned to cohort A or B based on TIL-score, and will be treated until disease progression or unacceptable toxicity. Safety will be monitored using the Pocock-type boundary rules. If the number of dose-limiting-toxicities is equal to or exceeds a predefined number of patients, accrual will be halted.

**Main inclusion criteria**

- Histologically confirmed HER2+ BC on a metastatic lesion
- Progression during previous trastuzumab or TDM-1 therapy
- Measurable disease according to RECIST 1.1
- Administration of at least 1 and maximum of 3 lines of palliative chemotherapy or antibody-drug conjugates
- Metastatic lesion for biopsy
- LDH < 2x ULN

**Endpoints**

- **Primary endpoint**: ORR according to RECIST 1.1
- **Secondary endpoints**: Evaluation of clinical benefit rate and progression-free survival according to RECIST 1.1, overall survival and safety
- **Translational endpoints**: exploration of treatment-induced intra-tumoral and systemic changes with a focus on NK-cells and CD8+ T-cells

**Statistical considerations**

Activity and safety will be determined separately for patients with high and low TILs using a Simon’s-two –stage design (figure 2).

- **H0**: true response rate is 10%
- **H1**: true response rate is 35%

The null hypothesis will be rejected if 4 or more responders are observed in 19 patients. This study yields a type I error rate of 0.1 and power of 0.9.

**Accrual & Contact**

The MIMOSA-trial is currently open for accrual in the Netherlands Cancer Institute (Amsterdam, The Netherlands).

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**Clinicaltrials.gov NCT04307329 | No conflicts of interest to declare**