

Lay language summary – Trop-2 exploratory analysis for ESMO 2023

Human trophoblast cell-surface antigen-2 (Trop-2) is a protein that is only present at low levels in healthy epithelial cells. However, in many types of cancer it can be also found at high levels. Increased Trop-2 levels have been related to increased aggressiveness of the tumor, metastasis, and poor outcomes.

Particularly in breast cancer (BC), the highest Trop-2 levels have been reported in triple-negative breast cancer (TNBC) followed by Hormone Receptor-positive (HR+) BC, with the lowest Trop-2 levels in Human Epidermal Growth Factor Receptor 2-positive (HER2+) BC.

Antibody-drug conjugates (ADC) are novel drugs formed by a targeted therapy (monoclonal antibody) linked to a chemotherapy agent that attacks a specific tumor protein. ADCs blocking Trop-2 are currently being developed for the treatment of TNBC and HR+ BC. However, the role of Trop-2 in HER2+ BC remains less explored. The capacity of Trop-2 to predict the evolution of the disease or to predict the treatment response (two important parameters for clinicians) is still not well studied in HER2+ BC.

The present study is a sub-analysis performed in a subgroup of patients from the PHERGain trial (Pérez-García JM, 2021) with HER2+ early-stage BC who were treated with the current standard therapy for this patient population: a combination of chemotherapy (docetaxel and carboplatin) and dual HER2-targeted therapy (trastuzumab and pertuzumab). Here we analyzed Trop-2 expression and its relationship with patients' characteristics as well as the pathological complete response (pCR, the absence of any residual cancer cells after treatment) in a subgroup of patients from the PHERGain trial.

For this analysis, the tumor samples that were taken from patients' biopsies at baseline were analyzed for Trop-2 expression with immunohistochemistry. This technique quantified the amount of this protein present in the tumor tissue and tumors were classified into three groups according to different Trop-2 levels in: "low", "intermediate" and "high", respectively.

This analysis included a total of 41 patients with HER2+ BC that were treated with anti-HER2 therapy plus chemotherapy. Of these, 28 (68.3%) had tumors expressing Trop-2 (called Trop2+), and 13 (71.7%) had tumors not expressing Trop-2 (called Trop2-). When analyzing tumors by subgroups of Trop-2 expression, 17 patients had Trop-2 low tumors, 14 patients had Trop-2 intermediate tumors, and 10 patients had Trop-2 high tumors.

Investigators found that patients expressing the Trop-2 protein (Trop2+) had lower pCR rates, which means they were less likely to respond to the treatment, whereas patients without the Trop-2 protein (Trop2-) had a significantly higher probability to achieve a response (50% and 92.3%, respectively; $p=0.014$).

Furthermore, when comparing the probability to achieve a pCR in patients according to the different Trop-2 expression levels (low, intermediate, and high), an inverse correlation was found, which means that patients with the highest levels of the Trop-2 protein had the lowest probability to respond to the treatment, and vice versa, and this difference was statistically significant (30% and 88.2%, respectively; $p=0.002$).

In summary, Trop-2 appears to be a factor of resistance to anti-HER2 therapy, and this protein may be considered for future research in order to select patients with HER2+ breast cancer who could benefit from ADCs against Trop-2.