Whole-transcriptome analysis links trastuzumab sensitivity of breast tumors to both HER2 dependence and immune cell infiltration

Triulzi T.[1,*], De Cecco L.[2,*], Sandri M.[1], Prat A.[3,4], Giussani M.[1], Paolini B.[5], Carcangiu M.L. [5], Canevari S.[2], Bottini A.[6], Balsari A.[1,7], Menard S.[1], Generali D.[6], Campiglio M.[1], Di Cosimo S.[8], Tagliabue E.[1]

[1]Department of Experimental Oncology and Molecular Medicine, Molecular Targeting Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

[2]Department of Experimental Oncology and Molecular Medicine, Functional Genomics Core Facility, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

[3]Translational Genomics Group, Vall d'Hebron Institute of Oncology, Barcelona, Spain

[4]Medical Oncology Department, Hospital Clínic i Provincial, Barcelona, Spain

[5]Department of Pathology, Anatomic Pathology A Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

[6]Dipartimento di Terapia Molecolare e Farmacogenomica, Istituti Ospitalieri di Cremona, Italy

[7]Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Italy

[8]Department of Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

[*]These authors have contributed equally to this work

ABSTRACT

While results thus far demonstrate the clinical benefit of trastuzumab, some patients do not respond to this therapy. To identify a molecular predictor of trastuzumab benefit, we conducted whole-transcriptome analysis of primary HER2+ breast carcinomas obtained from patients treated with trastuzumab-containing therapies and correlated the molecular portrait with treatment benefit.

The estimated association between gene expression and relapse-free survival allowed development of a trastuzumab risk model (TRAR), with *ERBB2* and *ESR1* expression as core elements, able to identify patients with high and low risk of relapse. Application of the TRAR model to 24 HER2+ core biopsies from patients treated with neo-adjuvant trastuzumab indicated that it is predictive of trastuzumab response. Examination of TRAR in available whole-transcriptome datasets indicated that this model stratifies patients according to response to trastuzumab-based neo-adjuvant treatment but not to chemotherapy alone. Pathway analysis revealed that TRAR-low tumors expressed genes of the immune response, with higher numbers of CD8-positive cells detected immunohistochemically compared to TRAR-high tumors.

The TRAR model identifies tumors that benefit from trastuzumab-based treatment as those most enriched in CD8-positive immune infiltrating cells and with high *ERBB2* and low *ESR1* mRNA levels, indicating the requirement for both features in achieving trastuzumab response.