

CASE STUDY

Understanding HER2 double equivocal carcinomas to best tailor targeted therapies in breast cancer

Who: Laura Annaratone, PhD – Pathology Division, Department of Medical Sciences, University of Turin

My scientific work is mainly focused on experimental and clinicopathological studies with the key mission to translate the achievements of basic science to the patient's bedside.

I have been working to improve the quality of diagnostic tests and innovate breast cancer diagnosis by focusing on the pre-analytical phase in surgical pathology, to guarantee the optimal quality for any downstream assays, especially those contemplating molecular analyses. To sort out the main requests of oncologists, I am involved in the development of molecular methods for a more precise quantification of biomarkers, thus leading to a more personalized therapeutic approach. The ambition is to improve the results of well-established biomarkers of targeted therapy, such as HER2, in specific scenarios where current companion diagnostics are not sufficient to answer a clinical question.

Why 3D Biology™ Technology?

Evaluation of prognostic and predictive factors in breast cancer is semi-quantitative: an accurate quantification would be warranted. To stratify breast carcinomas showing equivocal HER2 status, we used a nCounter® GX Custom CodeSet Assay to validate a classifier of 24 genes and we are currently using the Prosigna Assay. The nCounter® Vantage 3D™ Assays offer us the opportunity to complement our IHC, ISH, and transcriptome data. We would like to exploit the RNA:Protein Solid Tumor Assay for FFPE to evaluate HER2 and related phospho-proteins in a more quantitative way.

Aim of the project:

Double equivocal carcinomas represent a real challenge for oncologists, who have to face the dilemma "to treat or not to treat." ASCO/CAP guidelines stress the need for data defining their biology and clinical behavior. The aim of this project is to stratify double equivocal breast cancers to pave the way to a more informed decision about therapy for patients affected by a breast carcinoma showing an equivocal HER2 result.

Methods:

We have already selected a series of 28 FFPE double equivocal breast cancers i.e. showing HER2/CEP17 ratio <2 and HER2 copy number 4-6. RNA has been extracted following microdissection and by using a nCounter GX Custom CodeSet Assay we validated a classifier of 24 genes we have recently devised by global transcriptomics that enables stratification of these carcinomas into 3 categories. We are currently subjecting the cohort to the Prosigna assay to derive the PAM50-defined molecular subtype and the risk of recurrence (ROR). Given that HER2 mutations in therapy naïve patients are described to be preferentially identified in breast carcinomas displaying low HER2 levels, we will also sequence by Sanger Sequencing the entire gene with a particular focus on exons 8 and all exons of the TK domain, where most of the somatic mutations have been described so far. The Vantage 3D™ RNA:Protein Solid Tumor Assay for FFPE will be used to complement our IHC, ISH, and transcriptome data: in particular, we will study the total and phospho-protein content of double equivocal carcinomas, with the opportunity to assess HER2 protein expression with high specificity.

nCounter® Vantage 3D™ Assay selection:

nCounter Vantage 3D RNA:Protein Solid Tumor Assay for FFPE

“This assay could identify a protein classifier to better stratify double equivocal breast cancers. Disregulation of HER2 signaling in cancer involves an excess of signals that stimulate cancer cells to grow and spread.”

Laura Annaratone, PhD

Pathology Division, Department of Medical Sciences, University of Turin



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