

**NF1 Alterations are Linked to Increased HER2 Expression in Breast Cancer—Letter**Donatella Gambini<sup>1</sup>, Federica Natacci<sup>2</sup>, Claudia Cesaretti<sup>2</sup>, and Nicola Fusco<sup>3,4</sup>

We read with great interest the research of Wang and colleagues who found a high prevalence ( $n = 9/13$ , 69%) of human epidermal growth factor receptor (HER)2-enriched tumors in neurofibromin (NF)1-altered breast cancers (1). The notion that NF1 mutations and HER2 copy number (CN) gain/amplification could act synergistically opens new doors in the study of breast cancers occurring in neurofibromatosis type 1 (NF-1) syndrome.

We retrospectively analyzed our clinical records of NF-1 patients and retrieved all invasive breast cancers with available HER2 data by IHC and/or *in situ* hybridization (ISH). Taken together, 19 tumors were identified in 15 patients (age 33–75, median 54). In our cohort, 4 (21%) cases were HER2<sup>+</sup>, including 3 cases with IHC score 3+ and 1 case with IHC score 2+ and ISH+. These observations parallel those of Uusitalo and colleagues, where the reported rate of HER2 positivity in NF-1 patients was 31% ( $n = 8/26$ ; ref. 2), similar to that of all breast cancers. One of the possible explanations of the extraordinarily high frequency of HER2<sup>+</sup> tumors observed by Wang and colleagues could be related to the inclusion criteria, as 3 (23%) cases were pure ductal carcinoma *in situ* (DCIS) and all resulted in HER2<sup>+</sup>. Hence, 45%–60% of DCIS are reported to be HER2<sup>+</sup> in the general

population, harboring low risk of progression toward invasive forms of disease (3). Of note, invasive breast cancers associated with HER2<sup>+</sup> DCIS are usually HER2<sup>-</sup> (4).

The lack of overlap between HER2 protein overexpression and gene gain/amplification in NF-1 represents another intriguing finding of the authors, as only 22% of positive samples by IHC were found to be HER2-amplified. In our experience, a concern of detecting the HER2 status using microarray-based assays is their possible artifactual output, particularly when genomic DNA from bulk (i.e., non-microdissected) tumor samples is profiled. The American Society of Clinical Oncology and College of American Pathologists recommend performing HER2 analysis by IHC and, in equivocal cases (score 2+), ISH (5). Also, the cBioPortal ([www.cbioportal.org](http://www.cbioportal.org)), despite providing HER2 CN data, allows for the interrogation of HER2 status by IHC and ISH.

As also pointed out by Wang and collaborators, data on breast cancer in NF-1 are limited by the small cohorts of patients included in the few studies available to date. Additional issues could be represented by the heterogeneity in inclusion criteria (e.g. invasive tumors, DCIS), data collection (e.g. retrospective/prospective, clinicopathologic features, survival and NF1/2 status), and methods (e.g. IHC, ISH, next-generation sequencing, gene expression, somatic/germline analyses). To this end, we believe that a multicentric and, importantly, synergic data collection among different Centers with expertise in NF-1 and breast cancer would be warranted to robustly characterize the biology underpinning these rare conditions.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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