Published OnlineFirst February 21, 2019; DOI: 10.1158/1940-6207.CAPR-18-0392

Letter to the Editor

Cancer Prevention Research

NF1 Alterations are Linked to Increased HER2 Expression in Breast Cancer–Letter

Donatella Gambini[1], Federica Natacci[2], Claudia Cesaretti[2], and Nicola Fusco[3,4]

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 $HER2^+$, including 3 cases with IHC score 3+ and 1 case with ICH 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 $HER2^+$ 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 $HER2^+$. Hence, 45%–60% of DCIS are reported to be $HER2^+$ in the general population, harboring low risk of progression toward invasive forms of disease (3). Of note, invasive breast cancers associated with $HER2^+$ DCIS are usually $HER2^-$ (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), 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.

Received October 14, 2018; revised November 13, 2018; accepted January 15, 2019; published first February 21, 2019.

[1]Division of Medical Oncology, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy. [2]Medical Genetics Unit, Woman-Child-Newborn Department, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy. [3]Division of Pathology, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy. [4]Department of Biomedical, Surgical, and Dental Sciences, University of Milan, Milan Italy.

Corresponding Author: Nicola Fusco, Division of Pathology, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Via Francesco Sforza, 35, Milan 20122, Italy. Phone: 3902-5503-8425; Fax 3902-5503-4608; E-mail: nicola.fusco@unimi.it

doi: 10.1158/1940-6207.CAPR-18-0392

References

1. Wang X, Kallionpää RA, Gonzales PR, Chitale DA, Tousignant RN, Crowley JP, et al. Germline and somatic NF1 alterations are linked to increased HER-2 expression in breast cancer. Cancer Prev Res 2018;11:655–63.
2. Uusitalo E, Kallionpää RA, Kurki S, Rantanen M, Pitkäniemi J, Kronqvist P, et al. Breast cancer in neurofibromatosis type 1: overrepresentation of unfavourable prognostic factors. Br J Cancer 2017; 116:211–7.
3. Parham DM, Pinder SE. The impact of human epidermal growth factor receptor 2 neoadjuvant monoclonal antibody (trastuzumab) therapy in ductal carcinoma in situ of the breast. Histopathology 2017; 70:1009–11.
4. Borgquist S, Zhou W, Jirström K, Amini RM, Sollie T, Sørlie T, et al. The prognostic role of HER2 expression in ductal breast carcinoma in situ (DCIS); a population-based cohort study. BMC Cancer 2015;15:468.
5. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 2013;31:3997–4013.

Published OnlineFirst February 21, 2019; DOI: 10.1158/1940-6207.CAPR-18-0392

AACR American Association for Cancer Research

Cancer Prevention Research

NF1 Alterations are Linked to Increased HER2 Expression in Breast Cancer–Letter

Donatella Gambini, Federica Natacci, Claudia Cesaretti, et al.

Cancer Prev Res 2019;12:195-196. Published OnlineFirst February 21, 2019.