

Guest Editorial

Biomarker discordance during tumor progression

Naoki Niikura^a and Naoto T. Ueno^{b,*}

^a*Department of Breast and Endocrine Surgery, Tokai University School of Medicine, Kanagawa, Japan*

^b*Section of Translational Breast Cancer Research, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

Molecular biomarkers are used by clinicians to guide selection of the most appropriate systemic therapy for metastatic breast cancer: endocrine therapy, chemotherapy, or human epidermal growth factor receptor 2 (HER2) – targeted therapy, such as trastuzumab or lapatinib. With increased understanding that molecular biomarker status can change during tumor progression such that biomarker status is discordant between the primary tumor and metastatic tumors, interest in the role of biopsy of metastatic disease has increased. However, biopsies of suspected metastases are not always performed in routine oncologic practice. Furthermore, whether selecting targeted therapy on the basis of the estrogen receptor (ER), progesterone receptor (PR), or HER2 status of metastatic tumors can prolong survival is not known, and selection of targeted therapy on the basis of the molecular biomarker status of metastatic disease is controversial.

Research has shown that patients with discordance in molecular biomarker status between the primary tumor and metastatic tumors have poor survival rates. However, it is unclear whether these differences in biomarker status are a result of preanalytic variables or reflect true differences in biology based on heterogeneity of clonal populations in breast cancer.

Another issue is that variations in tissue processing can lead to erroneous results of biopsy of metastatic disease. False-negative results with respect to ER, PR, and HER2 expression because of inadequate biopsy techniques, improper fixation, or poor choice of biopsy location have been well described.

This issue of *Cancer Biomarkers* presents articles by some of the leading investigators in biomarker discordance between primary and metastatic tumors in breast cancer.

Dr. Yun Gong discusses biomarker discordance from the point of view of pathologists. She points out that differences in testing methods for the tumor pairs obtained from the same patient can contribute to discordance. For ER testing, for example, biochemical ligand-binding assays were used in the 1980s but were later gradually replaced by immunohistochemical analysis.

Drs. Elyse E. Lower and Shagufta Khan review discordance in hormone receptor status. They conclude that discordance between primary and metastatic tumors occurs in approximately 20% of cases and that loss of hormone receptor status is more common than gain. The loss of sensitivity to hormones or HER2-targeted therapies may herald tumor resistance, similar to antibiotic resistance.

Drs. Osama Moussa, Colin Purdie, Sarah Vinnicombe, and Alastair M. Thompson report on one prospective study of biomarker discordance and how biomarker changes influence patient care. They state

*Corresponding author: Naoto T. Ueno, Section of Translational Breast Cancer Research, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. E-mail: nueno@mdanderson.org.

that although the number of prospective studies of biomarker discordance in breast cancer is relatively small and most of those studies included small numbers of patients, their findings regarding the frequency of biomarker discordance confirm those of the many retrospective studies of biomarker discordance.

Drs. Shaheenah Dawood and Ana M. Gonzalez-Angulo discuss discordance in biomarkers measured before and after neoadjuvant chemotherapy. They discuss not only ER, PR, and HER2 but also Ki67. These authors believe that the incidence of biomarker discordance will most likely increase. Changes in biomarkers such as ER, PR, and HER2 from positive to negative status after neoadjuvant chemotherapy, although unlikely to impact patient care, appear to have a prognostic impact.

Finally, we discuss HER2 discordance between primary and metastatic tumors. Changes in HER2 status from positive in the primary tumor to negative in metastases lead to changes in patient care and have a

prognostic impact. It is still unclear whether patients with loss of HER2 overexpression should be treated with HER2-targeted therapy.

One of our aims in this issue is to thoroughly review biopsy technique (e.g., fine-needle aspiration, core needle biopsy), pathology review, data analysis (by immunohistochemistry, fluorescence in situ hybridization, or cDNA microarray), and data interpretation. All of these techniques may affect the way biomarker information can be applied to determine the best treatment for the patient, but these issues have not been carefully examined to date.

The care of patients with metastatic breast cancer is becoming an increasingly important global issue, and we hope that this issue of *Cancer Biomarkers* stimulates further clinical and basic research in this field. In addition, we hope that this issue will serve as a guide for oncologists looking for better ways to care for patients with metastatic breast cancer.