

# Redefining the HER2 Oncobiomarker: A Relevant Case Report

## Introduction

In multiple studies anti HER2 therapy combined with chemotherapy demonstrated a marked improvement in disease free survival as adjuvant therapy and as treatment for metastatic breast cancer compared to chemotherapy alone for patients with tumors defined as being HER2 positive [1]. Because of these remarkable results, an expert ASCO/CAP panel in 2013 expanded the definitions of HER2 positive tumors with the hope of allowing more patients to receive and potentially benefit from receiving anti HER2 therapy [2].

In this report, a patient whose tumor would have been defined as HER2 negative until 2007 but after 2013 has been defined as HER2 positive is presented. Per current National Comprehensive Cancer Network Guidelines (NCCN) guidelines, anti HER2 therapy combined with chemotherapy is considered the preferred treatment for her metastatic disease [1]. However, after 2013 CDK4/6 inhibitors in combination with aromatase inhibitor therapy have been shown to be very effective therapy for metastatic breast cancer and would be considered a preferred choice had the HER2 status of her tumor been based on the 2007 guidelines [3]. Yet, CDK4/6 inhibitors are only approved for patients with HER2 negative breast cancers.

This report underscores the dilemma that occurs when the definition of a molecular marker as a predictor of benefit is expanded to include additional tumors that previously would have been labeled “negative” but would now be considered “positive”. Whenever possible, the expansion (or contraction) of the definition of a positive molecular marker of efficacy should be based on clinical reports of the efficacy of the targeted agents in patients with such tumors.

## Case Report

JL is a 42-year old patient who underwent bilateral mastectomies in July 2012 for a T2 N1 invasive ductal breast cancer. The cancer was said to be estrogen receptor positive (90%), progesterone receptor positive (20%) and HER2 negative (IHC=0). After receiving adjuvant chemotherapy with 4 cycles of docetaxel and cyclophosphamide, she began adjuvant tamoxifen therapy in December 2012. She discontinued the adjuvant tamoxifen therapy in December 2016. In May 2017 she presented with severe back pain and an MRI of her whole spine showed multiple enhancing lesions throughout her spine and a T12 tumor that “largely replaced” that vertebral body. A staging CAT scan of her chest abdomen and pelvis showed diffuse bony and lung metastases as well as innumerable liver metastases.

The largest metastasis in the liver was roughly 30mmx28mm and a biopsy confirmed a diagnosis of adenocarcinoma (ER positive (95%), PR positive (99%), HER equivocal (HER2 IHC=2+)). A HER2 dual probe FISH assay demonstrated a ratio of 1.76 (signals/chromosome 17 centromeres) (negative) and a HER2 signals per nucleus result of



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4.98 (considered equivocal). Per ASCO/CAP and NCCN guidelines, alternative chromosome 17 probe FISH testing by NeoGenomics was done (NeoGenomics Laboratories Inc., Fort Myers, FL 33913). The result was “positive based on HER2 to SSMCR” (Smith Magenis Syndrome Critical Region) ratio.

As a result of the above assays the patient’s tumor was classified as HER2 positive and she was offered the preferred regimen per the NCCN guidelines of taxane therapy combined with trastuzumab and pertuzumab [1]. The patient sought a second opinion where it was recommended that she instead receive a CDK4/6 inhibitor in combination with aromatase inhibitor therapy after first undergoing a bilateral oophorectomy.

## Discussion

The use of anti HER2 drugs in breast cancers defined as HER2 positive might be considered the mother of modern clinical precision oncology. HER2 protein overexpression or HER2 gene amplification are pivotal examples of identifying an oncobiomarker of targeted therapy efficacy. The efficacy of the use of trastuzumab combined with chemotherapy compared to chemotherapy alone for prolonging survival in metastatic disease or for reducing the likelihood of recurrence after surgery (roughly a 40% relative risk reduction) has resulted in thousands of lives being saved or prolonged [1]. The 2007 expert ASCO/CAP panel appropriately recommended that basically the same criteria for defining a tumor as HER2 positive used in the adjuvant trials be used as the predictive marker for endorsing trastuzumab use [4].

However, as was the recent case with the PD-L1 expressing NSCLCs [5], the results with trastuzumab use were so robust and toxicities so modest that in 2013 the ASCO/CAP expert panel of 17 pathologists and two medical oncologists expanded the definition of HER2 positive cancer to include tumors to now be defined as HER2 positive based only on gene amplification using alternative chromosome 17 probe FISH assays or polysomy for chromosome 17, as two examples [2]. The authors acknowledged that clinical data supporting their expansion to include patients with tumors that in 2007 would have been defined as HER2 negative was supported by very little clinical data. Their extrapolations aimed to include additional patients seemed nonetheless reasonable based on some

limited clinical data and data for concordance in the case of the alternative assays for the same metric (e.g. alternative probes for gene amplification). The panel endorsed confirmatory clinical trials directed at patients with tumors meeting only the 2013 criteria for HER2 positivity [2]. JL is a patient whose metastatic tumor would have been classified as HER2 negative before 2013, but based only on the expanded 2013 ASCO/CAP guideline, that same tumor is now classified as HER-2 positive.

The 2013 panel concluded that their decisions to expand the defining criteria were made so that “the right patient receives the right treatment (2, page 4000).” Unfortunately, in expanding the definition of HER2 positive disease, the expert ASCO/CAP guideline veered from the fundamental principles for identifying predictive markers of efficacy. For example, they added new surrogates such as polysomy with little clinical data to support their use. In this case, polysomy might be considered endorsing an unproven surrogate of a proven predictive marker. However, in contrast to the use of EGFR kinase inhibitors in lung cancer and rescinding anti-EGFR antibodies use in colorectal cancers harboring a RAS mutation there were no large bodies of clinical data to rely on to determine whether breast cancers defined as HER2 positive by the new definitions benefitted from anti HER2 therapy [6-8].

Finally, while it seemed reasonable to endorse these relatively non-toxic anti HER2 drugs with limited clinical results to support their use in patients whose tumors only met one of the 2013 definitions, the treatment landscape changed for HER2 negative metastatic disease with the introduction and FDA approval of CDK4/6 inhibitors. Relatively well-tolerated and oral, CDK 4/6 inhibitors in combination with aromatase inhibitors result in a roughly 55% response rate as first line metastatic disease therapy, although their use is currently limited only to patients whose breast cancers are HER2 negative [3]. JL’s metastatic breast cancer met the 2013 definition of having HER2 positive disease (but not the 2007 definition) and therefore it is unclear whether she should receive CDK4/6 inhibitor therapy, anti HER2 therapy or, at least at some point, both.

Heraclitus wrote “no man can stand in the same river twice,” since the river changes and the man changes. Another interpretation of his wisdom is that an opportunity lost may be lost forever. In spite

of more than 20 years of anti-HER2 therapies which have benefitted hundreds of thousands of woman, it remains unclear which patients with tumors deemed HER2 positive by one of the 2013 expanded definitions will benefit from these remarkable drugs.

Once a clinical trial demonstrates efficacy for a targeting agent, expansion of the definition of the “positive” predictive marker of efficacy used in that trial by showing concordance using other assays for the same metric, lowering the threshold for defining the patient’s tumor as “positive” or by identifying a surrogate for the predictive marker all present uncertainty. The best remedy is to conduct clinical trials judging the efficacy of the targeting drug for tumors identified as “positive” only by the proposed new definitions.

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