First-in-Human Molecular Imaging of HER2 Expression in Breast Cancer Metastases Using the $^{111}$In-ABY-025 Affibody Molecule

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The expression status of human epidermal growth factor receptor type 2 (HER2) predicts the response of HER2-targeted therapy in breast cancer. ABY-025 is a small reengineered Affibody molecule targeting a unique epitope of the HER2 receptor, not occupied by current therapeutic agents. This study evaluated the distribution, safety, dosimetry, and efficacy of $^{111}$In-ABY-025 for determining the HER2 status in metastatic breast cancer.

**Methods:** Seven patients with metastatic breast cancer and HER2-positive ($n = 5$) or -negative ($n = 2$) primary tumors received an intravenous injection of approximately $100 \mu$g ($\sim140$ MBq) of $^{111}$In-ABY-025. Planar y-camera imaging was performed after 30 min, followed by SPECT/CT after 4, 24, and 48 h. Blood levels of radioactivity, antibodies, shed serum HER2, and toxicity markers were evaluated. Lesional HER2 status was verified by biopsies. The metastases were located by $^{18}$F-FDG PET/CT 5 d before $^{111}$In-ABY-025 imaging. **Results:** Injection of $^{111}$In-ABY-025 yielded a mean effective dose of 0.15 mSv/MBq and was safe, well tolerated, and without drug-related adverse events. Fast blood clearance allowed high-contrast HER2 images within 4–24 h. No anti-ABY-025 antibodies were observed. When metastatic uptake at 24 h was normalized to uptake at 4 h, the ratio increased in HER2-positive metastases and decreased in negative ones ($P < 0.05$), with no overlap and confirmation by biopsies. In 1 patient, with HER2-positive primary tumor, $^{111}$In-ABY-025 imaging correctly suggested a HER2-negative status of the metastases. The highest normal-tissue uptake was in the kidneys, followed by the liver and spleen. **Conclusion:** $^{111}$In-ABY-025 appears safe for use in humans and is a promising noninvasive tool for discriminating HER2 status in metastatic breast cancer, regardless of ongoing HER2-targeted antibody treatment.

**Key Words:** Affibody; breast cancer metastases; clinical study; HER2 receptor; $^{111}$In imaging

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Today, treatment of breast cancer is based on the biologic profile of the individual tumor. Knowledge of the human epidermal growth factor receptor type 2 (HER2) status is crucial to predict the response of HER2-targeted therapy (1). Patients with breast cancer overexpressing HER2 have improved survival when treated with HER2-targeting agents such as trastuzumab, pertuzumab, and trastuzumab emtansine (2–10).

The analysis of HER2 expression is usually based on a surgical specimen of the primary tumor or, in case of neoadjuvant therapy or inoperable disease, on a biopsy sample from the tumor (11). The pathologic analysis includes immunohistochemistry and in some cases fluorescence in situ hybridization (FISH). Therapy for patients with disseminated disease is often based on histopathologic classification of the primary tumor and not of the metastases. Disparities in HER2 expression of primary breast cancer and metastases have been reported. Metaanalysis of 26 studies including 2,520 patients revealed discordance in HER2 expression between the primary tumor and local lymph node metastases in the range of 2.4%–7.2% and discordance with distant metastases in the range of 6.9%–18.6%, with an absolute variation for all studies in the range of 0%–40% (12). A recent symposium publication including 2,845 patients reported absolute variations in the same range (13). Another recent study on 182 patients, with 28% discordance, indicated that patients with loss of HER2 expression in metastases had shorter overall survival than patients with unchanged expression (14).

The biopsy procedure can be inconvenient or even harmful for the patient, demanding lesions of suitable size and carrying the risk of sampling errors. Heterogeneity of HER2 expression within lesions and differences in expression between lesions in the same patient further limit the use of biopsy for correct diagnosis. Thus, improved methods for determining the HER2 status in patients with metastatic breast cancer are needed to optimize treatment regimes. One approach is molecular imaging using a radiolabeled tracer targeting HER2.

Molecular imaging allows whole-body detection of aberrant gene expression (i.e., proteomic abnormalities). Radiolabeled trastuzumab has been clinically evaluated as a HER2-specific molecular imaging agent (15,16). We used an imaging molecule with about 23 times smaller molecular weight, that is, Affibody molecules (Affibody AB), and preclinical studies have shown promising results (17). Affibody molecules are small, approximately 6.5-kDa, imaging agents based on a nonimmunoglobulin scaffold. Target-specific Affibody molecules are selected from a library of several billion unique variants providing high-affinity binders to a variety of targets such as HER2 and have shown good imaging properties in xenograft models (17–23). The HER2-binding Affibody molecule used in this study binds with picomolar affinity to the extracellular...
domain 3 of the receptor, that is, to an epitope not overlapping with the epitopes for trastuzumab (domain 4) or pertuzumab (domain 2), thus permitting imaging during ongoing antibody therapy (20, 24, 25).

Recently, clinical data using the first-generation HER2-binding Affibody molecule, ABY-002, demonstrated the feasibility of HER2 imaging with SPECT (111In) and PET (68Ga) in breast cancer patients (26). However, high liver uptake prevented visualization of liver metastases. ABY-025, used in the present clinical study, is a second-generation Affibody molecule with improved biochemical and biophysical characteristics, designed by protein engineering using an iterative approach of changing 11 amino acids (about 20% of the molecule) outside the HER2-binding region (18, 27).

In this first-in-human study with 111In-ABY-025 SPECT/CT, we evaluated safety and tolerability and explored uptake in tumor metastases and background uptake in normal organs. It was also of interest to study the ability of 111In-ABY-025 to discriminate between HER2-positive and -negative metastases.

**MATERIALS AND METHODS**

**Patients**

Seven female patients (mean age, 61.3 y; range, 46–70 y) receiving treatment for recurrent metastatic breast cancer were enrolled into the study (Table 1). Five of the patients were diagnosed with HER2-positive primary tumors, and 2 had HER2-negative tumors and served as controls.

**Inclusion and Exclusion Criteria**

The protocol criteria for inclusion and exclusion are detailed in supplemental material (available at http://jnm.snmjournals.org). Briefly, patients with a diagnosis of metastatic breast cancer and a known HER2 classification of the primary tumor (HER2-positive: score of 3+ using HercepTest [DAKO] or FISH-positive, or score of 2+ with HercepTest and FISH-positive; HER2-negative: score 0 or 1+ using HercepTest, or score of 2+ but FISH-negative) were potential participants. Ongoing treatment was not an exclusion criterion.

**Approvals**

The Swedish Medical Products Agency, the regional ethics committee in Uppsala, and the radiation protection ethics committee in Uppsala approved the study. Written informed consent was obtained from all participants. The study was registered as a clinical trial with the identifiers EudraCT 210-021078-12 and NCT01216033.

**Patient Characterization and Safety Assessment**

In accordance with the study protocol, all patients underwent physical examination at least 7 d before, immediately before, and 7 d after injection of 111In-ABY-025. The standard clinical chemistry of blood and urine was investigated according to the approved protocol. Possible adverse effects were investigated orally and with written patient questionnaires before and after 111In-ABY-025 injection (day 0) and 1, 7, 21, and 42 d later. Blood samples for determination of shed serum HER2 were taken immediately before injection, and the assays (DIVA Centaur HER2/neu test; Siemens Healthcare Diagnostics) were thereafter performed at Laboratory Limbach, Heidelberg, Germany. The presence of anti-ABY-025 antibodies was determined in samples taken before, 21 d after, and 42 d after injections, using an ELISA developed by Affibody AB and performed at Clinical Chemistry and Pharmacology Laboratory at Uppsala University Hospital, Sweden.

**18F-FDG PET/CT and Other Clinical Imaging**

The metastatic status of patients was known before inclusion on the basis of conventional imaging. 18F-FDG PET/CT imaging was performed 5 d before the 111In-ABY-025 administrations to identify the size and location of viable metastases in all patients. The patients fasted 6 h before 18F-FDG injection. A scan (Discovery VCT; GE Healthcare) from head to thighs was performed 3 h after intravenous injection of 5 MBq of 18F-FDG. A low-dose CT scan (auto-mA, 20–80) without contrast enhancement was used for attenuation correction and anatomic localization. PET images were reconstructed using a clinical protocol supplied by the vendor, and all relevant corrections for quantitative imaging were applied. The acquired data were evaluated using Hermes Hybrid Viewer (Hermes Medical) and an Advance workstation (GE Healthcare). For each lesion detected by PET/CT, the maximum standardized uptake value was noted. The volume of each tumor lesion was calculated by a thresholding technique that included all voxels with at least 42% of the maximum standardized uptake value. Additionally, MR, ultrasound, or contrast-enhanced CT was applied when needed for biopsies and further patient management.

**111In-ABY-025 Imaging**

111In-ABY-025 was prepared essentially as described earlier (18). ABY-025 of good-manufacturing-practice grade was provided by Affibody in vials containing 100 μg. ABY-025 was labeled with 111In at the Department of Nuclear Medicine, Uppsala University Hospital. Patients were not required to fast before injection. 111In-ABY-025, about 100 μg,

**TABLE 1**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>HER2 status in primary tumor (HercepTest)</th>
<th>Primary tumor SER/PgR</th>
<th>Pretreatment serum HER2 (μg/L)</th>
<th>Metastasis locations on 18F-FDG PET/CT</th>
<th>Injected 111In-ABY-025 (MBq)</th>
<th>On trastuzumab during imaging</th>
<th>Therapy history*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69</td>
<td>3+</td>
<td>/-/-</td>
<td>21</td>
<td>Lymph node</td>
<td>131</td>
<td>Yes</td>
<td>S, R, C, T, L</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>3+</td>
<td>/+/-</td>
<td>26</td>
<td>Lymph node, liver, bone</td>
<td>135</td>
<td>Yes</td>
<td>S, R, C, E, T, L</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>3+</td>
<td>/-/</td>
<td>56</td>
<td>Lymph node, bone, liver, adrenal</td>
<td>139</td>
<td>Yes</td>
<td>S, R, C, T, L</td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>3+</td>
<td>/+/-</td>
<td>8.8</td>
<td>Lymph node, lung, bone, brain, thyroid</td>
<td>153</td>
<td>Yes</td>
<td>S, R, C, E, T, L</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>1+</td>
<td>/-/-</td>
<td>16</td>
<td>Lymph node, bone</td>
<td>137</td>
<td>No</td>
<td>S, R, C</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>0</td>
<td>/+/-</td>
<td>12</td>
<td>Bone, liver, lung</td>
<td>139</td>
<td>No</td>
<td>S, R, C, E</td>
</tr>
<tr>
<td>7</td>
<td>57</td>
<td>3+</td>
<td>/+/-</td>
<td>23</td>
<td>Lymph node, bone</td>
<td>154</td>
<td>Yes</td>
<td>S, C, E, T, L</td>
</tr>
</tbody>
</table>

*More information on therapy history is provided in the supplemental material.

ER = estrogen receptor; PgR = progesterone receptor; S = surgery; R = radiotherapy; C = chemotherapy; E = endocrine therapy; T = trastuzumab; L = lapatinib.
Uptake of $^{111}$In in Tumor-Free Areas of Organs with Highest Uptake on SPECT Images After Injection of $^{111}$In-ABY-025

<table>
<thead>
<tr>
<th>Site</th>
<th>4 h</th>
<th>24 h</th>
<th>48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left kidney</td>
<td>0.084 ± 0.031</td>
<td>0.103 ± 0.030</td>
<td>0.085 ± 0.027</td>
</tr>
<tr>
<td>Right kidney</td>
<td>0.090 ± 0.034</td>
<td>0.111 ± 0.035</td>
<td>0.093 ± 0.032</td>
</tr>
<tr>
<td>Liver</td>
<td>0.032 ± 0.013</td>
<td>0.025 ± 0.010</td>
<td>0.022 ± 0.009</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.009 ± 0.005</td>
<td>0.007 ± 0.005</td>
<td>0.006 ± 0.004</td>
</tr>
</tbody>
</table>

Data are percentage injected radioactivity per gram of tissue (mean values and SD from all 7 patients).

Level of $^{111}$In in Blood Samples After Injection of $^{111}$In-ABY-025

<table>
<thead>
<tr>
<th>Time after injection</th>
<th>$^{111}$In level</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 min</td>
<td>$9.75 \times 10^{-3} \pm 3.90 \times 10^{-3}$</td>
</tr>
<tr>
<td>30 min</td>
<td>$6.12 \times 10^{-3} \pm 2.15 \times 10^{-3}$</td>
</tr>
<tr>
<td>2 h</td>
<td>$3.46 \times 10^{-3} \pm 1.25 \times 10^{-3}$</td>
</tr>
<tr>
<td>6 h</td>
<td>$2.03 \times 10^{-3} \pm 0.70 \times 10^{-3}$</td>
</tr>
<tr>
<td>24 h</td>
<td>$0.63 \times 10^{-3} \pm 0.17 \times 10^{-3}$</td>
</tr>
<tr>
<td>48 h</td>
<td>$0.32 \times 10^{-3} \pm 0.06 \times 10^{-3}$</td>
</tr>
<tr>
<td>7 d</td>
<td>$0.10 \times 10^{-3} \pm 0.01 \times 10^{-3}$</td>
</tr>
</tbody>
</table>

Data are percentage injected radioactivity per milliliter of blood (mean values and SD from all 7 patients).

Metastases Analyzed for $^{111}$In-ABY-025 Uptake Using SPECT/CT at Different Times After Injection

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Metastases detected with $^{18}$F-FDG PET/CT</th>
<th>Metastases with detectable $^{111}$In-ABY-025 uptake</th>
<th>HER2 status of biopsies (immunohistochemistry)</th>
<th>HER2 status of selected lesions from imaging data using 24/4-h quotient</th>
<th>HER2 status of primary tumor (Table 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>2 2 3</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>10 13 13</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>10 11 11</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>16 21 19</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>4</td>
<td>71</td>
<td>3 12 13</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>37 37 36</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>30 32 34</td>
<td>No biopsy available</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*No $^{111}$In-ABY-025 uptake was visible on SPECT images of a few small lesions defined as metastases by $^{18}$F-FDG PET/CT in patients 1, 2, 3, and 7. Because of sensitivity limit of SPECT, it is not known whether these few were HER2-positive or HER2-negative.

**$^{111}$In-ABY-025 uptake seen on $^{18}$F-FDG PET/CT–defined metastases from patients 4, 5, and 6 gave low signals from large metastases and no signals from small metastases.

The 249 analyzed metastases were detected with $^{18}$F-FDG PET/CT 5 d before injection of $^{111}$In-ABY-025.
Table 4. The mean uptake of 111In-ABY-025 in HER2-positive metastases was at least 0.006 and 0.005 dose for the patients was 0.15 images taken 4, 24, or 48 h after injection (Table 4). The mean uptake of 111In-ABY-025 in HER2-positive metastases was at least 1 order of magnitude higher than a calculated uptake for homogeneous tissues (examples for patients 1, 2, 3, and 7 are shown in Fig. 1). A liver and spleen. Uptake in the salivary glands and bowels was also visualized. No correlation was found between any organ uptake and discrimination between metastases.

Uptake in Metastases

In the HER2-positive patients, large metastases (1 cm) identified by 18F-FDG PET/CT could be visualized with 111In-ABY-025 in the first whole-body planar scan approximately 30 min after injection. Most metastases could be detected with high quality on images taken 4, 24, or 48 h after injection (Table 4). The mean uptake of 111In-ABY-025 in HER2-positive metastases was at least 1 order of magnitude higher than a calculated uptake for homogeneous distribution of radioactivity in the body at 24 h after injection. The HER2-positive metastases were visualized in different locations and tissues (examples for patients 1, 2, 3, and 7 are shown in Fig. 1). A positive and HER2-negative lesions could be discriminated by calculating the decay-corrected 24/4-h uptake quotient. HER2-positive and HER2-negative metastases invariably showed a quotient greater than 1 and less than 1, respectively (Fig. 3). The difference between the groups classified as HER2-positive and HER2-negative was significant using a rank test (P < 0.05), with no overlap between the groups. The discriminatory capacity of this quotient was verified by immunohistochemistry on biopsied lesions.

Reevaluation of the original primary tumor tissue from patient 4 showed a heterogeneous HER2 expression, varying from 0 to 3+ (immunohistochemistry examples are shown in Figures 2A, 2B, and 2C), but the tumor was scored 3+ since more than 10% of the cells were 3+. The analysis of 111In-ABY-025 uptake in the metastases indicated low or no HER2 expression (arrow in Fig. 3), that is, were HER2-negative. Immunohistochemistry analysis of the biopsy samples from patient 4 after 111In-ABY-025 imaging showed scores from 0 to 1+ (immunohistochemistry examples are shown in Figs. 2F, 2G, and 2H). Thus, biopsy analysis of the metastases from patient 4 supported the use of 24/4-h quotients for discrimination.
The results of this first-in-human exploratory study indicate that 111In-ABY-025 can be used as a whole-body-oriented, noninvasive agent to discriminate between HER2-positive and HER2-negative metastases. A single intravenous injection was well tolerated and safe and gave an effective patient dose of approximately 21 mSv.

DISCUSSION

The rapid clearance of 111In from blood and normal organs allowed HER2 imaging of large (>1 cm) metastases 30 min after injection and gave images with good contrast after 4, 24, and 48 h. The levels of shed serum-HER2 did not appear to affect normal-organ uptake or blood kinetics.

The high uptake of 111In-ABY-025 in metastases from patients 1, 2, 3, and 7 provided excellent HER2 visualization throughout the body. Immunohistochemistry analysis of biopsies confirmed the overexpression of HER2. Thus, imaging with 111In-ABY-025 can identify HER2-positive metastases. However, large lesions could also be visualized in HER2-negative patients 5 and 6, although with weak signals (Table 4). This can be explained by the fact that tumors with HercepTest scores 0 and 1+ may have up to 15,000–25,000 and 80,000–110,000 HER2 receptors per cell, respectively (28). Thus, SPECT-based imaging appears sensitive enough to visualize even low HER2 expression. Preclinical studies have shown that discrimination between tumors with high and low levels of HER2 expression is possible, either using Affibody molecules with low specific radioactivity (23) or using the fast clearance of radioactivity from tumors with low HER2 expression (29). In the present study, the decay-corrected 24/4-h uptake ratio was used to determine the HER2 status at both patient and lesion level. The average 111In-ABY-025 uptake increased significantly in all lesions from 4 to 24 h and remained increased at 48 h for HER2-positive patients 1, 2, 3, and 7. In contrast, lesions from HER2-negative patients 5 and 6 showed decreased 111In-ABY-025 uptake from 4 to 24 h. The 24/4-h uptake ratios were invariably greater than 1 for HER2-positive lesions and less than 1 for HER2-negative lesions. The validity of this approach was supported by data from patient 4 (primary tumor HercepTest score, 3+) demonstrating low 111In-ABY-025 uptake in the metastases. Analysis of all lesions from this patient showed 24/4-h quotients of less than 1, typical for low HER2 expression, and immunohistochemistry analysis of biopsies confirmed low HER2 expression with HercepTest scores of 0 or 1+.

The 24/4-h quotient method requires a 2-d protocol. A single-time-point protocol using SPECT/CT appears to be feasible (supplemental material) but may optimally require PET technique since the sensitivity and absolute quantification are better than for SPECT. Preclinical studies have demonstrated that Affibody molecules can be labeled with positron emitters such as 68Ga and 18F with preserved HER2-targeting capacity (22,30–32).

**FIGURE 2.** Patient 4 changed from HER2-positive primary tumor to HER2-negative metastases. Column A shows examples of variations in HER2 expression (immunohistochemistry) in primary tumor. More than 10% of tumor cells in primary tumor had strong circumferential HER2 staining of their entire cell membrane, and patient was therefore declared HER2-positive. B shows 18F-FDG PET/CT scan 5 d before SPECT. In total, 71 metastases were detected (Table 4). C shows HER2 scan 4 h after injection of 111In-ABY-025. No HER2-expressing metastases could be detected in this scan, but 3 metastases with low HER2 expression could be detected in SPECT/CT sections after 4 h and more were detected after 24 h (Table 4). However 24/4-h quotients indicated that all these metastases were HER2-negative, as verified by immunohistochemistry analysis of biopsy samples. Column D shows examples of immunohistochemistry analyses of 3 different metastases: thyroid metastasis that scored 0 (top), calcified thyroid metastasis that scored 0 (middle), and bone metastasis that scored 1+ (bottom). Bars in immunohistochemistry images correspond to 50 μm.

**FIGURE 3.** Plots of 111In-ABY-025 uptake ratios in metastatic lesions defined by 18F-FDG PET/CT. In total, 108 lesions were included in analysis. (A) Average 111In uptake at 24 and 48 h calculated for each patient with HER2-positive metastases and normalized to uptake at 4 h after injection. 111In uptake increased significantly in all lesions from 4 h (●) to 24 h (●) and remained increased at 48 h (▲) after injection (Kruskal–Wallis ANOVA, P = 0.01). (B) Average 111In uptake at 24 h normalized to uptake at 4 h for patients 1, 2, 3, and 7 with HER2-positive metastases (●) and for patients 4, 5, and 6 with HER2-negative metastases (□). There was no overlap between values for HER2-positive and HER2-negative metastases, and difference was significant (Mann–Whitney, P < 0.05). Mean values and SE estimates are given. Arrow in B indicates data for patient 4, that is, patient who had HER2-positive primary tumor but HER2-negative metastases. No drug-related adverse events or anti-ABY-025 antibodies were observed.
Interestingly, the use of $^{111}$In-ABY-025 allowed HER2 imaging of known liver metastases in patient 2. This is an improvement since liver metastases could not be visualized using the first-generation anti-HER2 Affibody molecule, ABY-002 (Supplemental Fig. 1). ABY-025, used in the current study, has been obtained by protein engineering to increase hydrophilicity, increase thermal stability, increase production characteristics, and, as shown in animal experiments, lower liver uptake. The present study suggests that the changes engineered into ABY-025 provide clinical utility. The physiologic liver uptake varied between the patients. Patient 2 had the lowest physiologic liver uptake and fasted before administration of $^{111}$In-ABY-025, whereas patients eating before administration had higher physiologic liver uptake.

Radiolabeled trastuzumab has been evaluated earlier for HER2 imaging (15,16), and image quality has been reported to be optimal 4–5 d after injection (15), compared with 4–24 h using $^{111}$In-ABY-025. The limited number of reported clinical studies does not permit a detailed comparison of sensitivity and specificity of radiolabeled trastuzumab versus $^{111}$In-ABY-025 in the clinical setting. The unique binding epitope of ABY-025, which is different from the epitopes of either trastuzumab or pertuzumab (24), allowed imaging during trastuzumab treatment.

CONCLUSION

Our findings indicate that imaging of breast cancer metastases with $^{111}$In-ABY-025 is feasible and might be valuable for selection of patients who may, or may not, benefit from HER2-targeted therapies, hence improving treatment utility and cost-effectiveness.

DISCLOSURE

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REFERENCES


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