Human Epidermal Growth Factor Receptor 2 (HER2) PET Imaging of HER2-Low Breast Cancer with [^{68}Ga]Ga-ABY-025: Results from a Pilot Study

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Patients with HER2-low metastatic breast cancer (mBC), defined as an immunohistochemistry (IHC) score of 1+ or 2+ without HER2 gene amplification, may benefit from HER2 antibody–drug conjugates. Identifying suitable candidates is a clinical challenge because of spatial and temporal heterogeneity in HER2 expression and discrepancies in pathologic reporting. We aimed to investigate the feasibility and safety of HER2-specific PET imaging with [^{68}Ga]Ga-ABY-025 for visualization of HER2-low mBC. **Methods:** A prospective pilot study was done with 10 patients who had HER2-low mBC, as part of a phase 2 basket imaging study with [^{68}Ga]Ga-ABY-025 in HER2-expressing solid tumors. Patients were recruited at the Breast Clinic at the Karolinska University Hospital, Stockholm, Sweden. PET/CT images were acquired 3 h after injection of 200 MBq of [^{68}Ga]Ga-ABY-025. The SUV_{max} was used to quantify tracer uptake. Ultrasound-guided tumor biopsies were guided by results from the HER2 PET. The main outcome—the safety and feasibility of HER2 PET in patients with HER2-low mBC, measured the occurrence of possible procedure-related adverse events. **Results:** Ten patients with HER2-low mBC underwent [^{68}Ga]Ga-ABY-025 PET/CT with paired tumor biopsies. No adverse events occurred. In all patients, [^{68}Ga]Ga-ABY-025–avid lesions with substantial intra- and interindividual heterogeneity in tracer uptake were noted. In 8 of 10 patients with ABY-025–avid lesions, the HER2-low status of the corresponding lesions was confirmed by IHC or in situ hybridization. Two patients had an IHC score of 0 in the tumor biopsies:1 in a cutaneous lesion with a low SUV_{max} and 1 in a liver metastasis with a high SUV_{max} but a "cold" core. **Conclusion:** The visualization of HER2-low mBC with [^{68}Ga]Ga-ABY-025 PET/CT was feasible and safe. Areas of tracer uptake showed varying levels of HER2 expression on IHC. The observed intra- and interindividual heterogeneity in [^{68}Ga]Ga-ABY-025 uptake suggested that HER2 PET might be used as a tool for the noninvasive assessment of disease heterogeneity and has the potential to identify patients in whom HER2-targeted drugs can have a clinical benefit.

Key Words: HER2 PET; HER2-low breast cancer; [^{68}Ga]Ga-ABY-025

Received Oct. 12, 2023; revision accepted Jan. 11, 2024.
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Published online Mar. 28, 2024.

J Nucl Med 2024; 65:700–707
DOI: 10.2967/jnumed.123.266847

The recognition of human epidermal growth factor receptor 2 (HER2)-low breast cancer, present in about 50% of patients, has profoundly impacted the view of breast cancer clinicians on the role of HER2 as a therapy-predictive biomarker. HER2-low expression is currently defined as an immunohistochemistry (IHC) score of 1+ or 2+ without gene amplification assessed by in situ hybridization (ISH) (*1*).

Although having HER2-low metastatic breast cancer (mBC) does not have prognostic implications in terms of survival (*2*,*3*), there is a clear therapy-predictive value based on the findings from clinical trials with the HER2-targeted antibody–drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) (*4*,*5*). Since 2022, T-DXd has been approved by both the Food and Drug Administration and the European Medicines Agency for the treatment of HER2-low mBC with disease progression after at least 1 line of palliative systemic chemotherapy (*6*,*7*).

Several diagnostic challenges exist concerning identifying patients who have HER2-low breast cancer and can derive a treatment benefit from HER2 ADCs such as T-DXd: uniformity in testing and consistency in reporting are suboptimal (*2*,*8*), and a biopsy from a single lesion might not reflect the total disease burden because of spatial and temporal heterogeneity in HER2 expression (*9*). Moreover, repeated invasive biopsies are burdensome for patients and not always technically possible or practically feasible (e.g., those from sanctuary sites in the lungs or brain).

Molecular imaging techniques such as PET with HER2-specific tracers (hereafter, HER2 PET) have until today been used to identify HER2-positive tumors. Tracers such as [^{89}Zr]Zr-trastuzumab, [^{18}F]FBEM-trastuzumab, [^{68}Ga]Ga-DOTA-F(ab′)$_2$-trastuzumab, [^{89}Zr]Zr-Df-HER2-Fab-PAS200, [^{18}F]GE266, and [^{68}Ga]Ga-ABY-025 have been evaluated in HER2-positive tumors in clinical settings (*10*). However, no prospective studies have been performed to investigate whether HER2-low mBC can be visualized

by the HER2-specific molecular imaging tracer [^{68}Ga]Ga-ABY-025 (*11*,*12*).

The purpose of our prospective pilot study was thus to determine whether HER2 PET with the Affibody (Affibody AB)-based HER2 tracer [^{68}Ga]Ga-ABY-025, combined with contrast-enhanced CT, is a safe and feasible method for identifying metastatic lesions with HER2-low status in patients with previously biopsy-verified HER2-low breast cancer. To test this hypothesis, we compared the level of tracer uptake on PET with HER2 expression determined by IHC and ISH of tumor biopsies from 10 patients with mBC. In this study, we showed that HER2 PET with [^{68}Ga]Ga-ABY-025 is a promising, noninvasive alternative to tumor biopsies.

MATERIALS AND METHODS

Study Design

This study is part of an ongoing phase II single-center, open-label basket imaging study with the HER2 tracer [^{68}Ga]Ga-ABY-025 for patients with HER2-expressing solid tumors (EU CT 2022-500448-39-00; ClinicalTrials.gov registration number NCT05619016). The study was approved by the Swedish Medical Product Agency and the Ethical Review Authority (Dnr 5.1–2022–58345). All study participants provided written informed consent for participation in the study. In this report, we present the findings from a preplanned pilot study of 10 patients with HER2-low mBC.

Patients

Patients were recruited at the Breast Clinic of the Karolinska Comprehensive Cancer Center, Stockholm Sweden. Eligible patients were informed about the possibility to participate in the trial. All participants provided written informed consent before inclusion. The study was performed in compliance with the study protocol, the Declaration of Helsinki, International Conference on Harmonisation-Good Clinical Practice guidelines, and current national and international regulations governing the conduct of clinical trials.

Inclusion criteria for the pilot study of HER2-low mBC were an age of 18 y or older, an adequate performance status (World Health Organization performance status of ≤2), an estimated life expectancy of greater than 12 wk, and the ability to provide written informed consent. Previously biopsy-verified breast cancer with low HER2 expression on IHC should have been available from the patient files (i.e., HER2 IHC score of 1+ or 2+ [ISH negative]), preferably from a metastatic lesion, alternatively from the primary tumor. Patients should have had at least 1 metastatic lesion of 10 mm or larger available for biopsy. In certain cases, a previously acquired biopsy could be accepted for comparison with HER2 PET findings, in case the biopsied lesion could be identified on PET/CT and no systemic cancer therapies had been given during the period between the biopsy and the HER2 PET.

Exclusion criteria were significantly impaired renal function, allergy to iodinated contrast medium, other manifested malignancy except for basal cell carcinoma of the skin, inadequate organ function, pregnancy or lactation, and an increased risk of complications from biopsies—that is, an increased risk for bleeding.

Radiopharmaceuticals and Image Acquisition

Good manufacturing practice–grade ABY-025 was provided by Affibody AB. The automated and current good manufacturing practice–compliant radiosynthesis of [^{68}Ga]Ga-ABY-025 was performed on the Modular-Lab PharmTracer (Eckert & Ziegler) at the Karolinska University Hospital radiopharmacy facilities (*13*). Depending on the radiosynthesis yield, 100–250 MBq of [^{68}Ga]Ga-ABY-025 solution for injection was intravenously administered. At the time of injection, a 45-min-long dynamic scan from the collarbone level to the iliac crest was performed; this scan was followed by static scanning 3 h after injection according to previously established optimization of the tumor-to-background ratio (TBR) (*14*). Imaging was performed on a Biograph 6 PET/CT (Siemens) scanner; static PET images were acquired from the base of the skull to midthigh (4 min/bed position). The static PET scanning was preceded by non–contrast-enhanced low-dose CT for attenuation correction. After PET imaging, diagnostic contrast-enhanced CT was performed for anatomic correlation of PET findings and image fusion.

Image Analysis and Interpretation

Two readers, a board-certified radiologist/specialist in nuclear medicine, and a radiologist/nuclear medicine specialist in training, respectively, independently performed the analysis of the [^{68}Ga]Ga-ABY-025 PET/CT images.

Using the image software Syngo.via (Siemens), lesions with focal tracer uptake correlating to metastases on CT and suitable for ultrasound-guided biopsy were annotated, and their location was provided to the interventional radiologist. To correlate the level of tracer uptake to HER2 expression according to the reference standard, semiquantitative image parameters (SUV_{max} and SUV_{mean}) were used. These were extracted from manually applied volumes of interest on the lesions that were about to be biopsied and defined using 40% threshold isocontouring. To evaluate the heterogeneity of tracer uptake in metastases within each patient, volumes of interest were applied on a maximum of 5 areas with focal tracer uptake suggesting metastases per organ system (i.e., liver, bone, breast, skin, lymph nodes, lungs).

TBRs were calculated by dividing the measured tumor SUV_{max} by the SUV_{mean} in the spleen. To explore options for calculating tracer-specific TBRs and to evaluate suitable cutoff levels for the discrimination of lesion HER2 expression, additional as-large-as-possible spheric volumes of interest were applied in the left ventricular myocardium, healthy liver parenchyma if such was available, and the spleen. The last was chosen on the basis of the results of previous studies in which the spleen was deemed to be the most suitable reference tissue for discriminating between IHC HER2-positive and -negative metastases (*14–16*).

Correlations between IHC and metrics from PET images were investigated using the Spearman rank correlation coefficient.

All lesions defined as metastatic on CT were evaluated for [^{68}Ga]Ga-ABY-025 uptake and the possibility of obtaining a biopsy to discover false-negative HER2 PET results. SUV_{max} was assessed in a maximum of 5 metastases per organ (i.e., liver, bone, breast, skin, lymph nodes, lungs) in each patient, including (when there were more than 5 metastases) the lowest and the highest SUVs per organ.

Tissue Sampling and Analysis (Reference Standard)

The site of the biopsy was determined by the radiologist at the Department of Nuclear Medicine of Karolinska University Hospital, who referred information about potential biopsy sites to the interventional radiologist at the Department of Radiology, Karolinska University Hospital, Stockholm, Sweden. The biopsies were performed on an outpatient basis under sterile conditions after local anesthesia and were guided by ultrasound based on findings from the previous HER2 PET/CT. Large needle diameters (1.2 mm) were used to increase the chances of obtaining representative material and to minimize the risk of sample bias due to spatial heterogeneity in HER2 expression. Two or 3 biopsies up to 22 mm in length were obtained from each selected lesion. The biopsies were placed in sterile sealed bakers containing formalin solution and transported to the local pathology laboratory, where IHC and ISH analyses of HER2 expression were executed as part of the clinical routine. The material was stained with monoclonal rabbit anti–HER-2/*neu* antibody (clone 4B5; Roche Tissue Diagnostics), and the VENTANA HER2 Dual ISH DNA Probe Cocktail Assay (Roche Tissue Diagnostics), VENTANA Silver ISH DNP Detection

Kit, and VENTANA Red ISH DIG Detection Kit were used in accordance with the manufacturer's instructions (BenchMark ULTRA IHC/ISH Staining Module; Roche Tissue Diagnostics).

IHC and ISH results served as the reference standard. For the definition of HER2 positivity in mBC, the 2018 American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline for HER2 testing in breast cancer (*17*) was used. HER2-low mBC was defined as an IHC score of 1+ or 2+ without HER2 gene amplification assessed by ISH.

Because of the previously described challenge in the pathologist's assessment of HER2-low status, all tumor samples were sent for central reevaluation once inclusion was completed. In case of disagreements between the original evaluation and the reevaluation, the central review was regarded as decisive.

Patient Safety

To monitor, treat, and prevent adverse events and adverse reactions, all participants were monitored with repeated clinical examinations and supervision of vital parameters, including blood pressure, pulse, breathing rate, and temperature, during the stay at the nuclear medicine department before injection of [^{68}Ga]Ga-ABY-025 and 1 and 4 h after administration. A follow-up telephone contact with the patients was performed for safety assessment 24 h after injection of the study drug by the study nurse.

Statistical Analysis and Power Calculation

The aim of this study was to evaluate a diagnostic modality for a new indication, and no data on diagnostic accuracy were available during study planning. Therefore, this study was considered a pilot study without a basis for calculating the need for achieving sufficient statistical power. Descriptive analytics are used to present the findings.

RESULTS

Patient Characteristics

From November 2022 up to June 2023, 11 patients with a previously biopsy-verified HER2-low mBC were recruited according to the flow chart in Figure 1. Table 1 represents patient characteristics and previous tumor characteristics of the 10 patients with paired HER2 PET and tumor biopsies. Nine of 10 patients had pretreated mBC, most having received treatment with antihormonal agents combined with CDK4/6 inhibitors and different cytostatic agents. One patient received 2 doses of trastuzumab 2 y before HER2 PET, but otherwise no patients received HER2-targeted therapies.

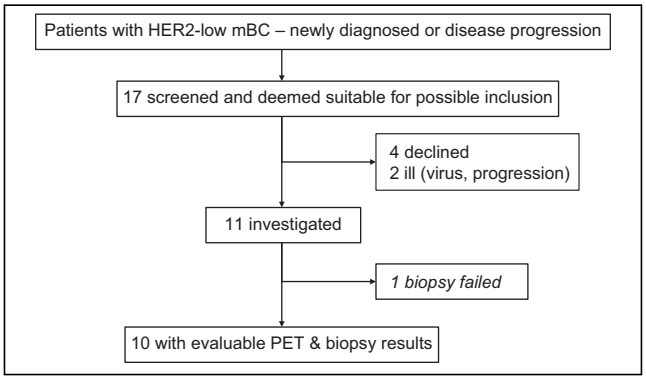

FIGURE 1. Flowchart of accrual and study-related investigations in pilot study of HER2 PET with [^{68}Ga]Ga-ABY-025 for patients with HER2-low mBC.

Study-Related Investigations

PET/CT imaging was performed after injection of 173 ± 39 MBq of [^{68}Ga]Ga-ABY-025 with a cold peptide dose of 350–510 μg.

In 9 of 10 patients, biopsies were acquired after HER2 PET (median, 5 d [range, 4–9 d]); for the convenience of 1 participant, a liver biopsy obtained 28 d before HER2 PET was used as a reference as no systemic treatment was administered in between and the biopsied metastasis could be identified on CT (patient 8). The most frequent site of biopsy was the liver (n = 7), followed by soft-tissue lesions (1 in lymph node, 1 in local relapse in breast, and 1 cutaneous metastasis).

Safety Assessment

All patients tolerated the study-related investigations, including HER2 PET, well. No adverse events or adverse reactions occurred.

Results from Paired HER2 PET and Tumor Biopsy

Table 2 summarizes the results from the study-related investigations with HER2 PET and tumor biopsies. ABY-025–avid metastatic lesions were noted in all 10 patients, with SUV_{max} in biopsied lesions that ranged from 3.7 to 33.4 (Fig. 2). In 8 of 10, the tumor biopsy confirmed the HER2-low status, whereas no HER2-positive tumors were found. Two patients had an IHC score of 0 in the tumor biopsies: 1 in a cutaneous lesion with a low SUV_{max} (3.7) and 1 in a liver metastasis with a high SUV_{max} (24.9) but a "cold" core because of necrosis on CT. A moderate, not statistically significant correlation between SUV_{max} and HER IHC was found, with r = 0.41 (P = 0.24) (Fig. 3). Of note, patient 5 was considered to have a false-negative tumor biopsy (Fig. 4).

In both patients with triple-negative breast cancer (n = 3) and those with lobular tumors (n = 3), ABY-025–avid metastatic lesions were seen. No skeletal punctions were performed, but clear ABY-025–avid lesions were noted in skeletal metastases.

All metastatic lesions on CT that could be biopsied were also avid for [^{68}Ga]Ga-ABY-025 uptake, and no false-negative HER2 PET results were discovered in this pilot cohort.

TBR on HER2 PET

As shown in Table 2, low SUV_{max} and SUV_{mean} were noted in the spleen and myocardium. No obvious correlation between TBR and IHC using the spleen as a reference was found (Table 2). In the liver, enhanced background uptake was noted; in 5 of 10 patients, the SUV in the healthy liver parenchyma could not be measured because of massive liver metastases.

Disease Heterogeneity on HER2 PET

Figure 5 represents SUV_{max} per patient in a maximum of 3 metastases per organ, as well as the mean SUV_{max} of ABY-025–avid metastases on HER2 PET. Clear interindividual heterogeneity in ABY-025 tracer uptake was noted between patients, and intraindividual heterogeneity was noted between different metastases in the same patient. Even within different organ systems, differences in SUV_{max} in metastases were noted. The SUV_{max} in all patients ranged from 2.3 to 39.1; in liver, lymph node, and bone metastases, the SUV_{max} ranged from 10.7 to 39.1, 2.7 to 19.5, and 2.7 to 34.3, respectively.

DISCUSSION

The results of this pilot study show that PET/CT with [^{68}Ga]Ga-ABY-025 is a feasible, tolerable and safe procedure to identify patients with biopsy-verified HER2-low breast cancer, suggesting a potential for HER2 PET to be used as a noninvasive tool to select

TABLE 1
Characteristics of Patients Included in Pilot Study, Previous Treatment, and Tumor Biology Features

Patient	Year of birth	Year of mBC diagnosis	Previous palliative systemic therapies in metastatic setting	Breast cancer type	Previous metastatic biopsies			
					Previous biopsy site	ER/PR/Ki-67	HER2 IHC	HER2 ISH
1	1945	2015	Letrozol, eribulin, paclitaxel, fulvestrant, exemestane + palbociclib, vinorelbin	Ductal	Liver	100/100/10	2	1.54
					Liver	100/95/17	2	2.4
					Liver	100/0/16	2	2.7
2	1962	2022	Newly diagnosed mBC	Ductal	Primary tumor	100/90/38	1	
3	1957	2016	Anastrozole, fulvestrant + palbociclib, capecitabine	Ductal	Liver	100/0/25	2	1.0
4	1966	2018	Letrozole/palbociclib, PEGylated doxorubicin, tamoxifen, capecitabin	Ductal	Liver	50/0/43	1+	
5	1972	2020	Anastrozole/goserelin/ palbociclib, fulvestrant/ ribociclib	Lobular	Primary tumor (intracranial disease)	100/70/20	2	
6	1974	2019	Capecitabin, eribulin, carboplatin/paclitaxel, sacituzumab govitecan	Lobular	Breast/skin	0/0/10	1+	
7	1973	2018	Fulvestrant/ribociclib	Ductal	Breast (relapse)	80/0/32	2+	2,3
8	1949	2020	Letrozole, fulvestrant/ribociclib	Ductal	Bone	100/0/30	0	
9	1963	2014	Paclitaxel, letrozole, fulvestrant/ribociclib, capecitabin	Ductal	Liver	90/5/1		
					Bone	100/50/10		
10	1966	2020	Eribulin, capecitabin	Lobular	Bone	0/0/15		2–4/2–4/1.0

ER = estrogen receptor; PR = progesterone receptor.

TABLE 2
Study-Related Findings from HER2 PET and Paired Tumor Biopsy in 10 Patients in HER2-Low Pilot Study

		HER2 PET/CT results								Study-specific biopsies			
			SUV for spleen		SUV for liver*		SUV for left myocardium						
Patient	Lesion site(s)	SUV_{max} for tumor	Max	Mean	Max	Mean	Max	Mean	TBR	Site	ER/PR/Ki-67	HER2 IHC biopsy	HER2/C17 gene amplification quote
1	Liver	12.9	2.6	1.9	9.1	7.8	3.1	2.2	6.8	Liver	100/100/19	1+	2.85/1.0/2.85
2	Bone, lymph nodes	6.1	3.9	2.6	13.7	7.0	4.4	3.0	2.3	Lymph node	0/0/95	1+	
3	Liver	28.7	3.0	1.8	NA	NA	4.1	2.6	15.9	Liver	80/70/NA	2+	3.3/2.3/1.4
4	Bone, liver	10.7	5.0	3.3	NA	NA	3.2	2.2	3.2	Liver	80/70/78	1+	4.4/2.5/1.76
5	Bone, liver	24.9	3.9	2.6	13.4	10.2	4.1	2.9	9.6	Liver	30/0/60	0	
6	Bone, skin, liver	3.7	2.8	2.2	NA	NA	3.1	2.1	1.7	Skin	0/0/39	0	
7	Breast, brain	10.3	2.3	1.7	13.8	11.0	3.8	2.9	6.1	Breast	60/0/40	2+	3.6/1.45/2.48
8	Liver	33.4	2.7	2.1	13.3	9.7	4.1	3.0	15.9	Liver	95/0/3	2+	1.3/1.8/0.7
9	Bone, liver	19.0	3.0	2.3	NA	NA	3.7	3.0	8.3	Liver	95/95/13	2+	2.25/1.55/1.45
10	Liver, bone	12.0	2.7	1.6	NA	NA	2.7	1.8	7.5	Liver	0/0/33	2+	2.65/1.35/1.96

*Only given when possible to identify area without scatter from metastases in liver.
Max = maximum; NA = not available.

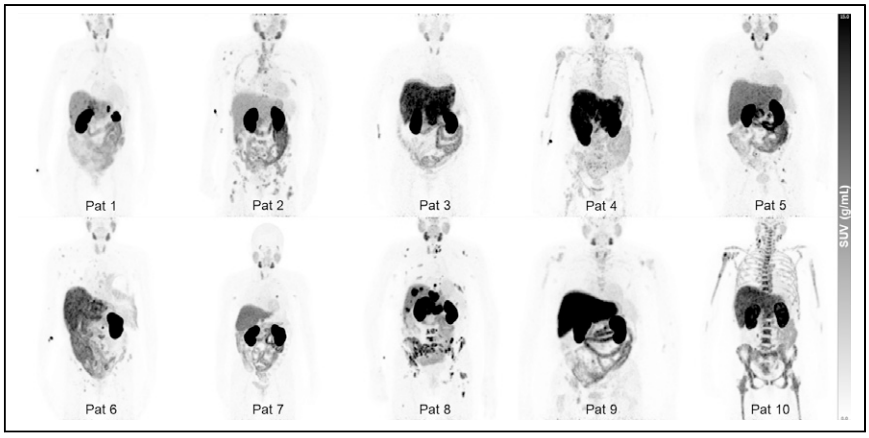

FIGURE 2. Maximum-intensity-projection values from all 10 patients included in pilot study of HER2 PET with [^{68}Ga]Ga-ABY-025. Pat = patient.

patients who might benefit from HER2 ADCs. All patients included in this pilot study had ABY-025–avid metastatic lesions, and in 8 of 10, HER2-low status was confirmed by regularly used IHC/ISH analyses. Disease heterogeneity based on inter- and intraindividual differences in SUV_{max} was noted. In 1 patient with an IHC HER2 score of 0, SUV_{max} was only slightly higher than background signal, and in the other patient with an IHC HER2 score of 0, the biopsy was likely obtained from a central area in the tumor with a cold core surrounded by high ABY-025 uptake.

The recognition that patients with HER2-low tumors derive a clear clinical benefit from treatment with the HER2-targeted antibody-drug conjugate T-DXd has had profound practice-changing implications for the management of about half of patients with mBC. Additional approvals for T-DXd are anticipated in other tumor types with HER2-low expression, supported by promising clinical data in patients with carcinosarcoma uteri and gastro-esophageal cancer (*18*,*19*). Furthermore, several other tumors have been found to have varying levels of HER2 expression, thereby opening a large cancer patient population that might in the future have an indication for HER2-targeted therapies (*20*).

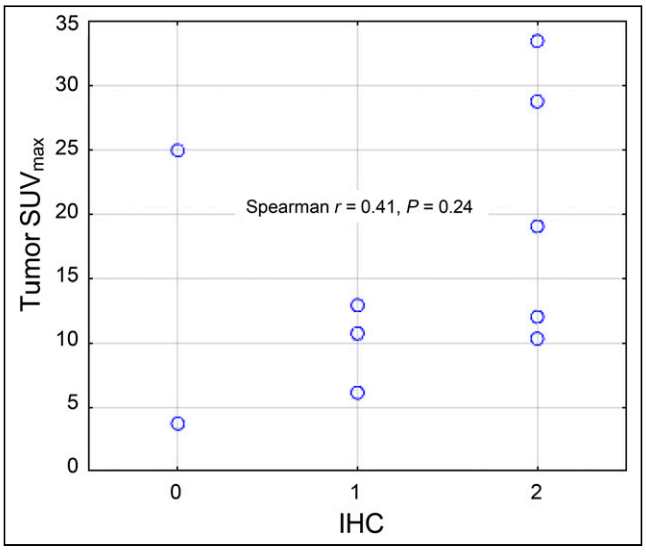

FIGURE 3. Correlation between HER2 IHC in biopsies of metastatic lesions and SUV_{max} on HER2 PET.

A challenging dilemma in clinical practice revolves around the selection of patients for HER2 ADC therapies, such as T-DXd. There is an urgent need for tools to optimize the risk-benefit profile, encompassing both potential toxicities as well as economic expenditures. Up to now, limited data are available regarding the spatial and temporal heterogeneity and dynamics of HER2-expression in HER2-low tumors, compounded by not-yet-standardized testing practices. Notably, HER2-positive mBC can shift from positive to negative and vice versa in around 15% of patients during disease progression (*21*).

Recent exploration of HER2-low status heterogeneity involved 10 patients with a total of 306 tumor biopsies, revealing coexisting HER2-low and HER2-nonexpressing lesions in 8 of 10 patients (*9*). Of note, the fact that the included patients in this pilot study all had previously biopsy-verified HER2-low mBC whereas 2 had a tumor biopsy with a HER2 IHC score of 0 proved that HER2 expression is dynamic over time. Suboptimal reproducibility in pathologically assessing HER2-low status has been documented (*2*,*8*), although this issue was not observed in our pilot study (data not shown). Another complicating issue is the fact that invasive biopsies are not always technically feasible or practically viable, particularly from challenging sites like the lungs or brain.

PET imaging with a HER2-specific tracer might be a way to solve these issues, but up to now, prospective studies dedicated to this patient population is still lacking (*11*,*12*). The issue of nonrepresentative tumor biopsies is clearly illustrated by patient number 5, who had multiple ABY-025 tracer–avid lesions on HER2 PET imaging, despite a tumor biopsy indicating an IHC score of 0. According to current indications and approvals, she would not have been a candidate for treatment with T-DXd, although HER2 PET showed the presence and accessibility of the target receptor. A question that follows here is whether the observed responses in the

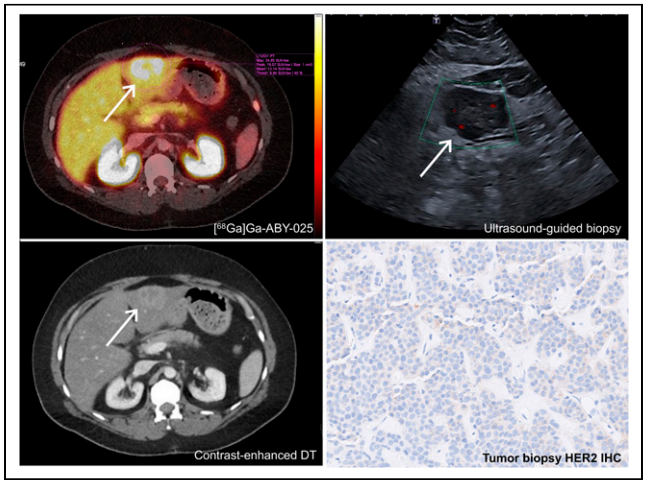

FIGURE 4. Representative images from patient with SUV_{max} of 24.9 and HER2 IHC score of 0 in biopsy specimen. Metastatic lesion in segment 3 of liver shows inhomogeneous intravenous contrast uptake due to central necrosis (arrows). Inhomogeneous nature of metastatic lesion was verified under ultrasound before biopsy. Liver biopsy (bottom right) shows status for HER2 IHC score of 0.

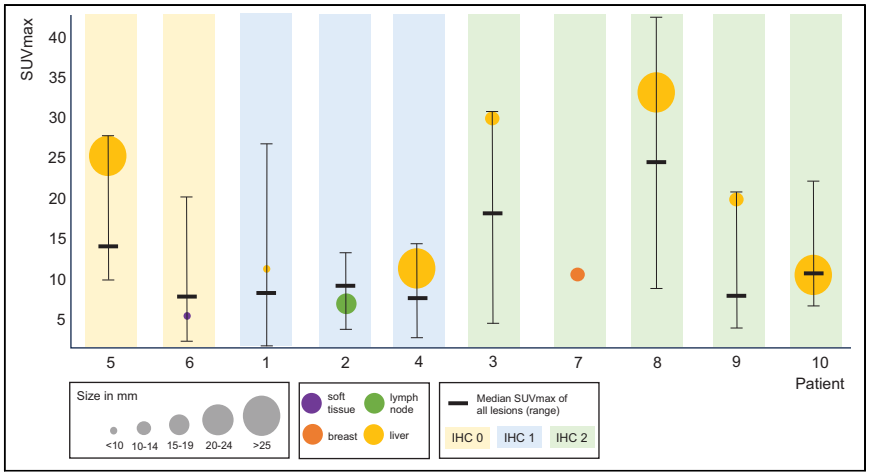

FIGURE 5. Disease heterogeneity noted on HER2 PET. Per patient, biopsied lesion, median SUV_{max}, and range of all tumor lesions measured on HER2 PET are indicated by thick black line. HER2 IHC result is also shown.

DAISY trial might also have been steered by nonrepresentative biopsies due to heterogeneity in low levels of HER2 expression (*22*).

Two studies with HER2-specific PET tracers have indirectly provided data on the imaging of HER2-low mBC: 1 trial with [^{68}Ga]Ga-ABY-025 and 1 trial with [^{89}Zr]Zr-trastuzumab (*14*,*23*). In the AFFIBODY-3 study (*14*), 40 patients with HER2-positive primary breast cancer or mBC underwent serial PET with both [^{68}Ga]Ga-ABY-025 and ^{18}F-FDG. A higher SUV_{max} on HER2 PET was associated with a more pronounced metabolic response on [^{18}F]FDG PET shortly after the initiation of HER2-targeted systemic therapy. In the AFFIBODY-3 trial (*14*), 6 patients had a HER2-negative (IHC score of 0) tumor biopsy and 16 patients had a HER2-low tumor (called "HER2 borderline" by the authors). Eleven of these 22 patients had an SUV_{max} of greater than 6 in the biopsied lesion, and 1 patient who had a tumor with a HER2 IHC score of 0 had an SUV_{max} slightly over 20. Four patients who had a study biopsy with a HER2 IHC score of 0 but clear [^{68}Ga]Ga-ABY-025 tracer uptake on HER2 PET showed a complete response on treatment with the HER2 ADC trastuzumab emtansine. In line with our observation in a patient with SUV_{max} of 24.9 but an IHC score of 0 in a biopsied lesion (Fig. 4), the authors pose that this may be explained by nonrepresentative sampling (*14*). In a small study of 11 patients who underwent PET imaging with [^{89}Zr]Zr-trastuzumab, similar observations were done with clear PET tracer avidity in 3 of 11 patients, although tumor biopsies showed HER2-negative status (*23*). It would be highly interesting to know whether, with the current knowledge of HER2-low disease, these tumors were IHC1–2+ HER2-low tumors. The discrepancies between [^{68}Ga]Ga-ABY-025–avid lesions and negative IHC results stress not only the value of image-guided biopsies, but also of precision placement of the needle during such biopsies.

All HER2-expressing metastases in our study showed an SUV_{max} higher than 6, a noteworthy finding that correlates with the prediction of therapy response according to previous findings (*14*). The cutoff SUV_{max} mentioned earlier needs to be further validated in a larger patient cohort and correlated not only with HER2 status in the metastatic burden but also in therapeutic responses.

The small sample size of this pilot study limits the possibility to draw broader conclusions based on the data presented here. It would have been highly interesting to have performed more tumor biopsies, guided by the PET images, especially from bone metastases that are notoriously difficult to assess HER2 status on but constitute a large burden of disease for patients with mBC. In a continued study we plan to extend the sample size, investigate the therapy-predictive role of HER2 PET for clinical benefit of HER2-targeted therapies and study whether a PET-based treatment selection strategy performs equally well compared with the current reference standard with a tumor biopsy.

CONCLUSION

The imaging of HER2-low mBC using [^{68}Ga]Ga-ABY-025 PET/CT has proven to be both feasible and safe. The regions displaying tracer accumulation exhibited different degrees of HER2 expression as determined by IHC. The detected variations in [^{68}Ga]Ga-ABY-025 uptake, both within individuals and among different patients, indicate that HER2 PET could serve as a valuable noninvasive tool for evaluating the heterogeneity of the HER2-low mBC. This precision imaging tool has the potential to identify patients who may benefit clinically from HER2-targeted drugs, as well as to enhance the biologic understanding of HER2-low cancers. For this purpose, prospective trials focusing on the therapy-predictive role of HER2 PET for the benefit of HER2 ADCs are warranted.

DISCLOSURE

The study was financed by grants from the Swedish government under the ALF Agreement (SLL20200025), Sjöbergstiftelsen (929649), and the Swedish Breast Cancer Society (Bröstcancerförbundet; 190850) and Function Medical Diagnostics at Karolinska University Hospital. Nikolai Brun and Fredrik Frejd are employed by Affibody AB, which discovered the ABY-025 tracer. Johan Hartman obtained speaker's honoraria or advisory board remunerations from Roche, Novartis, AstraZeneca, Eli Lilly, and MSD; received institutional research grants from Cepheid, Roche, and Novartis; and is a shareholder in Stratipath AB. Jonas Bergh received research grants from Amgen, AstraZeneca, Bayer, Merck, Pfizer, Roche, and Sanofi-Aventis to Karolinska Institutet, Karolinska University Hospital, or both. Jonas Bergh is coauthor of a chapter titled "Prognostic and Predictive Factors in Early, Nonmetastatic Breast Cancer" in *UpToDate* with honoraria to Asklepios Medicin AB. Jonas Bergh has stocks in Stratipath AB, being involved in artificial intelligence–based diagnostics for breast cancer. Jonas Bergh is chairperson for Coronis and Asklepios Cancer Research AB. Jonas Bergh has received honoraria from Roche and AstraZeneca for chairmanship and lectures at scientific meetings and consultations for Stratipath AB. Renske Altena has received study support to Karolinska Institutet from Roche and speaker honoraria to Karolinska University Hospital from Seagen, Roche, and Ipsen. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

Affibody AB provided the precursor ABY-025. We thank the study participants and colleagues at the Breast Clinic at the Karolinska Comprehensive Cancer Center.

KEY POINTS

QUESTION: Can HER2-low breast cancer be visualized with the HER2-specific tracer [^{68}Ga]Ga-ABY-025 for PET?

PERTINENT FINDINGS: In a pilot study of 10 patients with HER2-low mBC, PET imaging with the Affibody tracer[^{68}Ga]Ga-ABY-025 was feasible and safe. In all patients, [^{68}Ga]Ga-ABY-025–avid lesions were noted, with substantial intra- and interindividual heterogeneity in tracer uptake.

IMPLICATIONS FOR PATIENT CARE: The observed intra- and interindividual heterogeneity in [^{68}Ga]Ga-ABY-025 uptake suggested that HER2 PET might be used as a tool for the noninvasive assessment of disease heterogeneity and has the potential to identify patients in whom HER2-targeted drugs can have a clinical benefit.

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