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Noninvasive assessment of human epidermal growth factor receptor 2 (HER2) in esophagogastric cancer using ^{89}Zr-trastuzumab PET: a pilot study

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Running Title: ^{89}Zr-trastuzumab PET in HER2+ EG cancer

ABSTRACT (350/350)

Variations in HER2 expression between the primary tumor and metastases may contribute to drug resistance in HER2-positive metastatic esophagogastric cancer (mEGC). ^{89}Zr-trastuzumab positron emission tomography (HER2 PET) holds promise for noninvasive assessment of variations in HER2 expression and target engagement. The aim of this study is to describe HER2 PET findings in patients with mEGC. **Methods:** Patients with HER2-positive mEGC were imaged with HER2 PET, ^{18}F-fluorodeoxyglucose PET (FDG PET), and computed tomography (CT). Lesions were annotated using measurements (on CT) and maximum standardized uptake values (on HER2 PET). Correlation of visualized disease burden among imaging modalities with clinical and pathologic characteristics was performed. **Results:** Thirty-three patients with HER2+ mEGC were imaged with HER2 PET and CT (12% esophageal, 64% gastroesophageal junction, and 24% gastric adenocarcinoma), 26 of whom were also imaged with FDG PET. More lesions were identified on FDG PET (median, 7 [range, 1-14]) than HER2 PET (median, 4 [range, 0-11]). Of the 8 lesions identified on HER2 but not FDG PET, 3 (38%) were in bone and 1 was in the brain. Of the 68 lesions identified on FDG but not HER2 PET, 4 (6%) were in bone and the remainder were in the lymph nodes (35, 51%) and liver (16, 24%). Of the 33 total patients, 23 (70%) were HER2 imaging positive (≥50% of tumor load positive). Only 10 patients had 100% of the tumor load positive; 2 had 0% positive. When only patients receiving HER2-directed therapy as first-line treatment were considered (n=13), median progression-free survival (m-PFS) therapy was not significantly different between HER2 imaging-positive and -negative patients. Median PFS for patients with at least one intense or very intense lesion (standardized uptake value ≥10) was 16 [95% CI: 11-not reached] months (n=7), compared with 12 [95% CI: 6.3-not reached] months for patients without an intense or very intense lesion (n=6) (*P*=0.35).

Conclusions: HER2 PET may identify heterogeneity of HER2 expression and allow assessment of lesions throughout the entire body. A potential application of HER2 PET is noninvasive evaluation of HER2 status including assessment of intra-patient disease heterogeneity not captured by standard imaging or single site biopsies.

Keywords: 3-5

HER2 heterogeneity, esophageal adenocarcinoma, gastric adenocarcinoma, trastuzumab, HER2 PET

Esophagogastric cancer (EGC) is the third most common cause of cancer-related death worldwide, and 20%-30% of patients with metastatic EGC (mEGC) have human epidermal growth factor receptor 2 (HER2)-positive disease.(*1–4*) On the basis of data from two trials—the phase III randomized controlled ToGA,(*5*) which demonstrated improved response rate and survival when trastuzumab was added to chemotherapy, and the phase III Keynote-811,(*6,7*) which demonstrated a better response rate and survival when trastuzumab was added to chemotherapy in combination with PD-1 blockade—HER2 is a validated treatment target in mEGC. Although HER2 immunohistochemistry, HER2/CEP17 ratio, and ERBB2 gene copy number can be used to predict response to trastuzumab-based chemotherapy,(*8*) many patients with HER2-positive EGC develop resistance to HER2-directed therapies.(*3*) Heterogeneity of HER2 expression between the primary tumor and metastases and loss of HER2 expression during trastuzumab therapy contribute to therapeutic resistance in HER2-positive mEGC.(*9*) Whole-body imaging with ^{89}Zr-trastuzumab positron emission tomography (HER2 PET) has a potential advantage over single-site biopsy as it can noninvasively assess variations in HER2 expression and target engagement.

We previously published the pharmacokinetics, biodistribution, and dosimetry of ^{89}Zr-trastuzumab in HER2-positive mEGC.(*10*) HER2 PET images showed optimal tumor visualization 5-8 days after injection, and no clinically significant toxicities were observed. Here, we expand the cohort from 10 to 33 patients to further evaluate the baseline biodistribution of ^{89}Zr-trastuzumab and the association between imaging results and response to treatment. The distribution of ^{89}Zr-trastuzumab uptake, compared with standard imaging with ^{18}F-FDG PET (FDG PET) and computed tomography (CT), in HER2-positive mEGC and the ability of this metric to predict response to HER2-directed therapy have not been described. We sought to

investigate HER2 PET as a noninvasive tool to evaluate disease heterogeneity and predict response to treatment. We hypothesized that the intensity of ^{89}Zr-trastuzumab uptake, as measured by maximum standardized uptake value (SUV), and HER2 imaging positivity (≥50% of active lesions with ^{89}Zr-trastuzumab uptake) would be associated with response to HER2-directed therapy.

MATERIALS AND METHODS

Patients and Study Design

Eligible patients had HER2-positive (immunohistochemistry 3+, immunohistochemistry 2+ and fluorescence in situ hybridization [FISH] >2.0) mEGC, measurable or evaluable disease, Karnofsky performance ≥ 60% and adequate organ function. This was a single-site, prospective open-label pilot imaging protocol approved by the institutional review board and ethics committee at Memorial Sloan Kettering Cancer Center (ClinicalTrials.gov identifier NCT02023996). The study included two groups of patients who were imaged with HER2 PET, FDG PET, and CT. The purpose of imaging in the first group of patients (Group 1) was to find the optimal time for imaging following injection of the radiotracer and define its pharmacokinetics. Patients in Group 2 underwent imaging to increase the study sample size and accomplish the secondary objectives of the study including correlation with tumor molecular analysis and response to treatment, reported here. All patients gave informed consent for participation in the study. All visualized lesions (maximum 5/organ) were annotated in detail using individual-lesion measurements on CT and SUV on HER2 and FDG PET by Memorial Sloan Kettering radiologists. Clinical characteristics, including baseline demographic data and

previous treatments, were manually extracted from the medical record and managed using REDCap electronic data capture tools.(*11*,*12*) Visualized disease burden on each imaging modality and pathologic tumor characteristics were annotated for each patient.

^{89}Zr-Trastuzumab Drug Product

The details of the drug product, imaging protocol and biodistribution have been published previously.(*10*) The ^{89}Zr-trastuzumab was manufactured by the Memorial Sloan Kettering Radiochemistry and Molecular Imaging Probes Core Facility in compliance with a Food and Drug Administration investigational new drug application. Clinical-grade trastuzumab (Herceptin; Genentech) was conjugated with p-SCN-Bn-deferoxamine (Macrocyclics) chelator, followed by radiolabelling with ^{89}Zr, a positron emitter with a 78.4-h half-life. Patient unit doses of 185 MBq/3mg of ^{89}Zr-trastuzumab were mixed with nonradiolabeled trastuzumab to achieve a total mass of 50mg.

Imaging

Each patient underwent whole-body PET/CT from mid skull to proximal thigh in 3-dimensional mode with attenuation, scatter and other standard corrections applied and using iterative reconstruction. PET images were acquired 5 days after injection, based on the optimal imaging time of 5-8 days defined previously.(*10*) Patients receiving therapies directed at HER2 were offered repeat imaging 2 to 6 weeks post treatment, at the discretion of the treating physician and the study primary investigator, to evaluate changes in tumor uptake.

Patients underwent CT imaging of the chest, abdomen and pelvis at a median of 7 days from the date of HER2 PET (range 1-43 days). Localization in the tumor was defined as focal

accumulation greater than adjacent background in areas in which physiologic activity was not expected. SUVs normalized to lean body mass were determined. We subclassified each lesion as negative (SUV <3), low positive (SUV 3-5), moderate (SUV 5-10), intense (SUV 10-15), or very intense (SUV >15).

Definition of HER2 Imaging Positivity

Any lesion that was identified by one of the above imaging methods and was clinically determined to represent a tumor was categorized as an active lesion. A patient with a HER2-positive tumor was considered to be HER2 imaging positive if ≥50% of the active lesions were detectable by HER2 PET. The total number of active lesions identified on CT, FDG PET, and/or HER2 PET was used as the denominator for the tumor load. To determine HER2 imaging positivity, we divided the total number of lesions identified on HER2 PET by the tumor load.

Definition of HER2 Heterogeneity

Heterogeneity of HER2 status on biopsy was defined based on variation in HER2 overexpression in multiple disease sites biopsied (median 3 samples per patient, range 1-8). For example, a case with one lesion that was HER2 immunohistochemistry 3+ or 2+ and amplified by FISH and a second lesion that was either negative (immunohistochemistry 1+ or 0+) or equivocal by FISH would be classified as having heterogeneous disease. Genomic assessment of ERBB2 amplification was not used to establish heterogeneity, as not all patients underwent somatic mutation analysis. Heterogeneity of HER2 expression by HER2 PET was defined in the protocol, on the basis of previously published data,(*13*) by the percentage of tumor load that showed tracer uptake. Group stratification was as follows: Group A, the entire tumor load

showed tracer uptake (100%); Group B, the dominant part of the tumor load showed tracer uptake (≥50%); Group C, only a minor part of the tumor load showed tracer uptake (<50%); and Group D, the entire tumor load lacked tracer uptake (0%). Groups B and C were considered to have heterogeneous uptake (>0% and <100% of tumor load positive).

Statistical Analysis

The primary objectives of the protocol were to evaluate the feasibility of detecting tumors using HER2 PET in the first 10 patients with HER2-positive EGC and to evaluate the safety, biodistribution and pharmacokinetics of ^{89}Zr-trastuzumab, all of which were reported previously.(*10*) HER2 PET imaging was considered feasible based on antibody-imaging-positivity in 7 or more of the 10 patients in the first cohort. Secondary objectives, reported here, were to describe tumor molecular analysis with imaging results, and to evaluate imaging results in the context of response to treatment. HER2 imaging positivity was estimated based on the 33 patients with the one-sided 90% confidence limit. Patients with ≥50% of the total tumor load with ^{89}Zr-trastuzumab uptake were considered HER2 imaging positive, and patients with <50% were considered HER2 imaging negative.

Overall survival (OS) and progression-free survival (PFS) were calculated from the date of treatment until time of death (for OS) or until the date of progression or death, whichever came first (for PFS). Patients who did not experience the event of interest by the end of the study were censored at the time of last available follow up (for OS) or last available CT (for PFS). Since the study population was heterogeneous and included both patients receiving first-line treatment for metastatic disease and those receiving treatment for refractory disease, we restricted the OS and PFS analyses to the homogenous group of patients who were receiving

first-line therapy at the time of the HER2 PET (n=13). OS and PFS were estimated using Kaplan-Meier methods and compared between subgroups (A/B vs. C/D; SUV intensity) using the permutated log-rank test. All *P* values were based on 2-tailed statistical analysis, and $P < .05$ was considered to indicate statistical significance. All analyses were performed using R version (4.0.4)

RESULTS

Summary of Patients

Thirty-three patients with metastatic HER2-positive gastric (24%), gastroesophageal junction (GEJ) (64%), or esophageal (12%) adenocarcinoma were imaged with HER2 PET and CT, and 26 of these patients were also imaged with FDG PET (Table 1). HER2 status was assessed using biopsy or resection specimens of the primary tumor (21/33, 64%) or metastasis (12/33, 36%) and was confirmed by immunohistochemistry 3+ (26/33, 79%), immunohistochemistry 2+ and amplification by FISH (6/33, 18%), or ERBB2 amplification by next-generation sequencing with MSK-IMPACT (1/33, 3%). All patients had metastatic disease at the time of enrollment; the majority of patients had metastases to the lymph nodes (23/33, 70%) and/or liver (19/33, 58%), followed by lung (11/33, 33%), peritoneum (8/33, 24%), bone (3/33, 9%), and/or other tissues. Most patients underwent prior treatment with HER2-directed therapy (20/33, 61%, had received at least one line of HER2-directed therapy); the median time from diagnosis to HER2 PET was 13 months. The median number of lines of therapy received at the time of HER2 PET was 2 (range, 1-6), and the median number of total lines of therapy received throughout the course of illness was 3 (range, 1-9). Thirty patients (91%) were

receiving HER2-directed therapy and 13 (39%) were receiving first-line HER2-directed therapy at the time of HER2 PET (Supplemental Table 1). Among patients receiving HER2-directed therapy at the time of HER2 PET, the median time on treatment was 4 (range, 0-47) months for all patients and 14 (range, 4-47) months for those receiving first-line therapy (Supplemental Table 2).

The total number of lesions identified on each imaging modality is summarized in Table 1. The median (range) number of lesions identified by each modality is as follows: baseline CT, 5 (1-15); HER2 PET, 4 (0-11); and FDG PET, 7 (1-14) (Supplemental Table 3).

^{89}Zr-Trastuzumab PET Captures Nonstandard Disease Sites

The potential clinical applications of HER2 PET imaging include identification of disease sites not captured by standard imaging, establishment of sites of HER2 heterogeneity not captured by biopsy, and early assessment of response to HER2-directed therapy. We included specific case examples to illustrate these points. The first is a case of metastatic HER2+ GEJ poorly differentiated carcinoma in which HER2 PET identified a right cerebellar metastasis (SUV 2.6) that had not been detected on FDG PET (Figure 1A). The finding was confirmed on brain MRI, and the patient underwent stereotactic radiosurgery to treat this lesion.

Among all patients, more total lesions were visualized on FDG PET (n=178) than on HER2 PET (n=135) (Figure 1B). Of the total lesions positive on HER2 PET, the majority were in lymph nodes (41/135 [30%]) or the liver (32/135 [24%]). For FDG PET, the majority were also in lymph nodes (70/178 [39%]) or the liver (48/178 [27%]). However, primary tumor and bone lesions were detected at a higher frequency on HER2 PET (primary tumor: 21/135 [16%]; bone: 10/135 [7%]) than on FDG PET (primary tumor: 18/178 [10%]; bone: 11/178 [6%]).

Five patients had at least one lesion positive on HER2 PET and negative on FDG PET (range, 0-4); 18 patients had at least one lesion positive on FDG PET and negative on HER2 PET (range, 0-8). Of the 8 lesions that were positive on HER2 PET and negative on FDG PET, 3 were in the bone (38%) and 3 were in lymph nodes (38%) (Figure 1B). In contrast, most lesions that were positive on FDG PET and negative on HER2 PET were in the lymph nodes (35/68 [51%]) and the liver (16/68 [24%]); only 4 of 68 (6%) were in the bone.

HER2 PET Illustrates HER2 Heterogeneity

The next case example illustrates heterogeneous liver uptake of the radiotracer on HER2 PET, suggesting that HER2 overexpression is heterogeneous (Figure 2A). However, liver biopsy for this patient, obtained from a single site of ^{89}Zr-trastuzumab avidity, showed HER2 immunohistochemistry 3+ and, as expected, did not capture the intra-patient heterogeneity seen on imaging.

As defined in our prespecified analysis, patients with ≥50% of the total tumor load with ^{89}Zr-trastuzumab uptake were considered HER2 imaging positive, and patients with <50% were considered HER2 imaging negative. As described in Methods, we stratified patients into four groups by percentage of tumor load that showed tracer uptake.(*13*) Of the 33 patients, 23 (70%) were HER2 imaging positive (Group A or B) (one-sided 90% confidence limit, 57% for feasibility) (Figure 2B). Only 10 patients had 100% of the tumor load positive; 2 had 0% positive. Of the 30 patients who were receiving HER2-directed therapy at the time of the scan, 20 (66%) had ≥50% active lesions (Group A or B). Of the 13 patients who were receiving first-line HER2-directed therapy at the time of the scan, 8 (62% of the group, 24% of the total cohort) had ≥50% active lesions (Group A or B). Although all the patients without any tracer uptake (6%

of the cohort) were receiving second-line or later treatment, the majority of patients receiving advanced lines of therapy were HER2 imaging positive, supporting the notion that HER2 remains a relevant biomarker beyond the first-line setting.

We next describe the proportion of patients in Group A or B and Group C or D with at least one intense or very intense lesion on HER2 PET. Among those with ≥50% of tumor load positive (Group A or B), 57% of patients had at least one intense or very intense lesion, while only 20% in those with <50% of tumor load positive (Group C or D) had at least one intense or very intense lesion. Biopsy proven HER2 heterogeneity was present in 30% of patients in Group A or B and in 20% of patients in Group C or D. A slightly higher proportion of patients in Group A or B (61%) had received trastuzumab therapy at the time of the scan, relative to those in Group C or D (50%).

In addition to looking at individual-lesion positivity by HER2 PET, we subclassified each lesion as negative (SUV <3), low positive (SUV 3-5), moderate (SUV 5-10), intense (SUV 10-15), or very intense (SUV >15). In the case example shown in Figure 2A for whom all biopsies were HER2 immunohistochemistry 3+, the tumor load positivity for ^{89}Zr-trastuzumab uptake was <50% (Group C). Although the patient had at least one intense or very intense lesion, the patient's progression-free survival (PFS) on second-line HER2-directed therapy (3 months) was less than the median among all patients with at least one intense or very intense lesion (5 months).

Survival of Patients Receiving First-Line Treatment at the Time of the Scan

Survival was evaluated only among patients receiving first-line HER2-directed therapy at the time of the HER2 PET (n=13). The baseline characteristics of this group are summarized in

Supplemental Table 4. Among surviving patients (n=2), the median (range) follow-up time was 50.0 (45.8-54.3) months. At the time of the data lock in July 2021, 11 total deaths and 12 progression events had been observed. When only patients receiving HER2-directed therapy in the first-line setting were considered, the median PFS was 15 [95% confidence interval (CI): 8.6-not reached] months.

The median PFS among patients in group A or B (n=8) was 14 [95% CI: 11.0-not reached] months, compared with 15 [95% CI: 8.6-not reached] months among patients in group C or D (n=5) (Figure 2C). Among patients receiving HER2-directed therapy in the second-line setting, the majority of patients in both groups (A/B n=7, C/D n=2) progressed or died before 3 months. Given the small number of patients in this subgroup, PFS should be interpreted with caution.

HER2 PET and Response to HER2-Directed Therapy

We next stratified patients by the presence or absence of at least one intense or very intense lesion on baseline HER2 PET and compared PFS among patients receiving first-line HER2-directed therapy at the time of the scan (n=13). The median PFS was 16 [95% CI: 11-not reached] months and 12 [95% CI: 6.3-not reached] months, respectively (Figure 2D). Given the small number of patients in this subgroup, PFS should be interpreted with caution.

The final two case examples (Figure 3) illustrate the potential role of HER2 PET in predicting response to HER2-directed therapy. In Figure 3A, a patient with HER2+ mEGC had ≥50% tumor load uptake of ^{89}Zr-trastuzumab on baseline imaging (group B) and at least one intense or very intense lesion. Both HER2 and FDG PET showed primary tumor avidity; less than 3 weeks after initiation of trastuzumab-based treatment, the primary tumor remained FDG

PET avid but was no longer avid on HER2 PET, indicating HER2 receptor saturation by trastuzumab. This patient had a PFS of 13 months on first-line HER2-directed therapy, and the disease remained HER2+ on post progression biopsy, with subsequent response to second-line HER2-directed therapy. In contrast, the patient in Figure 3B, who had ≥50% tumor load uptake of ^{89}Zr-trastuzumab on baseline imaging (Group B) but no intense or very intense lesions, had no change in primary tumor ^{89}Zr-trastuzumab uptake after initiation of first-line HER2-directed treatment and had a relatively short PFS of 6 months on treatment.

Patients Not Receiving HER2-Directed Therapy

Of the 3 patients who were not receiving HER2-directed therapy at the time of the scan, 1 underwent repeat liver biopsy that demonstrated equivocal HER2 status by both immunohistochemistry and FISH (the initial specimen, obtained at an outside institution, was HER2 immunohistochemistry 3+). The second patient recently had disease progression on HER2-directed therapy, and biopsy of a splenic lesion demonstrated HER2 immunohistochemistry 1-2+ and nonamplification on FISH. The third patient underwent repeat biopsy of the primary GEJ mass, which showed HER2 immunohistochemistry 1+ (negative); therefore, this patient did not receive additional HER2-directed therapy.

DISCUSSION

Our data suggest that antibody imaging with HER2 PET is feasible and allows noninvasive assessment of global variations in HER2 expression and target enhancement. HER2 PET identified bone lesions more so than soft tissue lesions. Compared with HER2 PET, FDG

PET identified more lymph node lesions and it is unclear whether these findings represent true disease or inflammation.

HER2 PET may help visualize heterogeneity of HER2 expression and allow assessment of lesions throughout the entire body. The percentage of tumor load positive for ^{89}Zr-trastuzumab varied among patients: approximately two-thirds of the patients in our study had ≥50% tumor load positivity and one-third had <50% positivity. The percentage of tumor load with tracer uptake was not significantly associated with PFS in the small subgroup analysis of patients receiving first-line HER2-directed therapy. The case example shown in Figure 1 highlights the potential for HER2 PET to identify lesions in the brain before symptomatic presentation, without a biopsy. This has not been previously demonstrated in the literature. In addition, the case example shown in Figure 2 illustrates the potential for biomarker-directed imaging to identify sites of disease heterogeneity that are not captured by standard imaging and biopsy. There was a trend toward improved PFS among patients with at least one lesion on HER2 PET with SUV greater than or equal to 10 who were receiving first-line HER2-directed therapy, though this difference was not significant. A larger study would be needed to associate HER2 PET findings with PFS.

Although the clinical application of evaluating disease heterogeneity by HER2 PET has not been clearly established for EGC, HER2 PET has been used to help guide clinical decision-making for other HER2+ tumor types. In a study of 20 patients with breast cancer, including 7 patients with metastases that were inaccessible for biopsy, HER2 PET was used to support clinical decision-making and changed management in 8 of 20 patients (40%).(*14*) Similarly, in a cohort of 12 patients with HER2-mutant lung cancer, pretreatment HER2 PET identified ^{89}Zr-trastuzumab-avid lesions in 4 patients, all of whom responded to HER2-directed therapy with

ado-trastuzumab emtansine (T-DM1); in contrast, among the 8 patients without uptake of ^{89}Zr-trastuzumab, only 3 (37%) responded to T-DM1 treatment.(*15*)

Our study demonstrates that intensity of ^{89}Zr-trastuzumab uptake varies between and within patients and can be used to stratify patients, although the clinical application of this has not yet been determined. At least one lesion with an SUV ≥10 on HER2 PET may be associated with response to HER2-directed therapy, though this remains to be validated in future studies. While the percentage of tumor load positive was used to establish feasibility in this study, it remains unclear whether this is a marker of likelihood to respond to HER2-directed therapy.

HER2 PET is limited by the high background tracer uptake in several key organs, including the liver, making it challenging to identify discrete tumors using this technique. The current study is limited by its descriptive design. In addition, the study is limited by patient exposure to trastuzumab prior to HER2 PET due to partial target saturation. Further investigation specifically including previously untreated patients is required to determine whether HER2 PET can be used as a clinical predictive tool in patients with HER2+ mEGC.

CONCLUSIONS

HER2 PET may identify heterogeneity of HER2 expression and allows assessment of lesions throughout the entire body. HER2 PET has a potential advantage over single-site biopsy in assessment of HER2 heterogeneity. Bone lesions were better identified than soft-tissue lesions on HER2 PET. Until further studies validate the preliminary clinical findings presented, we anticipate that HER2 PET will remain a valuable research tool.

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Disclaimer: None

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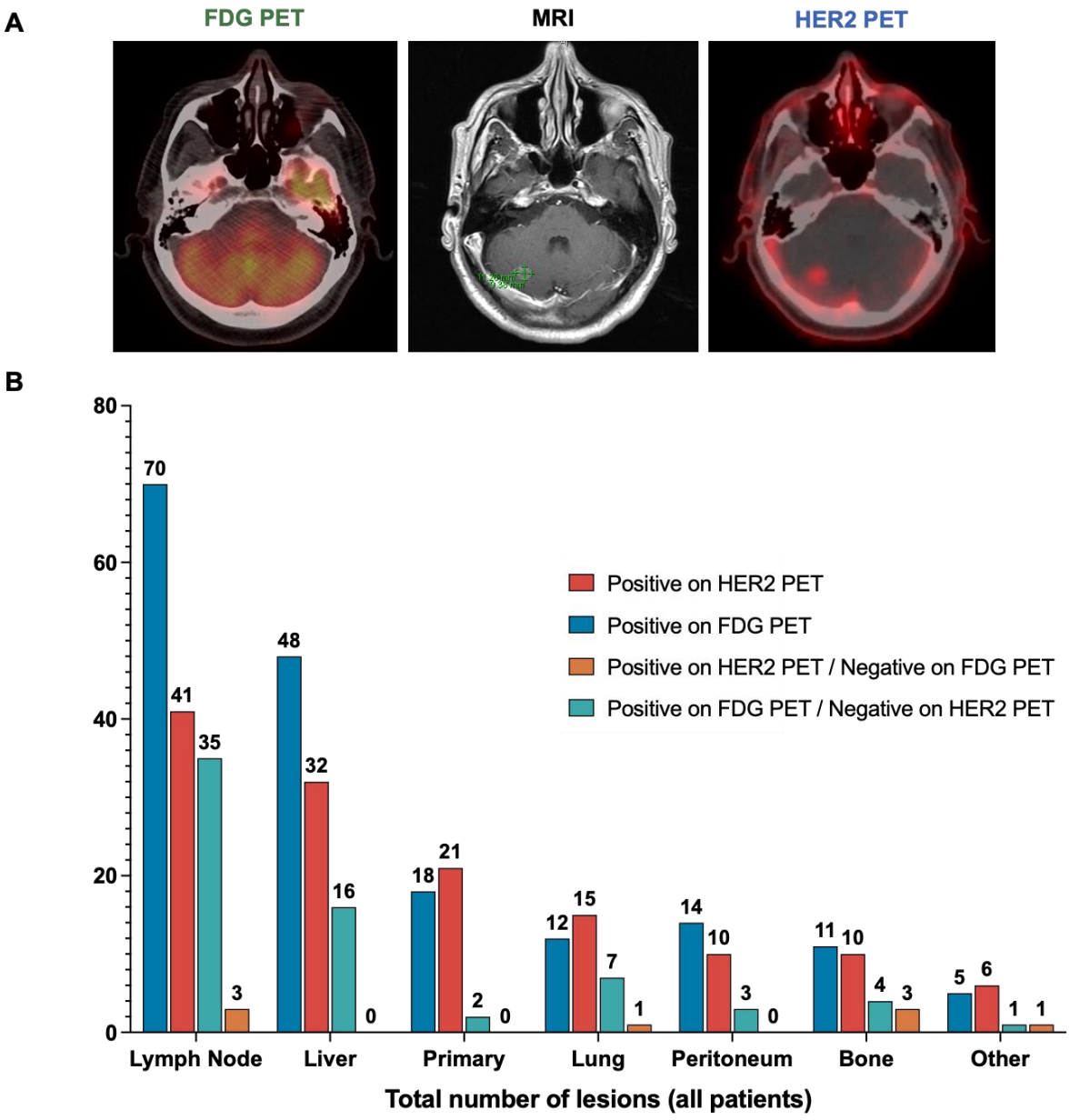


Figure 1. Disease sites captured by HER2 and FDG positron emission tomography. (A) FDG PET, magnetic resonance imaging (MRI), and HER2 PET images from a patient with cerebellar metastasis. The images shown are from a patient with de novo metastatic HER2+ gastroesophageal junction poorly differentiated carcinoma with mixed adeno and squamous differentiation. HER2 PET (right) demonstrated a right cerebellar metastasis (standardized

uptake value 2.6) without corresponding uptake on FDG PET (left) and confirmed on brain MRI (right). (B) The number of lesions identified by HER2 PET and FDG PET among all patients. The total number of lesions avid on HER2 PET (red) and FDG PET (blue) is shown. The total numbers of lesions better identified only on HER2 (orange) or FDG PET (green) are also shown.

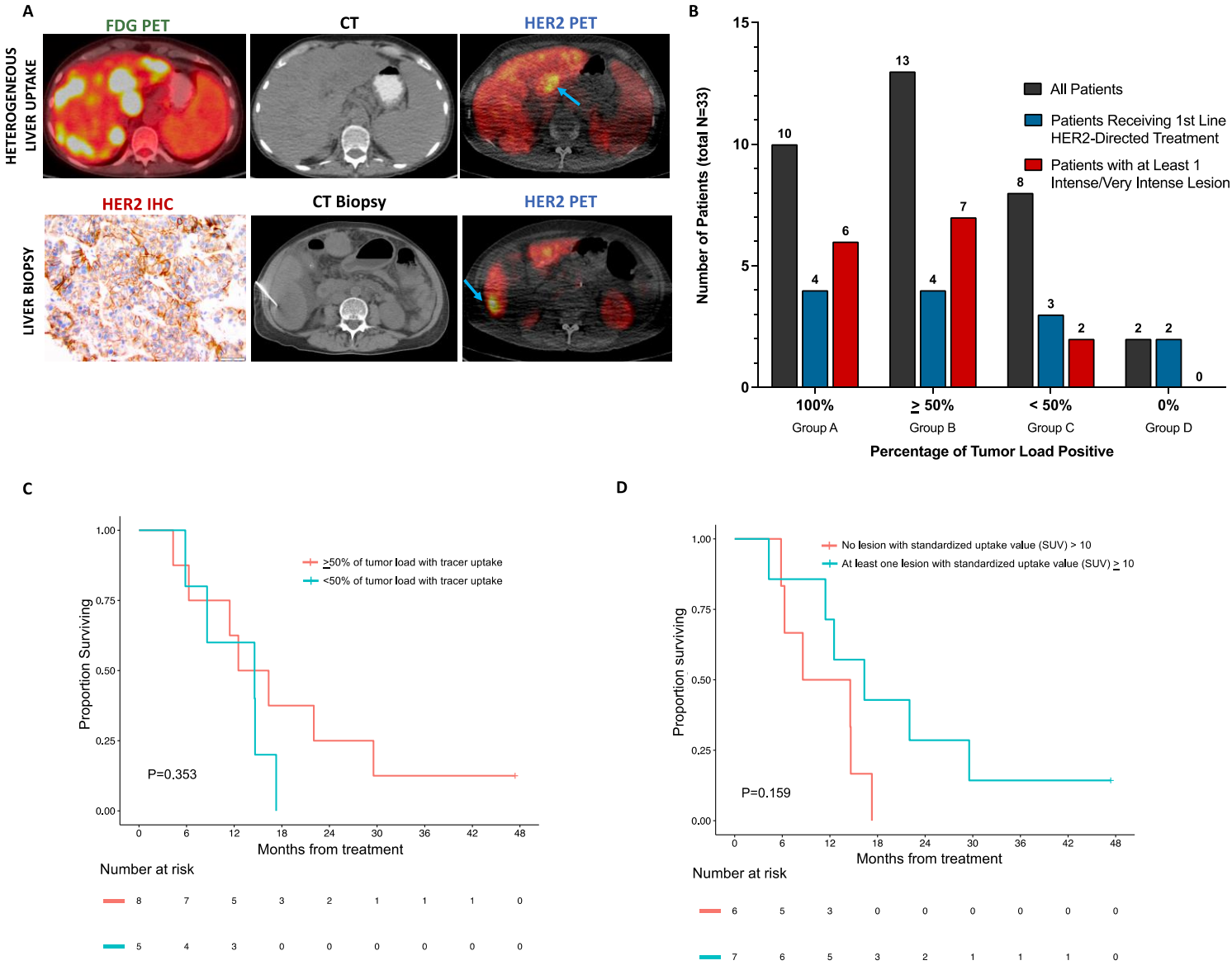
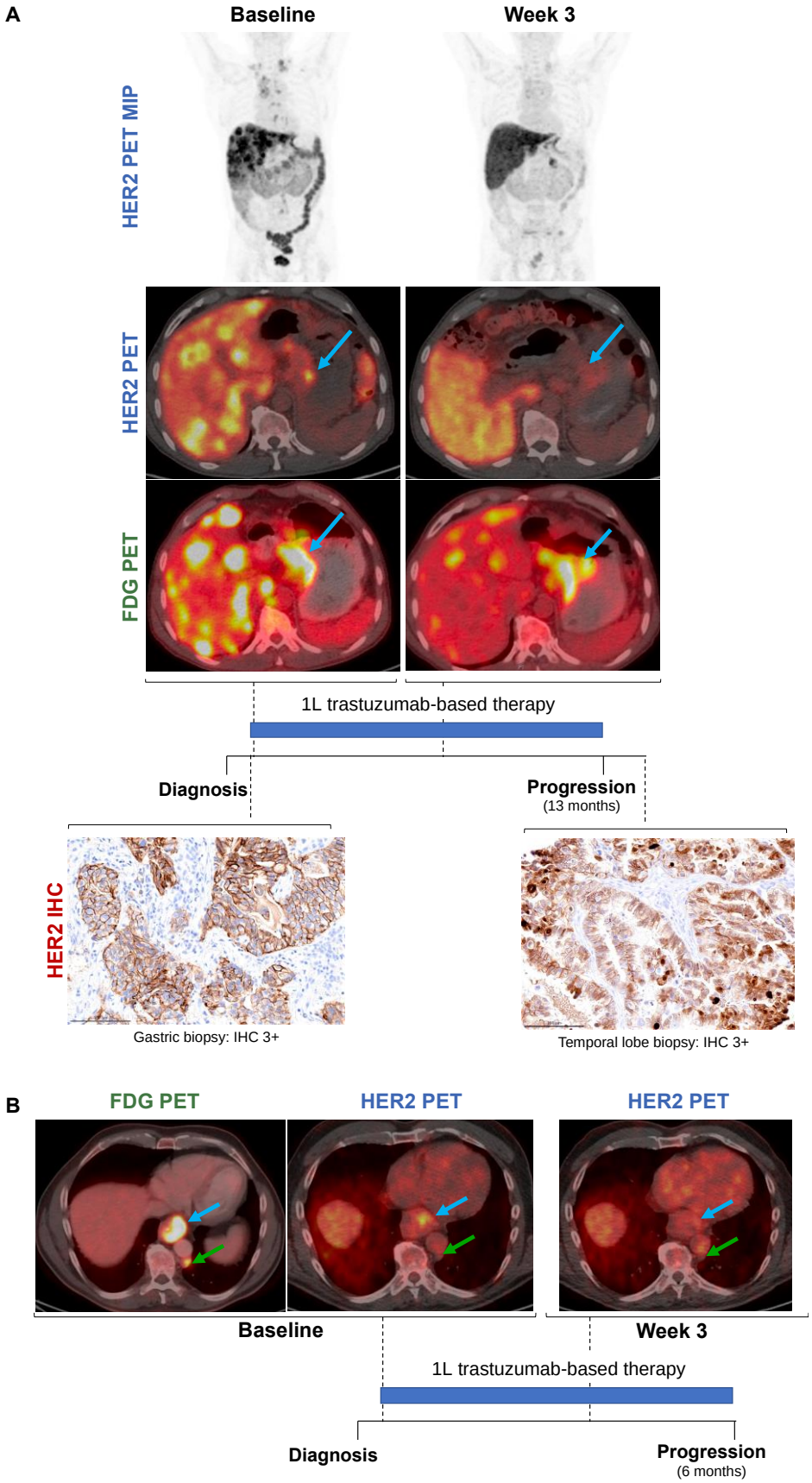


Figure 2. HER2 disease heterogeneity illustrated by ^{89}Zr-trastuzumab positron emission tomography (HER2 PET). (A) ^{18}F-FDG PET (FDG PET) and HER2 PET images from a patient with metastatic HER2+ gastric adenocarcinoma with heterogeneous HER2 expression in the liver. Heterogeneous ^{89}Zr-trastuzumab uptake on imaging is shown (blue arrows demonstrate positive lesions, upper figure). Liver biopsy at a site of ^{89}Zr-trastuzumab uptake demonstrates HER2 positivity with immunohistochemistry 3+ in 60% of cells (lower). (B) The percentage of

tumor load with ^{89}Zr-trastuzumab uptake. Patients were stratified into four groups by percentage of tumor load showing tracer uptake, as described in Methods. The total patients in groups A-D are shown in gray. The number of patients receiving first-line HER2-directed therapy in each group is represented in blue, and the number receiving second or later lines of therapy in each group is represented in light gray. Patients with at least one intense or very intense lesion on HER2 PET (standardized uptake value [SUV] ≥10) are represented in red. Of the 15 patients with at least one intense or very intense lesion (15/33 [45%]), 6 were in group A (6/33 [18%]) and 7 were in group B (7/33 [21%]). (C) Progression-free survival (PFS) stratified by percentage of tumor load positive in patients receiving first-line HER2-directed therapy (P=.353, using the permutated log-rank test comparing the two groups). (D) PFS stratified by presence of at least one lesion with intense or very intense ^{89}Zr-trastuzumab uptake (SUV ≥ 10) in patients receiving first-line HER2-directed therapy (P=.159, using the permutated log-rank test comparing the two groups).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Diagnosis
Progression
(13 months)
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Temporal lobe biopsy: IHC 3+
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FDG PET
HER2 PET
HER2 PET
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Diagnosis
Progression
(6 months)

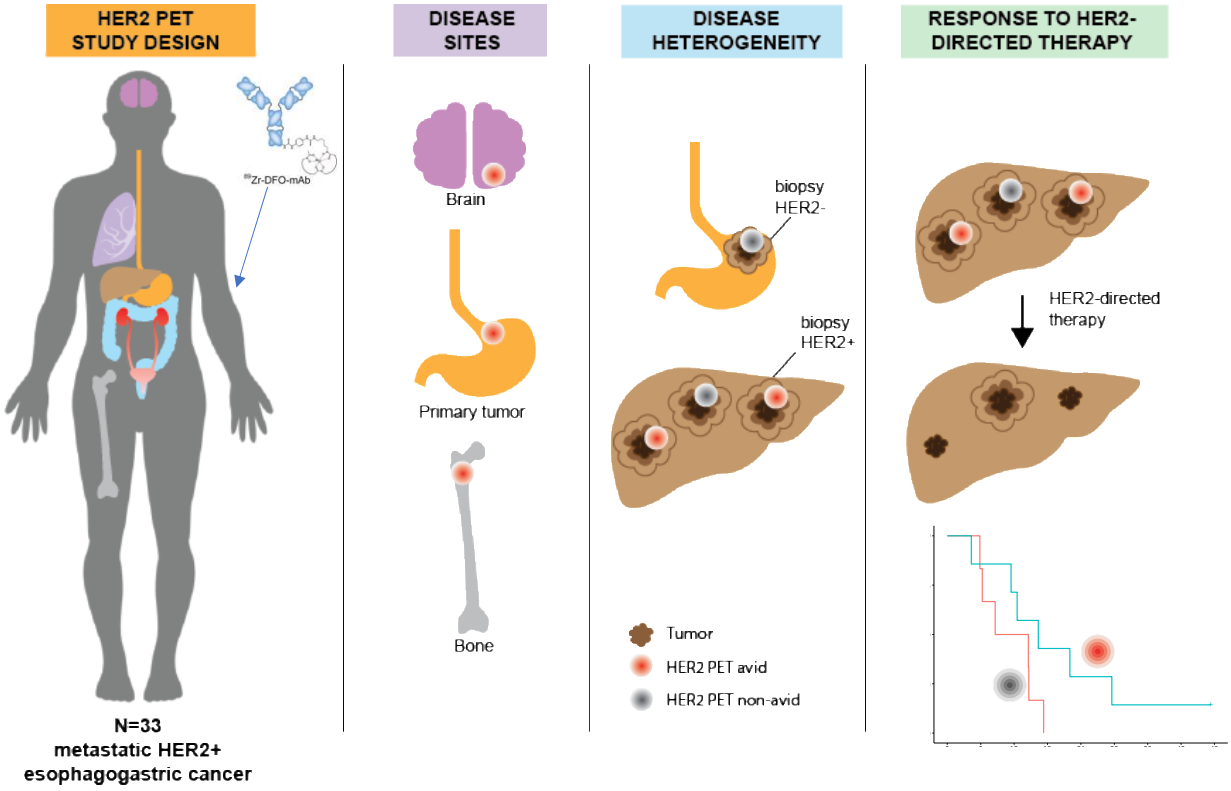
Figure 3. ^{89}Zr-trastuzumab positron emission tomography (HER2 PET) and early assessment of response to HER2-directed therapy. (A) ^{18}F-FDG PET (FDG PET), HER2 PET, and HER2 immunohistochemistry (IHC) in a patient with metastatic HER2+ esophagogastric cancer with a long response to first-line HER2-directed therapy. The patient had >50% of the tumor load with ^{89}Zr-trastuzumab uptake on baseline imaging (group B) and at least one lesion with SUV $\geq$ 10. While the primary tumor was avid on baseline HER2 and FDG PET, less than 3 weeks after initiation of trastuzumab-based treatment, the primary tumor remained FDG PET avid but was no longer avid on HER2 PET, likely indicating HER2 receptor saturation by trastuzumab. This patient had a progression-free survival of 13 months on first-line HER2-directed therapy. (B) FDG PET and HER2 PET in a patient metastatic HER2+ esophageal adenocarcinoma with a short response to first-line HER2-directed therapy. The patient had >50% of the tumor load with ^{89}Zr-trastuzumab uptake on baseline imaging (group B) but no lesions with SUV $\geq$ 10; the patient had no change in primary tumor ^{89}Zr-trastuzumab uptake (SUV 8.1 from 6.6, blue arrows) or in posterior left para-aortic node ^{89}Zr-trastuzumab uptake (green arrows) after initiation of first-line HER2-directed treatment. The patient had a relatively short progression-free survival of 6 months on treatment. 1L, first-line.

Table 1. Patient and treatment characteristics

Characteristic	Prior Trastuzumab (N=19)	No Prior Trastuzumab (N=14)	Total (N=33)
Age at diagnosis, years, median (range)	59 (40-76)	59 (34-79)	59 (34-79)
Patients with metastasis at diagnosis, N (%)	17 (89)	10 (71)	27 (82)
Primary tumor site, N (%)			
Esophageal	2 (11)	2 (14)	4 (12)
GEJ (Siewert I-II)	14 (74)	7 (50)	21 (64)
Gastric	3 (16)	5 (36)	8 (24)
Method used to confirm sample is HER2+, N (%)			
FISH	3 (16)	3 (21)	6 (18)
IHC	15 (79)	11 (79)	26 (79)
NGS	1 (5)	0 (0)	1 (3)
Patients with HER2 heterogeneous among samples, N (%)	3 (16)	6 (43)	9 (27)
Patients receiving HER2-directed therapy at the time of scan, N (%)	16 (84)	14 (100)	30 (91)
Lines of treatment at the time of HER2 PET, median (range)	3 (2-6)	1 (1-2)	2 (1-6)
Total lines of treatment received, median (range)	3 (2-7)	3 (1-9)	3 (1-9)
Time on treatment at the time of HER2 PET (days), median (range)	93 (0-212)	394 (7-1410)	126 (0-1410)
Total lesions detected on imaging (all patients)			
CT, median (range)	5 (1-11)	5.5 (1-15)	5 (1-15)
HER2, median (range)	4 (1-7)	3.5 (0-11)	4 (0-11)
FDG PET, median (range)	6.5 (1-13)	7 (1-14)	7 (1-14)
Patients with ≥1 lesion intense or very intense on HER2 PET, N (%)	8 (42)	7 (50)	15 (45)
Maximum SUV per patient on HER2 PET, median (range)	7.8 (3.20-23.8)	9.8 (0-22.2)	9.2 (0-23.8)
Mean SUV per lesion on HER2 PET, median (range)	6.5 (2.8-14.2)	7.8 (0-15.9)	7.0 (0-15.9)

Data are no. (%) or median (min-max). CT, computed tomography; FISH, fluorescence in situ hybridization; GEJ, gastroesophageal junction; IHC, immunohistochemistry; NGS, next-generation sequencing; PET, positron emission tomography; SUV, standardized uptake value.

Graphical Abstract



KEY POINTS

QUESTION: Is HER2 PET an effective tool for noninvasive assessment of variations in HER2 expression and target engagement in patients with HER2+ metastatic esophagogastric cancer?

PERTINENT FINDINGS: In a pilot study of HER2 PET in 33 patients with HER2+ metastatic esophagogastric cancer, 70% of patients were HER2 imaging positive ($\geq$ 50% of tumor load positive) and most patients had variable HER2 uptake across disease sites. Among patients receiving HER2-directed therapy as first-line treatment, median progression-free survival was longer for those with at least one intense or very intense lesion on HER2 PET.

IMPLICATIONS FOR PATIENT CARE: A potential application of HER2 PET is noninvasive evaluation of intra-patient heterogeneity of HER2 status not captured by single site biopsies in patients with HER2+ metastatic esophagogastric cancer.

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SUPPLEMENTARY MATERIALS

Supplemental Table 1. Summary of treatment at the time of HER2 PET.

Regimen	**Total (N)**
First-Line	**13**
Platinum doublet + Trastuzumab + Pembrolizumab	8
Platinum doublet + Trastuzumab	5
Second-Line	**10**
Taxane + Trastuzumab	1
Afatinib + Trastuzumab	6
Afatinib + Taxane	1
Afatinib	1
No Treatment	1
Third-Line	**6**
Afatinib + Trastuzumab	2
Afatinib	2
Platinum doublet + Trastuzumab	1
Platinum doublet	1
≥Fourth Line	**4**
Afatinib + Trastuzumab	3
Ipilimumab + Nivolumab	1
Total	**33**

Supplemental Table 2. Patient-level treatment data.

Pt	Tx Line	Tx to HER2 PET (d)**	Time on Tx (m)	Time to Progr (m)	BOR	Regimen
1	3*	0	3.7	3.7	PD	Afatinib
2	3*	-29	4.2	3.1	PD	Carboplatin + Irinotecan + Trastuzumab
3	1	9	16.6	17.5	unk	CAPOX + Trastuzumab
4	4*	0	4.9	4.8	SD	Afatinib + Trastuzumab
5	3*	44	2.8	3.3	SD	Afatinib
6	2*	-78	3.1	3.1	PR	Afatinib
7	3*	9	2.1	2.1	PD	Afatinib + Trastuzumab
8	1	-28	12.2	14.8	PR	FOLFOX + Trastuzumab
9	1	9	30.0	30.0	PR	DCF + Trastuzumab
10	3*	8	3.4	3.4	SD	Afatinib + Trastuzumab
11	5*	19	3.1	3.8	SD	Ipilimumab + Nivolumab
12	1	2	4.0	4.4	PR	DCF + Trastuzumab
13	2	0	0.2	0.7	PD	Docetaxel + Trastuzumab
14	5*	0	4.9	4.9	PR	Afatinib + Trastuzumab
15	2*	-1	7.1	7.1	SD	Afatinib + Trastuzumab
16	1	0	16.3	16.6	SD	DCF + Trastuzumab
17	2*	-12	1.6	1.5	PD	Afatinib + Trastuzumab
18	3*	0	3.7	4.0	PR	Carboplatin + Irinotecan
19	2*	-14	4.4	4.4	SD	Afatinib + Trastuzumab
20	6*	3	1.4	1.8	PD	Afatinib + Trastuzumab
21	2*	1	1.8	2.0	PD	Afatinib + Trastuzumab
22	2*	2	3.0	3.2	SD	Afatinib + Trastuzumab
23	2*	-5	2.1	2.1	PD	Afatinib + Trastuzumab
24	1	21	44.2	22.3	CR	Cisplatin + Capecitabine + Trastuzumab + Pembrolizumab
25	1	0	14.1	12.7	PR	CAPOX + Trastuzumab + Pembrolizumab
26	1	0	14.2	14.8	PR	CAPOX + Trastuzumab + Pembrolizumab
27	1	0	7.9	8.7	PR	CAPOX + Trastuzumab + Pembrolizumab
28	1	0	4.9	5.9	PR	CAPOX + Trastuzumab + Pembrolizumab
29	1	0	11.4	11.6	PR	CAPOX + Trastuzumab + Pembrolizumab
30	1	0	47.1	47.9	CR	CAPOX + Trastuzumab + Pembrolizumab
31	2*	15	0.0	0.0	NA	No treatment
32	2*	0	1.4	1.8	PD	Afatinib + Paclitaxel
33	1	0	5.7	6.4	PR	FOLFOX + Trastuzumab + Pembrolizumab

*Denotes patients who received prior trastuzumab

**Negative number indicates treatment started prior to the HER2 PET date. Positive number indicates treatment started after the HER2 PET date.

BOR, best overall response; CAPOX, Capecitabine + Oxaliplatin; CR, complete response; d, days; DCF, Docetaxel + 5-FU + Cisplatin; FOLFOX, 5-FU + Leucovorin + Oxaliplatin; m, months; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; Tx, treatment; unk, unknown.

Supplemental Table 3

Patient Number	Lesion Name	Lesion State CT	Short axis - Value	Short axis - Unit	Long axis - Value	Long axis - Unit	HER2 PET SUV	HER2 PET POS/NEG	FDG SUV	FDG PET POS/NEG
1	Lung upper lobe right	Present	5.2	mm	5.3	mm	1.1	neg	0.6	neg
1	Liver Segment II	Present	46	mm	64.4	mm	16.4	pos	5.8	pos
1	Liver Segment III	Present	37.7	mm	43.8	mm	8.1	pos	3.2	pos
1	liver seg 7	Absent					8.6	pos	3	pos
1	stomach	Absent					23.6	pos	7.56	pos
1										
1										
2	Peritoneum	Present	9	mm	9.9	mm		neg	2	pos
2	Peritoneum	Present	8.5	mm	9.9	mm	7.5	pos	6.9	pos
2	Liver Segment V	Present	7.5	mm	9.6	mm	6.6	pos	4.4	pos
2	Liver Segment VII	Present	26.7	mm	31.4	mm		neg		neg
2	Liver Segment V	Present	27.4	mm	28.1	mm		neg	2.6	pos
2	Adrenal gland left	Present	16.2	mm	22.4	mm	9.4	pos	5.7	pos
2	Peritoneum	Present	12.9	mm	16.3	mm		neg	4.3	pos
2	Peritoneum	Present	25.6	mm	30.8	mm	7.5	pos	6.9	pos
2	Lymph node R internal mammary	Absent					7.1	pos	2.8	pos
3	Lung lower lobe right	Present	6.3	mm	7.8	mm		Neg		
3	Lymph node para-aortic left	Present	11.5	mm	15.9	mm		Neg		
3	Lymph node para-aortic left	Present	17	mm	23.8	mm		Neg		
3	Lung upper lobe left	Present	11.8	mm	11.9	mm		Neg		
3										
3										
3										
4	Liver Segment V	Present	10.7	mm	14.3	mm	6.55	neg	3.3	pos
4	GEJ/gastric tumor	Absent					3.2	pos	2.1	pos
4										
4										
4										
4										
4										
5	Lung lower lobe left	Present	13.8	mm	15.9	mm	1.73	neg	2.67	pos
5	Lung lower lobe right	Present	9.8	mm	12.8	mm	1.2	neg	1.7	pos
5	Lung lower lobe right	Present	9.5	mm	13.9	mm	1.8	neg	5.9	pos
5	Lymph node pulmonary hilar right (10R)	Present	9.1	mm	12.1	mm	3	pos	1.32	pos
5	Lymph node paratracheal right	Present	10.4	mm	12.8	mm	1.8	neg	1.2	pos
5	Lung lower lobe left	Present	12.2	mm	15.3	mm	1.9	neg	2.3	pos
5	Lung upper lobe left	Present	11.1	mm	12.4	mm	2.17	pos	5.5	pos
5	Lung upper lobe right	Absent					3.2	pos	4.9	pos
6	Liver Segment III	Present	15.3	mm	15.6	mm	7.8	pos	8.8	pos
6	Lymph node	Present	7.6	mm	11.2	mm	2	neg	1.8	pos
6	Lymph node gastric left	Present	9.4	mm	11.8	mm	4	neg	5.6	pos
6	Lymph node gastric left	Present	10.7	mm	15.6	mm	3	neg	3.6	pos
6	Liver Segment VII	Present	13.9	mm	25.7	mm	6	neg	13.5	pos
6	Bone	Present	8.3	mm	10.1	mm	1.5	neg	2	pos
6	Bone vertebrae lumbar	Present	8	mm	8.9	mm	2.6	neg	2.3	neg
6	Lymph node splenic hilar	Present	9.8	mm	20.6	mm	2.8	neg	3.6	pos

Summary	Total	Total	Lung	LN	Bone	Liver	Primary	Peritoneum	Soft Tissue	Other
Zr pos lesions		**4**	4	0	0	0	3	1	0	0
FDG PET pos lesions		**4**	4	0	0	0	3	1	0	0
Pos Zr neg FDG		**0**	0	0	0	0	0	0	0	0
Pos FDG neg Zr		**0**	0	0	0	0	0	0	0	0
Zr neg lesions		**1**	1	1	0	0	0	0	0	0
FDG PET neg lesions		**1**	1	1	0	0	0	0	0	0
Total CT lesions		**3**	3	1	0	0	2	0	0	0
Zr pos lesions		**5**	5	0	1	0	1	0	2	0	1
FDG PET pos lesions		**8**	8	0	1	0	2	0	4	0	1
Pos Zr neg FDG		**0**	0	0	0	0	0	0	0	0
Pos FDG neg Zr		**3**	3	0	0	0	1	0	2	0	0
Zr neg lesions		**4**	4	0	0	0	2	0	2	0	0
FDG PET neg lesions		**1**	1	0	0	0	1	0	0	0	0
Total CT lesions		**8**	8	0	0	0	3	0	4	0	1
Zr pos lesions		**0**	0	0	0	0	0	0	0	0	0
FDG PET pos lesions	**NA**	NA									
Pos Zr neg FDG	**NA**	NA									
Pos FDG neg Zr	**NA**	NA									
Zr neg lesions		**4**	4	2	2	0	0	0	0	0	0
FDG PET neg lesions	**NA**	NA									
Total CT lesions		**4**	4	2	2	0	0	0	0	0	0
Zr pos lesions		**1**	1	0	0	0	0	1	0	0	0
FDG PET pos lesions		**2**	2	0	0	0	1	1	0	0	0
Pos Zr neg FDG		**0**	0	0	0	0	0	0	0	0	0
Pos FDG neg Zr		**1**	1	0	0	0	1	0	0	0	0
Zr neg lesions		**1**	1	0	0	0	1	0	0	0	0
FDG PET neg lesions		**0**	0	0	0	0	0	0	0	0	0
Total CT lesions		**1**	1	0	0	0	1	0	0	0	0
Zr pos lesions		**3**	3	2	1	0	0	0	0	0	0
FDG PET pos lesions		**8**	8	6	2	0	0	0	0	0	0
Pos Zr neg FDG		**0**	0	0	0	0	0	0	0	0	0
Pos FDG neg Zr		**5**	5	4	1	0	0	0	0	0	0
Zr neg lesions		**5**	5	4	1	0	0	0	0	0	0
FDG PET neg lesions		**0**	0	0	0	0	0	0	0	0	0
Total CT lesions		**7**	7	5	2	0	0	0	0	0	0
Zr pos lesions		**6**	6	0	0	1	3	1	1	0	0
FDG PET pos lesions		**13**	13	0	4	2	5	1	1	0	0
Pos Zr neg FDG		**0**	0	0	0	0	0	0	0	0	0
Pos FDG neg Zr		**7**	7	0	4	1	2	0	0	0	0
Zr neg lesions		**8**	8	0	4	2	2	0	0	0	0
FDG PET neg lesions		**1**	1	0	0	1	0	0	0	0	0
Total CT lesions		**13**	13	0	4	3	5	0	1	0	0

6	Liver Segment VIII	Present	11.2	mm	17.7	mm		7.1	neg		7.8	pos											
6	Liver Segment VIII	Present	13.6	mm	16.2	mm		9.1	pos		11.58	pos											
6	Peritoneum	Present	16.8	mm	30.8	mm		6.4	pos		10.7	pos											
6	Liver segment 6	Absent	13	mm	15	mm		10.7	pos		26.35	pos											
6	T7	Absent	11	mm	15	mm		5	pos		14.9	pos											
6	gastric tumor	Absent						3.9	pos		11	pos											
7	Liver Segment VI	Present	5.9	mm	6	mm		Neg			NA		**Zr pos lesions**		**1**	1	0	0	0	0	1	0	0	0
7	Liver Segment VIII	Present	10.4	mm	10.6	mm		Neg			NA		**FDG PET pos lesions**	**NA**	NA									
7	Liver Segment VII	Present	18.4	mm	21.7	mm		Neg			NA		**Pos Zr neg FDG**	**NA**	NA									
7	GE junction tumor	Absent						7.3	pos		NA		**Pos FDG neg Zr**	**NA**	NA									
7													**Zr neg lesions**		**3**	3	0	0	0	3	0	0	0	0
7													**FDG PET neg lesions**	**NA**	NA									
7													**Total CT lesions**		**3**	3	0	0	0	3	0	0	0	0
8	Lymph node subcarinal (7)	Present	35	mm	46.1	mm	na		neg		7.1	pos	**Zr pos lesions**		**2**	2	0	0	2	0	0	0	0	0
8	Lymph node paratracheal right	Present	18.7	mm	23.6	mm	na		neg		9	pos	**FDG PET pos lesions**		**7**	7	0	2	2	2	1	0	0	0
8	Liver Segment IVb	Present	17.7	mm	19.4	mm	na		neg		10.7	pos	**Pos Zr neg FDG**		**0**	0	0	0	0	0	0	0	0	0
8	Liver Segment VIII	Present	16.3	mm	25.7	mm	NA		neg		5.4	pos	**Pos FDG neg Zr**		**5**	5	0	2	0	2	1	0	0	0
8	Left iliac bone	Absent						3.9	pos		4.8	pos	**Zr neg lesions**		**5**	5	0	2	0	2	1	0	0	0
8	Primary tumor	Absent					na		neg		23.8	pos	**FDG PET neg lesions**		**0**	0	0	0	0	0	0	0	0	0
8	T3	Absent						3.6	pos		5.6	pos	**Total CT lesions**		**4**	4	0	2	0	2	0	0	0	0
8																								
8																								
8																								
8																								
9	Lymph node para-aortic left	Present	13.8	mm	15.3	mm	neg		neg	neg		neg	**Zr pos lesions**		**8**	8	3	5	0	0	0	0	0	0
9	Lymph node supraclavicular left (Level V)	Present	14.1	mm	19.6	mm		4.9	pos		9.2	pos	**FDG PET pos lesions**		**9**	9	3	6	0	0	0	0	0	0
9	Lung lower lobe right	Present	9.9	mm	16.2	mm		7.3	pos		7.7	pos	**Pos Zr neg FDG**		**0**	0	0	0	0	0	0	0	0	0
9	Lung lower lobe left	Present	8.8	mm	10.6	mm		4.4	pos		9.9	pos	**Pos FDG neg Zr**		**1**	1	0	1	0	0	0	0	0	0
9	Lung middle lobe right	Present	12	mm	12.4	mm		11.5	pos		14.1	pos	**Zr neg lesions**		**9**	9	0	4	0	5	0	0	0	0
9	Liver Segment VII	Present	18	mm	20.8	mm			neg			neg	**FDG PET neg lesions**		**8**	8	0	3	0	5	0	0	0	0
9	Liver Segment V	Present	33.7	mm	48	mm			neg			neg	**Total CT lesions**		**15**	15	3	7	0	5	0	0	0	0
9	Lymph node porta hepatis	Present	36	mm	43.8	mm		14.2	pos		19.9	pos												
9	Lymph node para-aortic left	Present	19.6	mm	21	mm		8.7	pos		14.1	pos												
9	Lymph node gastric left	Present	20.6	mm	25.7	mm		12.1	neg		15.6	pos												
9	Lung upper lobe left	Present	10.7	mm	13	mm			neg			neg												
9	Lung lower lobe right	Present	13.5	mm	14.4	mm			neg			neg												
9	Liver Segment VII	Present	19.4	mm	20.9	mm			neg			neg												
9	Liver Segment VIII	Present	31	mm	32	mm			neg			neg												
9	Liver Segment II	Present	20.2	mm	20.4	mm			neg			neg												
9	Lymph node right lower paratracheal	Absent						12.4	pos		20.6	pos												
9	Lymph node right hilar	Absent						9.6	pos		9.2	pos												
10	Liver Segment VI	Present	11.6	mm	12.7	mm		13.7	pos		7.3	pos	**Zr pos lesions**		**6**	6	0	0	1	5	0	0	0	0
10	Liver Segment V	Present	13.9	mm	13.9	mm		9.8	pos		5.2	pos	**FDG PET pos lesions**		**5**	5	0	0	0	5	0	0	0	0
10	Liver Segment IVa	Present	12.7	mm	13.5	mm		14.7	pos		5.7	pos	**Pos Zr neg FDG**		**1**	1	0	0	1	0	0	0	0	0
10	Liver Segment VIII	Present	12	mm	12.8	mm		13.1	pos		4.6	pos	**Pos FDG neg Zr**		**0**	0	0	0	0	0	0	0	0	0
10	Liver Segment V	Present	23.4	mm	27.3	mm		23.8	pos		13.3	pos	**Zr neg lesions**		**0**	0	0	0	0	0	0	0	0	0
10	T4	Absent						10.1	pos			neg	**FDG PET neg lesions**		**1**	1	0	0	1	0	0	0	0	0
10													**Total CT lesions**		**5**	5	0	0	0	5	0	0	0	0

11	Liver Segment VIII	Present	16.4 mm	17.6 mm		7.5 mild positive		6.3 pos			**Zr pos lesions**		**3**	3	0	0	0	2	1	0	0	0
11	Liver Segment V	Present	12.6 mm	15.3 mm		7.8 mildly pos		3.8 pos			**FDG PET pos lesions**		**4**	4	0	0	0	3	1	0	0	0
11	Liver Segment IVa	Present	13.2 mm	14.7 mm		6.9 visually neg		4.7 pos			**Pos Zr neg FDG**		**0**	0	0	0	0	0	0	0	0	0
11	gastric tumor					4.2 positive		8.7 pos			**Pos FDG neg Zr**		**1**	1	0	0	0	1	0	0	0	0
11											**Zr neg lesions**		**1**	1	0	0	0	1	0	0	0	0
11											**FDG PET neg lesions**		**0**	0	0	0	0	0	0	0	0	0
11											**Total CT lesions**		**3**	3	0	0	0	3	0	0	0	0
12	Liver Segment VII	Present	9.9 mm	11.7 mm	NA	neg- similar to liver		NA			**Zr pos lesions**		**5**	5	1	2	0	0	2	0	0	0
12	Liver Segment VII	Present	11.7 mm	13.1 mm	NA	neg					**FDG PET pos lesions**	**NA**	NA									
12	Lymph node celiac	Present	14.7 mm	18.5 mm		3.8 pos					**Pos Zr neg FDG**	**NA**	NA									
12	Lymph node paratracheal left	Present	18.3 mm	33.4 mm		3.7 pos					**Pos FDG neg Zr**	**NA**	NA									
12	Lung lower lobe right	Present	17 mm	18.8 mm		6.2 pos					**Zr neg lesions**		**4**	4	0	0	0	4	0	0	0	0
12	Liver Segment VIII	Present	14.5 mm	15.9 mm	NA	neg- similar to liver					**FDG PET neg lesions**	**NA**	NA									
12	Liver Segment VII	Present	14.8 mm	20 mm	NA	neg- similar to liver					**Total CT lesions**		**7**	7	1	2	0	4	0	0	0	0
12	Esophagus mid tumor	Absent				20.3 pos																
12	Esophagus lower tumor	Absent				14.9 pos																
13	Lymph node aortocaval	Present	12.6 mm	16.9 mm		7.5 pos		18.1 pos			**Zr pos lesions**		**4**	4	0	4	0	0	0	0	0	0
13	Lymph node para-aortic left	Present	12.9 mm	16.8 mm		7.6 pos		16.9 pos			**FDG PET pos lesions**		**5**	5	0	5	0	0	0	0	0	0
13	Lymph node paracaval	Present	11.1 mm	16.3 mm		5.9 pos		10.3 pos			**Pos Zr neg FDG**		**0**	0	0	0	0	0	0	0	0	0
13	Lymph node para-aortic left	Present	15.4 mm	19.5 mm		6.9 pos		16.5 pos			**Pos FDG neg Zr**		**1**	1	0	1	0	0	0	0	0	0
13	Lymph node mesenteric proximal	Present	16.9 mm	39.5 mm		3.6 neg		7.4 pos			**Zr neg lesions**		**1**	1	0	1	0	0	0	0	0	0
13											**FDG PET neg lesions**		**0**	0	0	0	0	0	0	0	0	0
13											**Total CT lesions**		**5**	5	0	5	0	0	0	0	0	0
14	Lymph node gastric left	Present	11.2 mm	14.7 mm		3.5 neg	NA	NA			**Zr pos lesions**		**1**	1	0	0	0	0	1	0	0	0
14	Spleen	Present	20.3 mm	34.9 mm		5 neg	NA	NA			**FDG PET pos lesions**	**NA**	NA									
14	gastric tumor	Absent				11.5 pos	NA	NA			**Pos Zr neg FDG**	**NA**	NA									
14											**Pos FDG neg Zr**	**NA**	NA									
14											**Zr neg lesions**		**2**	2	0	1	0	0	0	0	0	1
14											**FDG PET neg lesions**	**NA**	NA									
14											**Total CT lesions**		**2**	2	0	1	0	0	0	0	0	1
15	Peritoneum	Present	12.4 mm	16.5 mm		7.1 pos		7.5 pos			**Zr pos lesions**		**1**	1	0	0	0	0	0	1	0	0
15											**FDG PET pos lesions**		**1**	1	0	0	0	0	0	1	0	0
15											**Pos Zr neg FDG**		**0**	0	0	0	0	0	0	0	0	0
15											**Pos FDG neg Zr**		**0**	0	0	0	0	0	0	0	0	0
15											**Zr neg lesions**		**0**	0	0	0	0	0	0	0	0	0
15											**FDG PET neg lesions**		**0**	0	0	0	0	0	0	0	0	0
15											**Total CT lesions**		**1**	1	0	0	0	0	0	1	0	0
16	Stomach body	Present	53.4 mm	63.5 mm		17.5 pos		5.4 pos			**Zr pos lesions**		**3**	3	0	0	0	1	1	1	0	0
16	Liver Segment VIII	Present	36 mm	47.6 mm		6.1 pos		3.2 pos			**FDG PET pos lesions**		**3**	3	0	0	0	1	1	1	0	0
16	Peritoneum	Present	16.2 mm	22.2 mm		5.5 pos - mild		2.9 pos			**Pos Zr neg FDG**		**0**	0	0	0	0	0	0	0	0	0
16											**Pos FDG neg Zr**		**0**	0	0	0	0	0	0	0	0	0
16											**Zr neg lesions**		**0**	0	0	0	0	0	0	0	0	0
16											**FDG PET neg lesions**		**0**	0	0	0	0	0	0	0	0	0
16											**Total CT lesions**		**3**	3	0	0	0	1	1	1	0	0
17	Lymph node common iliac left	Present	26.8 mm	45.4 mm		5.1 pos		21.07 pos			**Zr pos lesions**		**6**	6	0	3	0	2	1	0	0	0
17	Lymph node para-aortic left	Present	23.6 mm	27.5 mm		6.7 pos		37.7 pos			**FDG PET pos lesions**		**7**	7	0	4	0	2	1	0	0	0
17	Liver Segment VIII	Present	17.5 mm	20.7 mm		4.2 pos		6.7 pos			**Pos Zr neg FDG**		**0**	0	0	0	0	0	0	0	0	0
17	Lymph node paracaval	Present	38.9 mm	65.1 mm		6.9 neg		33.1 pos			**Pos FDG neg Zr**		**1**	1	0	1	0	0	0	0	0	0

17	Lymph node para-aortic left	Present	24.3 mm	61.3 mm	6 pos	23.1 pos		**Zr neg lesions**		**1**	1	0	1	0	0	0	0	0	0
17	Liver Segment VI	Present	20.2 mm	21.5 mm	6.1 pos	9.1 pos		**FDG PET neg lesions**		**0**	0	0	0	0	0	0	0	0	0
17	gastric tumor	Absent			6.3 pos	11.9 pos		**Total CT lesions**		**6**	6	0	4	0	2	0	0	0	0
18	Peritoneum	Present	9.4 mm	9.7 mm	0.8 neg	1.3 pos		**Zr pos lesions**		**5**	5	0	1	0	0	1	2	0	1
18	Lymph node along left gastric artery	Present	13.2 mm	13.9 mm	0.9 neg	1.1 neg		**FDG PET pos lesions**		**6**	6	0	0	0	0	1	3	0	2
18	Peritoneum	Present	8.8 mm	10 mm	0.8 neg	0.9 neg		**Pos Zr neg FDG**		**1**	1	0	1	0	0	0	0	0	0
18	Lymph node paraesophageal thoracic lower (8Lo)	Present	12.5 mm	14.3 mm	3.2 pos	1 neg		**Pos FDG neg Zr**		**1**	1	0	0	0	0	0	0	0	1
18	Spleen	Present	14.7 mm	23.6 mm	4.9 pos	14.1 pos		**Zr neg lesions**		**3**	3	0	1	0	0	0	2	0	0
18	Peritoneum	Present	13.2 mm	18.9 mm	4.3 pos	5.9 pos		**FDG PET neg lesions**		**3**	3	0	2	0	0	0	1	0	0
18	Peritoneum	Present	13.8 mm	15.7 mm	13 pos	4.9 pos		**Total CT lesions**		**7**	7	0	2	0	0	0	4	0	1
18	gastric tumor	Absent			6.5 pos	11.1 pos													
18	Sigmoid - diverticulitis	Absent			13.3 limited evaluation due to	17.3 pos													
19	Lymph node paracaval	Present	12.8 mm	17.8 mm	9.7 pos	11.6 pos		**Zr pos lesions**		**7**	7	0	5	0	2	0	0	0	0
19	Lymph node aortocaval	Present	9.9 mm	12.6 mm	9.7 pos	9 pos		**FDG PET pos lesions**		**7**	7	0	5	0	2	0	0	0	0
19	Lymph node along left gastric artery	Present	11.1 mm	12.4 mm	9.3 pos	5.2 pos		**Pos Zr neg FDG**		**0**	0	0	0	0	0	0	0	0	0
19	Liver Segment II	Present	7.4 mm	8.4 mm	7.8 neg	5 neg		**Pos FDG neg Zr**		**0**	0	0	0	0	0	0	0	0	0
19	Liver Segment VIII	Present	31.2 mm	76 mm	20.7 pos	12.06 pos		**Zr neg lesions**		**1**	1	0	0	0	1	0	0	0	0
19	Liver Segment IVb	Present	31.8 mm	60.3 mm	5.4 pos	11.5 pos		**FDG PET neg lesions**		**1**	1	0	0	0	1	0	0	0	0
19	Lymph node porta hepatis	Present	40.3 mm	46.7 mm	11.8 pos	11.6 pos		**Total CT lesions**		**8**	8	0	5	0	3	0	0	0	0
19	Lymph node paracaval	Present	14.6 mm	27.7 mm	10.5 pos	10.7 pos													
20	Liver Segment VII	Present	13.1 mm	19.9 mm	4.2 neg	13.2 pos		**Zr pos lesions**		**2**	2	0	0	0	1	1	0	0	0
20	Liver Segment VIII	Present	10.8 mm	14.1 mm	3.5 neg	9.5 pos		**FDG PET pos lesions**		**10**	10	0	3	0	5	1	1	0	0
20	Lymph node para-aortic thoracical left (6)	Present	12.6 mm	16.7 mm	neg	11 pos		**Pos Zr neg FDG**		**0**	0	0	0	0	0	0	0	0	0
20	Peritoneum	Present	11.6 mm	11.6 mm	neg	10.7 pos		**Pos FDG neg Zr**		**8**	8	0	3	0	4	0	1	0	0
20	Lymph node para-aortic thoracical left (6)	Present	20.3 mm	23.4 mm	neg	2.5 pos		**Zr neg lesions**		**8**	8	0	3	0	4	0	1	0	0
20	Lymph node paraesophageal thoracic lower (8Lo)	Present	15.5 mm	20.7 mm	neg	6.1 pos		**FDG PET neg lesions**		**0**	0	0	0	0	0	0	0	0	0
20	Liver Segment IVa	Present	46.6 mm	49.2 mm	12.1 neg	10.4 pos		**Total CT lesions**		**9**	9	0	3	0	5	0	1	0	0
20	Liver Segment VII	Present	43.4 mm	51.8 mm	12.5 pos	12.1 pos													
20	Liver Segment VIII	Present	16.5 mm	16.8 mm	neg	13.7 pos													
20	Esophagus tumor	Absent			10.3 pos	15.2 pos													
21	Lung upper lobe right	Present	11.3 mm	16.9 mm	3.3 pos	NA		**Zr pos lesions**		**3**	3	3	0	0	0	0	0	0	0
21	Lung upper lobe left	Present	29.5 mm	35.9 mm	6.4 pos			**FDG PET pos lesions**	**NA**	NA									
21	Lung upper lobe left	Present	12.9 mm	14 mm	1.7 pos			**Pos Zr neg FDG**	**NA**	NA									
21								**Pos FDG neg Zr**	**NA**	NA									
21								**Zr neg lesions**		**0**	0	0	0	0	0	0	0	0	0
21								**FDG PET neg lesions**	**NA**	NA									
21								**Total CT lesions**		**3**	3	0	0	0	0	0	0	0	0
22	Lung lower lobe left	Present	12 mm	13.6 mm	2.7 pos	NA	NA	**Zr pos lesions**		**4**	4	3	0	0	1	0	0	0	0
22	Lung lower lobe right	Present	11.2 mm	13.2 mm	2.8 pos	NA	NA	**FDG PET pos lesions**	**NA**	NA									
22	Lung lower lobe right	Present	14.6 mm	15 mm	2.8 pos	NA	NA	**Pos Zr neg FDG**	**NA**	NA									
22	Liver Segment VIII	Present	26.1 mm	43.9 mm	13.3 neg	NA	NA	**Pos FDG neg Zr**	**NA**	NA									
22	Lung upper lobe left	Present	11.5 mm	14.8 mm	2.2 neg	NA	NA	**Zr neg lesions**		**4**	4	2	0	0	2	0	0	0	0
22	Lung upper lobe left	Present	9.2 mm	12.2 mm	1.59 neg	NA	NA	**FDG PET neg lesions**	**NA**	NA									
22	Liver Segment VIII	Present	33.4 mm	38.8 mm	16.6 pos	NA	NA	**Total CT lesions**		**8**	8	5	0	0	3	0	0	0	0
22	Liver Segment IVb	Present	26 mm	31.4 mm	10.2 neg	NA	NA												
23	Lung lower lobe right	Present	8.3 mm	9 mm	NA	not seen on CT		**Zr pos lesions**		**3**	3	2	0	0	0	1	0	0	0
23	Lung lower lobe right	Present	8.4 mm	9 mm	2.5 mild- pos			**FDG PET pos lesions**	**NA**										
23	Lung lower lobe right	Present	19.2 mm	34.8 mm	4.3 pos			**Pos Zr neg FDG**	**NA**										

23	gastroesophageal tumor	Absent					5.2	Mild pos			Pos FDG neg Zr	NA									
23											Zr neg lesions	1	1	1	0	0	0	0	0	0	0
23											FDG PET neg lesions	NA	NA								
23											Total CT lesions	3	3	3	0	0	0	0	0	0	0
24	Mediastinum	Present	17.7	mm	30.2	mm	10.3	pos	12.8	pos	Zr pos lesions	1	1	0	1	0	0	0	0	0	0
24											FDG PET pos lesions	1	1	0	1	0	0	0	0	0	0
24											Pos Zr neg FDG	0	0	0	0	0	0	0	0	0	0
24											Pos FDG neg Zr	0	0	0	0	0	0	0	0	0	0
24											Zr neg lesions	0	0	0	0	0	0	0	0	0	0
24											FDG PET neg lesions	0	0	0	0	0	0	0	0	0	0
24											Total CT lesions	1	1	0	1	0	0	0	0	0	0
25	Lymph node supraclavicular left (Level V)	Present	14.5	mm	22.5	mm	7.7	pos	8.26	pos	Zr pos lesions	11	11	0	4	0	5	1	1	0	0
25	Lymph node paratracheal right	Present	20.4	mm	32.8	mm	7.7	pos	7.6	pos	FDG PET pos lesions	14	14	0	7	0	5	1	1	0	0
25	Liver Segment VI	Present	26.5	mm	27.4	mm	12.7	pos	11.4	pos	Pos Zr neg FDG	0	0	0	0	0	0	0	0	0	0
25	Liver Segment V	Present	20.7	mm	23.4	mm	NEG	neg	8.3	pos	Pos FDG neg Zr	3	3	0	2	0	1	0	0	0	0
25	Liver Segment IVb	Present	17.5	mm	18.4	mm	16.8	pos	9.5	pos	Zr neg lesions	3	3	0	2	0	1	0	0	0	0
25	Peritoneum	Present	9.8	mm	11.4	mm	3.5	pos	2.2	pos	FDG PET neg lesions	0	0	0	0	0	0	0	0	0	0
25	Lymph node celiac	Present	19	mm	26.3	mm	2.1	neg	6.2	pos	Total CT lesions	13	13	0	7	0	5	0	1	0	0
25	Lymph node paratracheal right	Present	19.8	mm	34.1	mm	6.1	pos	9.4	pos											
25	Lymph node paratracheal left	Present	21.6	mm	23	mm	7.9	pos	7.7	pos											
25	Liver Segment VIII	Present	23.5	mm	24.1	mm	15	pos	8.3	pos											
25	Liver Segment VII	Present	18.6	mm	21.4	mm	18	pos	8.2	pos											
25	Lymph node para-aortic left	Present	42.2	mm	84.1	mm	NEG	neg	7.6	pos											
25	Lymph node left common iliac	Present	12	mm	18	mm	5.6	pos	6.7	pos											
25	gastric tumor	Absent					11.6	pos	10.5	pos											
25																					
25																					
25																					
25																					
25																					
26	Lymph node paratracheal right	Present	8.7	mm	12.2	mm	3.1	pos	1.9	pos	Zr pos lesions	2	2	0	1	0	0	1	0	0	0
26	Pleura	Absent						neg		neg	FDG PET pos lesions	5	5	0	4	0	0	1	0	0	0
26	Mediastinum	Present	11.3	mm	20.9	mm		neg	3.3	pos	Pos Zr neg FDG	0	0	0	0	0	0	0	0	0	0
26	Mediastinum	Present	10	mm	19.4	mm		neg	4.9	pos	Pos FDG neg Zr	3	3	0	3	0	0	0	0	0	0
26	Lymph node para-aortic	Absent						neg	9.69	pos	Zr neg lesions	4	4	1	3	0	0	0	0	0	0
26	esophagus tumor	Absent					4.4	pos	8.2	pos	FDG PET neg lesions	1	1	1	0	0	0	0	0	0	0
26											Total CT lesions	3	3	0	3	0	0	0	0	0	0
27	Lymph node para-aortic left	Present	13.4	mm	18.7	mm	2.6	neg	4.7	pos	Zr pos lesions	0	0	0	0	0	0	0	0	0	0
27	Lymph node para-aortic left	Present	16.8	mm	19.9	mm	2.8	neg	2.9	pos	FDG PET pos lesions	7	7	0	7	0	0	0	0	0	0
27	Lymph node aortocaval	Present	10.5	mm	11.8	mm	2.1	neg	2.9	pos	Pos Zr neg FDG	0	0	0	0	0	0	0	0	0	0
27	Lymph node para-aortic left	Present	8.7	mm	14.5	mm	1.8	neg	3.95	pos	Pos FDG neg Zr	7	7	0	7	0	0	0	0	0	0
27	Lymph node along left gastric artery	Present	17.6	mm	18.7	mm		neg	3.3	neg	Zr neg lesions	8	8	0	8	0	0	0	0	0	0
27	Lymph node retrocaval	Absent						neg	4.4	pos	FDG PET neg lesions	1	1	0	1	0	0	0	0	0	0
27	Lymph node retrocaval	Absent						neg	5.4	pos	Total CT lesions	5	5	0	5	0	0	0	0	0	0
27	Lymph node retrocaval	Absent						neg	3.1	pos											
28	Liver Segment V	Present	4.4	mm	7.7	mm	NEG	neg	3.2	pos	Zr pos lesions	3	3	0	1	0	1	1	0	0	0
28	Lymph node paracaval	Present	13.5	mm	32.3	mm	4.2	pos	6.3	pos	FDG PET pos lesions	8	8	0	3	0	4	1	0	0	0
28	Lymph node para-aortic left	Present	12.3	mm	18.5	mm	NEG	neg	3	pos	Pos Zr neg FDG	0	0	0	0	0	0	0	0	0	0

28	Lymph node	Present	17.2 mm	25.7 mm		neg		neg		**Pos FDG neg Zr**	**5**	5	0	2	0	3	0	0	0	0
28	Liver Segment VII	Present	13.8 mm	15.2 mm		4.5 pos		4.4 pos		**Zr neg lesions**	**10**	10	2	3	1	3	0	0	0	1
28	Liver Segment IVb	Present	9.4 mm	11.7 mm	NEG	neg		3.4 pos		**FDG PET neg lesions**	**5**	5	2	1	1	0	0	0	0	1
28	Spleen	Present	13.3 mm	23.7 mm		2.7 neg		neg		**Total CT lesions**	**9**	9	0	4	0	4	0	0	0	1
28	Lymph node	Present	20 mm	23.7 mm		neg		3.8 pos												
28	gastric tumor	Absent				4.8 pos		15.8 pos												
28	Left sacrum	Absent			NEG	neg	NEG	neg												
28	Liver segment VI	Absent	8 mm	12 mm	NEG	neg		3.4 pos												
28	Lung lower lobe right	Absent			NA	neg		neg												
28	Lung lower lobe left	Absent				neg		neg												
29	Lung upper lobe right	Present	8.8 mm	9.6 mm		1.92 pos		6.5 pos		**Zr pos lesions**	**8**	8	1	1	0	5	1	0	0	0
29	Liver Segment V	Present	14.6 mm	15 mm		16 pos		7.6 pos		**FDG PET pos lesions**	**8**	8	1	1	0	5	1	0	0	0
29	Liver Segment VI	Present	15.6 mm	16.8 mm		13.5 pos		6.2 pos		**Pos Zr neg FDG**	**0**	0	0	0	0	0	0	0	0	0
29	Lymph node celiac	Present	9.6 mm	12.4 mm		6.6 pos		3.7 pos		**Pos FDG neg Zr**	**0**	0	0	0	0	0	0	0	0	0
29	Liver Segment II	Present	7.9 mm	10.4 mm		8.2 pos		4.3 pos		**Zr neg lesions**	**0**	0	0	0	0	0	0	0	0	0
29	Liver Segment VIII	Present	19.1 mm	22.2 mm		13.4 pos		7.6 pos		**FDG PET neg lesions**	**0**	0	0	0	0	0	0	0	0	0
29	Liver Segment VIII	Present	16.4 mm	16.9 mm		11.6 pos		6.7 pos		**Total CT lesions**	**7**	7	1	1	0	5	0	0	0	0
29	gastric tumor	Absent				10 pos		14 pos												
30	Lymph node supraclavicular left (Level V)	Present	13.4 mm	16.8 mm		22.16 pos		3.8 pos		**Zr pos lesions**	**6**	6	0	5	0	0	1	0	0	0
30	Lymph node mediastinal	Present	15.3 mm	17 mm		12.4 neg		2.4 neg		**FDG PET pos lesions**	**6**	6	0	5	0	0	1	0	0	0
30	Lymph node gastric left	Present	12.3 mm	15.6 mm		5.56 pos		2.9 pos		**Pos Zr neg FDG**	**0**	0	0	0	0	0	0	0	0	0
30	Lymph node para-aortic left	Present	20.7 mm	23.4 mm		21.6 pos		5.9 pos		**Pos FDG neg Zr**	**0**	0	0	0	0	0	0	0	0	0
30	Lymph node paratracheal right	Present	19.4 mm	27 mm		12.43 pos		4.9 pos		**Zr neg lesions**	**1**	0	0	1	0	0	0	0	0	0
30	Lymph node upper abdominal - periportal	Present	21.8 mm	28.4 mm		22.11 pos		3.5 pos		**FDG PET neg lesions**	**1**	1	0	1	0	0	0	0	0	0
30	Primary tumor	Absent				14.93 pos		5.8 pos		**Total CT lesions**	**6**	6	0	6	0	0	0	0	0	0
31	Lymph node retrocrural	Present	11.4 mm	19.6 mm		4 POS		1.8 neg		**Zr pos lesions**	**7**	7	0	3	3	0	1	0	0	0
31	Lymph node paratracheal right	Present	12.8 mm	17.4 mm		neg		2 neg		**FDG PET pos lesions**	**3**	3	0	1	1	0	1	0	0	0
31	Lymph node superior mesenteric artery lateral right	Present	11.9 mm	19 mm		2.8 neg	na	neg		**Pos Zr neg FDG**	**4**	4	0	2	2	0	0	0	0	0
31	Lymph node supraclavicular left (Level V)	Present	16.6 mm	19.3 mm		5.4 POS	na	neg		**Pos FDG neg Zr**	**0**	0	0	0	0	0	0	0	0	0
31	Lymph node along left gastric artery	Present	18.2 mm	31.7 mm		4.5 POS		2.5 pos		**Zr neg lesions**	**3**	3	0	3	0	0	0	0	0	0
31	Lymph node aortocaval	Present	19 mm	26.4 mm	NEG	neg	NEG	neg		**FDG PET neg lesions**	**7**	7	0	5	2	0	0	0	0	0
31	Bone pelvic girdle left	Absent				3.5 POS		1.9 pos		**Total CT lesions**	**6**	6	0	6	0	0	0	0	0	0
31	Bone pelvic girdle left	Absent				3.6 POS	NEG	neg												
31	Bone pelvic girdle left	Absent				4.1 POS	NEG	neg												
31	Primary tumor	Absent				5.9 pos		5.2 pos												
32	Lymph node para-aortic left	Present	37.7 mm	58.1 mm		2.8 NEG		6.6 pos		**Zr pos lesions**	**6**	6	0	1	0	2	0	2	0	1
32	Lymph node celiac	Present	48.5 mm	73.5 mm		5.1 POS		6.9 pos		**FDG PET pos lesions**	**13**	13	1	6	0	2	1	2	0	1
32	Peritoneum	Present	28.7 mm	58.4 mm		3.1 POS		7.6 pos		**Pos Zr neg FDG**	**0**	0	0	0	0	0	0	0	0	0
32	Adrenal gland left	Present	41.2 mm	68.5 mm		7.7 POS		2.4 pos		**Pos FDG neg Zr**	**7**	7	1	5	0	0	1	0	0	0
32	Liver Segment IVa	Present	13.5 mm	18.1 mm		4.1 POS		9 pos		**Zr neg lesions**	**7**	7	1	5	0	0	1	0	0	0
32	Liver Segment IVb	Present	20.8 mm	26.8 mm		7.1 POS		7.2 pos		**FDG PET neg lesions**	**0**	0	0	0	0	0	0	0	0	0
32	Lymph node para-aortic right	Present	27.5 mm	40.6 mm	NA	NEG		7 pos		**Total CT lesions**	**10**	10	1	4	0	2	0	2	0	1
32	Lung lower lobe right	Present	6.2 mm	6.3 mm		1.1 NEG		6.6 pos												
32	Peritoneum	Present	15.9 mm	28.6 mm		6.8 POS		7.7 pos												
32	L supraclavicular node (6th lesion)	Present	12 mm	24 mm	NA	neg		6.6 pos												
32	Rt upper paratracheal - chest	Absent			NA	neg		3.4 pos												
32	subcarinal	Absent			NA	neg		5.4 pos												
32	GEJ tumor	Absent			NA	neg		8.5 pos												

33	Lymph node paraesophageal thoracic lower (8Lo)	Present	9	mm	14.1	mm	neg	neg		4.6	pos	
33	Lymph node para-aortic thoracical left (6)	Present	14	mm	17	mm	neg	neg		7.6	pos	
33	Lymph node along left gastric artery	Present	13.6	mm	14.9	mm	2.4	neg		3.3	pos	
33	Lymph node porta hepatis	Present	9	mm	10.8	mm	2.1	neg	na		neg	
33	Bone vertebrae cervical	Present	12.1	mm	15.9	mm	9.23	pos		11	pos	
33	Soft tissue abdominal wall	Present	22.4	mm	26.9	mm	3.8	pos		10.8	pos	
33	Liver Segment VI	Absent						neg			neg	
33	Liver Segment VII	Absent						neg		3.7	pos	
33	Esophagus	Absent					6.7	pos		30.7	pos	
33	Distal esophagus	Absent					6.5	pos		30.7	pos	
33	T1	Absent						neg	NA		neg	
33	right clavicle	Absent					4.1	pos		7.5	pos	
33	T5	Absent					3.8	neg		2.6	pos	
33	T6	Absent					9.2	neg		4.4	pos	
33	left sacrum	Absent					3.8	pos		3.9	pos	
33	T03 Lymph node mediastinal	Absent						neg	NA		neg	
33	gastric tumor	Absent					5	pos		11.11	pos	

Zr pos lesions	**7**	7	0	0	3	0	3	0	1	0
FDG PET pos lesions	**13**	13	0	3	5	1	3	0	1	0
Pos Zr neg FDG	**0**	0	0	0	0	0	0	0	0	0
Pos FDG neg Zr	**6**	6	0	3	2	1	0	0	0	0
Zr neg lesions	**9**	10	0	4	3	2	0	0	0	0
FDG PET neg lesions	**3**	3	0	1	1	1	0	0	0	0
Total CT lesions	**6**	6	0	4	1	0	0	0	1	0

Supplemental Table 4. Baseline characteristics patients receiving first-line therapy at the time of imaging.

	Total (N=13)
Characteristic	
Age at diagnosis, years, median [IQR]	61 [54, 65]
Patients with metastasis at diagnosis, N (%)	9 (69)
Primary tumor site, N (%)	
Esophageal	2 (15)
GEJ (Siewert I-II)	7 (54)
Gastric	4 (31)
Gender male, N (%)	12 (92)
Patients with HER2 heterogeneous among samples, N (%)	6 (46)
Patients receiving HER2-directed therapy at the time of scan, N (%)	13 (100)
Total lines of treatment received, median (range)	1 (1, 1)
Time on treatment at the time of ^{89}Zr-trastuzumab PET (days), median (range)	443 (131, 1441)
Total lesions detected on imaging (all patients)	
CT, median (range)	6 (1, 15)
^{89}Zr-trastuzumab, median (range)	3 (0, 11)
^{18}F-FDG PET, median (range)	7 (1, 14)
Patients with ≥1 lesion intense or very intense on ^{89}Zr-trastuzumab PET, N (%)	7 (54)
Maximum SUV per patient on ^{89}Zr-trastuzumab PET, median [IQR]	10.3 [4.4, 17.5]