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Molecular imaging as a tool to investigate heterogeneity of advanced HER2-positive breast cancer and to predict patient outcome under trastuzumab emtansine (T-DM1): the ZEPHIR trial

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Background: Only human epidermal growth factor receptor (HER)2 status determined by immunohistochemistry (IHC) and fluorescence *in situ* hybridization (FISH) has been validated to predict efficacy of HER2-targeting antibody-drug-conjugate trastuzumab emtansine (T-DM1). We propose molecular imaging to explore intra-/interpatient heterogeneity in HER2 mapping of metastatic disease and to identify patients unlikely to benefit from T-DM1.

Patients and methods: HER2-positive mBC patients with IHC3+ or FISH ≥2.2 scheduled for T-DM1 underwent a pretreatment HER2-positron emission tomography (PET)/computed tomography (CT) with ^{89}Zr-trastuzumab. [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG)–PET/CT was performed at baseline and before T-DM1 cycle 2. Patients were grouped into four HER2–PET/CT patterns according to the proportion of FDG-avid tumor load showing relevant ^{89}Zr-trastuzumab uptake (>blood pool activity): patterns A and B were considered positive (>50% or all of the tumor load 'positive'); patterns C and D were considered negative (>50% or all of the tumor load 'negative'). Early FDG–PET/CT was defined as nonresponding when >50% of the tumor load showed no significant reduction of FDG uptake (<15%). Negative (NPV) and positive predictive values (PPV) of HER2–PET/CT, early FDG response and their combination were assessed to predict morphological response (RECIST 1.1) after three T-DM1 cycles and time-to-treatment failure (TTF).

Results: In the 56 patients analyzed, 29% had negative HER2–PET/CT while intrapatient heterogeneity (patterns B and C) was found in 46% of patients. Compared with RECIST1.1, respective NPV/PPV for HER2–PET/CT were 88%/72% and 83%/96% for early FDG–PET/CT. Combining HER2–PET/CT and FDG–PET/CT accurately predicted morphological response (PPV and NPV: 100%) and discriminated patients with a median TTF of only 2.8 months [$n = 12$, 95% confidence interval (CI) 1.4–7.6] from those with a TTF of 15 months ($n = 25$, 95% CI 9.7–not calculable).

Conclusions: Pretreatment imaging of HER2 targeting, combined with early metabolic response assessment holds great promise for improving the understanding of tumor heterogeneity in mBC and for selecting patients who will/will not benefit from T-DM1.

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Key words: HER2-positive breast cancer, HER2 imaging, prediction of T-DM1 efficacy

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