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Predictors of ^{18}F-fluorodeoxyglucose positron-emission tomography-driven disease detection in patients with HER2[+] early breast cancer. A substudy of the PHERGAIN trial

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BACKGROUND

- Early metabolic evaluation using ^{18}F-FDG PET/CT (PET) might help to recognize patients (pts) with an increased probability of pathological complete response (pCR).[1]
- However, PET is not recommended for staging all pts with early breast cancer (EBC). Its diagnostic accuracy is reduced in conditions with a low rate of actively replicating cells.[2]
- There is a need to investigate the association between clinical, molecular, and metabolic tumor characteristics with the probability of disease detection by PET in a large cohort of pts.[2,3]
- PHERGAIN trial is assessing the early metabolic response by PET to neoadjuvant chemotherapy-free treatment with trastuzumab and pertuzumab, and the opportunity of chemotherapy de-escalation with a response-adapted strategy in pts with HER2[+] EBC **(Figure 1)**.
- In the present substudy, clinical, molecular, and metabolic predictors of disease detection using PET were evaluated.[4]

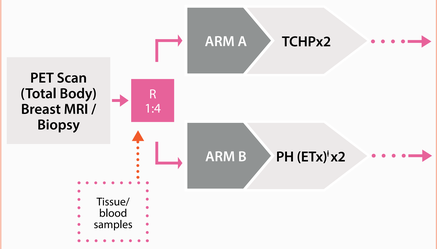
Figure 1. Inclusion phase of PHERGain trial

Key Eligibility Criteria:

1. Centrally confirmed HER2[+] stage I-IIIA EBC.
2. Tumor diameter ≥ 1.5 cm by MRI or ultrasound.
3. Presence of a breast PET-evaluable lesion.

Stratification factors

- Hormonal receptor status (+/-)



I All hormonal receptor-positive pts received ETx concomitantly with PH.

C: Carboplatin; D: Docetaxel; ETx: Endocrine therapy (letrozole post-menopausal/tamoxifen pre-menopausal); PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; H: Trastuzumab SC; HER2: Human Epidermal Growth Factor Receptor 2; HR: Hormonal receptor; MRI: Magnetic resonance imaging; P: Pertuzumab IV; R: Randomization; TCHP: Trastuzumab, pertuzumab, docetaxel, and carboplatin.

OBJECTIVES

- Correlation of PET status with the maximum standardized uptake value (SUV_{max}) and clinicopathological features in all HER2[+] EBC pts screened in the PHERGAIN trial.
- Assessment of HER2-enriched pts, stromal tumor-infiltrating lymphocytes (TILs), risk of recurrence (ROR) scores, and gene expression in PET[-] and PET[+] matched pts.

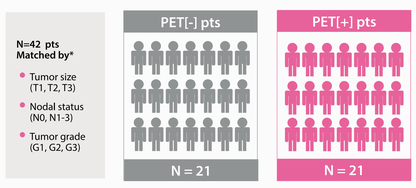
METHODS

- PHERGAIN eligibility criteria required at least one breast lesion with a SUV_{max} ≥1.5 x SUV_{mean} liver + 2 SD by PET. Out of 512 screened pts, 75 (14.7%) resulted PET[-].
- HER2-enriched subtype, TILs, ROR, and gene expression data were evaluated by prediction analysis of microarray 50 (PAM50) classifier and Vantage 3D Cancer Metabolism Panel.[4]
- Matched procedure selected a cohort of 21 PET[-] and 21 PET[+] pts **(Figure 2)**.

Statistical Methods

- Adjusted analysis based on the logistic regression model.
- Matched cohorts were analyzed with paired tests (Mc Nemar and Wilcoxon tests).
- Multiple testing issues with gene expression were controlled with false discovery rate (q-value<5%).

Figure 2. Matching selection



PET, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography.
*The matching uses a nearest neighbor procedure based on a logistic regression. Matched factors were selected in accordance their clinical relevance and significant association with PET status.

RESULTS - All pts screened (N=512)

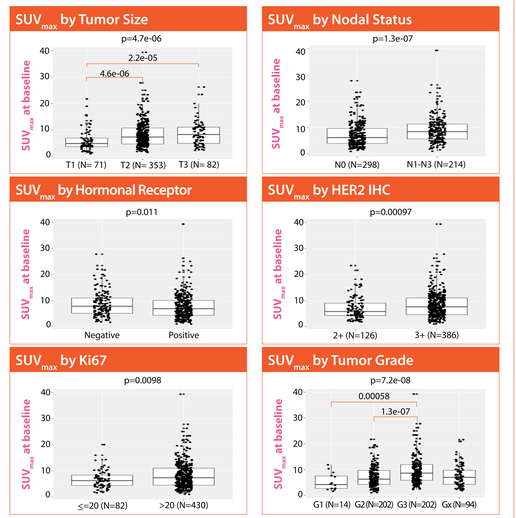
Table 1. Baseline characteristics of the pts

Characteristics, N (%)		All patients (N=512)	PET[-] (N=75)	PET[+] (N=437)	p-value*
Age in years,	median (range)	52 (20-83)	52 (36-83)	51 (20-82)	0.155
Tumor size by MRI,	median (range)	32 (9-157)	30 (14-100)	32 (9-157)	0.181
Tumor size (T)	T1	77 (15)	19 (25.3)	58 (13.3)	**0.01**
	T2	353 (69)	46 (61.3)	307 (70.3)	
	T3	82(16)	10 (13.3)	72 (16.5)	
SUV_{max} at baseline,	median (range)	7.1 (1-39.3)	2.7 (1-7.3)	8 (2.1-39.3)	**<0.01**
Nodal status (N)	N0	298 (58.2)	62 (86.7)	236 (54)	**<0.01**
	N1- 3	214 (41.8)	13 (13.3)	201 (46)	
Hormonal status	[-]	162 (31.6)	21 (28)	141 (32.3)	0.464
	[+]	350 (68.4)	54 (72)	296 (67.7)	
HER2 IHC status	2+	126 (24.6)	24 (32)	102 (23.3)	0.11
	3+	386 (75.4)	51 (68)	335 (76.7)	
Ductal carcinoma	No	91 (17.8)	21 (28)	70 (16)	**0.013**
	Yes	421 (82.2)	54 (72)	367 (84)	
Tumor Grade (G)	G1 to G2	216 (42.2)	43 (57.3)	173 (39.6)	**<0.01**
	G3	202 (39.5)	13 (17.3)	38 (43.3)	
	Gx	94 (18.4)	19 (25.3)	75 (17.2)	
Ki67(%)	≤20	82 (16)	16 (21.3)	66 (15.1)	0.177
	>20	430 (84)	59 (78.7)	371 (84.9)	

*In adjusted analyses, PET[-] tumors had lower tumor size, histological grade, and lymph node involvement than PET[+] tumors.

G: Grade; HER2: Human Epidermal Growth Factor Receptor 2; IHC: Immunohistochemistry; MRI: Magnetic resonance imaging; N: Nodal status; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; SUVmax,: The maximum standardized uptake value; T: Tumor size.

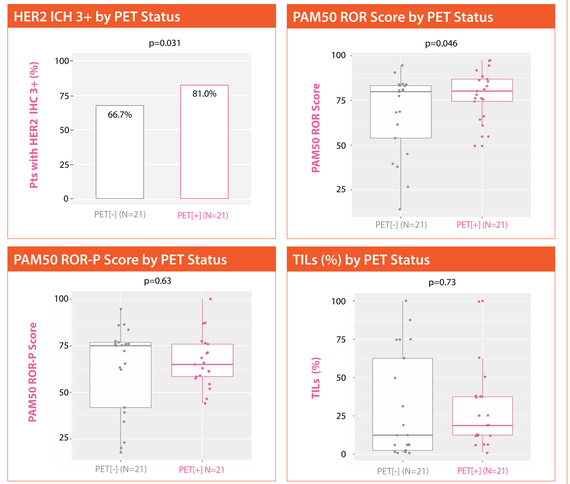
Figure 3. Association between SUV_{max} levels and baseline characteristics



G: Grade; HER2: Human Epidermal Growth Factor Receptor 2; IHC: Immunohistochemistry; N: Nodal status; SUVmax: The maximum standardized uptake value; T: Tumor size; TILs: Tumor-infiltrating lymphocytes.

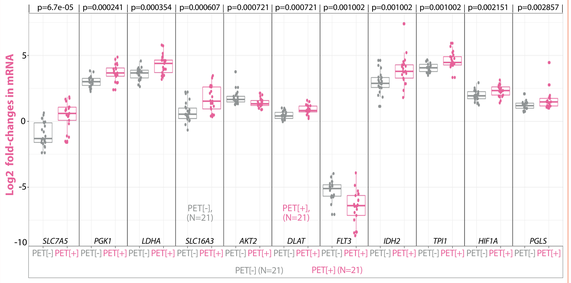
RESULTS - Cohort of 21 PET[-] and 21 PET[+] matched pts

Figure 4. PAM50 gene signatures by PET status



HER2: Human Epidermal Growth Factor Receptor 2; IHC: Immunohistochemistry; PAM50: Prediction analysis of microarray 50; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; ROR-S: Risk of recurrence based on subtype; ROR-P: Risk of recurrence based on subtype and proliferation; TILs: Tumor-infiltrating lymphocytes.

Figure 5. Analysis of cancer metabolism genes according to PET status



PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; mRNA: Messenger ribonucleic acid.
*Genes reported achieved the q-value <5% criteria for False Discovery Rate adjustment. Comparison of gene expression between PET[-] and PET[+] cohorts and relative p-values are shown.

RESULTS

- SUV_{max} was associated with tumor size, lymph node involvement, hormone receptor status, HER2 protein expression levels, Ki67 index, and histological grade **(Figure 3)**.
- PET[-] tumors had lower tumor size, histological grade, and lymph node involvement than PET[+] tumors **(Table 1)**.
- A decreased risk of recurrence and lower proportion of HER2-enriched subtype by PAM50 characterized PET[-] tumors with respect to PET[+] tumors **(Figure 4)**.
- Among PET[-] pts, genes involved in glucose metabolism (*DLAT, IDH2, LDHA, PGK1, PGLS, and TPI1*), hypoxia signaling (HIF1A), and carbon metabolism (*SLC7A5, SLC16A3*) were under expressed, whereas genes involved in the mTOR pathway (*AKT2*) and growth factor receptor (*FLT3*) were overexpressed compared to PET[+] pts **(Figure 5)**.

CONCLUSIONS

Considering the heterogeneity of HER2[+] disease, these results may need to be considered for an appropriate selection of PET[+] pts in HER2[+] EBC.

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Conflicts of interest: https://www.medsir.org/response

Trial registration: NCT04240106. Date of registration: January 27, 2020.