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PREDICTOR OF BENEFIT FROM DOSE-DENSE PACLITAXEL CHEMOTHERAPY FOR PATIENTS WITH HORMONE RECEPTOR-POSITIVE HER2-NEGATIVE BREAST CANCER. A GEICAM/9906 SUB-STUDY

Miguel Martin[1,2,3], Alvaro Rodriguez-Lescure[3,4], Lourdes Calvo[3,5], Eveline Chen[6], Manuel Ruiz-Borrego[3,7], Cesar A. Rodriguez[3,8], Noelia Martinez-Jañez[3,9], Emilio Alba[2,3,10,11], Kevin Tran[6], Ignacio Pelaez Fernandez[3,12], Isabel Alvarez[3,13], Miguel Angel Seguí[3,14], Alberto de la Cruz[3,15], Vicente Valero[6], Antonio Anton-Torres[3,16], Raquel Andres[3,17], Kepa Amillano[3,18], Jose J. Ponce-Lorenzo[3,19], Severina Dominguez Fernandez[3,20], Jesus Herranz[3], Raul Rincon[3], Rosalia Caballero[3], Ana Santaballa Bertran[3,21], Angel Guerrero-Zotano[3,22], W. Fraser Symmans[6]

1.Department of Medical Oncology, Hospital General Universitario Gregorio Marañon Instituto de Investigacion Sanitaria Gregorio Marañon, Universidad Complutense, Madrid, Spain;2.Oncology Biomedical Research National Network (CIBERONC-ISCIII), Madrid, Spain;3. GEICAM, Spanish Breast Cancer Group, Madrid, Spain;4.Hospital General Universitario de Elche, Elche, Spain;5.Complejo Hospitalario Universitario de A Coruña, A Coruña, Spain;6.The University of Texas MD Anderson Cancer Center, Houston, Texas;7.Hospital Universitario Virgen del Rocio, Sevilla, Spain;8.Oncology Department, Hospital Universitario de Salamanca, IBSAL, Salamanca, Spain;9.Medical Oncology Department, Hospital Ramon y Cajal, Madrid, Spain;10.Unidad de Gestion Clinica Intercentros de Oncologia Medica, Hospitales Universitarios Regional y Virgen de la Victoria, Malaga, Spain;11.The Biomedical Research Institute of Malaga, Malaga, Spain;12.Medical Oncology Department, Hospital Universitario de Cabueñes, Gijon, Spain;13.Medical Oncology, Hospital Universitario Donostia-Biodonostia, San Sebastian, Spain;14.Department of Medical Oncology, Consorcio Hospital Universitario Parc Tauli, Sabadell, Spain;15.Centro Oncologico de Galicia, La Coruña, Spain;16.Universidad de Zaragoza, Instituto Investigación Sanitaria Aragón, Hospital Universitario Miguel Servet, Zaragoza, Spain;17.Medical Oncology Department, University Hospital Lozano Blesa, Zaragoza, Spain;18.Hospital Universitari Sant Joan de Reus, Reus, Spain;19.Oncology Department, Dr. Balmis General University Hospital, Alicante Institute for Health and Biomedical Research (ISABIAL), Alicante, Spain;20.Hospital Universitario Araba - Txagorritxu, Vitoria, Spain;21.Medical Oncology Department., La Fe Health Research Institute (IISLaFe), La Fe University Hospital, Valencia Spain;22.Instituto Valenciano de Oncologia (IVO), Valencia, Spain

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INTRODUCTION

$SET_{ER/PR}$ index is a genomic test designed to measure endocrine transcriptional activity that is related to estrogen receptor (ER) and progesterone receptor (PR), but not proliferation. Higher values of $SET_{ER/PR}$ index indicate greater endocrine transcriptional activity in the cancer. It was previously reported that levels of $SET_{ER/PR}$ index below 0.75 predicted benefit from dose-dense (q2-week), vs conventional (q3-week) anthracycline-paclitaxel chemotherapy (CT) for patients (pts) with hormone receptor-positive (HR+) lymph node-positive breast cancer (BC) in the CALGB 9741 trial. Since that was the first report of a test that could predict benefit from a dose-dense taxane-based CT in HR+ BC, we sought to independently test its predictive validity. The seminal phase III GEICAM/9906 trial established sequential anthracycline and weekly paclitaxel (FEC+P) as superior to anthracycline (FEC) in node-positive HR+ BC pts, but in HR+ BC no biomarker could predict a benefit.

OBJECTIVE

In this analysis, we sought to independently test the $SET_{ER/PR}$ assay predictive value at predefined 0.75 cutoff point in pts with HR+/HER2- lymph node-positive BC from the phase III GEICAM/9906 trial (NCT00129922).

MATERIALS AND METHODS

We conducted a blinded independent validation study in 647 HR+/HER2- tumor RNA samples from GEICAM/9906 BC pts (51.9% of the trial's cohort), isolated from corresponding formalin-fixed paraffin-embedded (FFPE) BC surgical specimens. GEICAM translational laboratory sent the de-identified tumor RNA samples to the MDACC laboratory for blinded testing with results returned to the GEICAM statistician. Predefined cutoff point was $SET_{ER/PR}$ index <0.75. Clinical endpoints were distant recurrence-free interval (DRFI) and overall survival (OS, secondary endpoint). Multivariable Cox proportional hazards models including $SET_{ER/PR}$ index, treatment arm and their interaction term were used to calculate hazard ratios with 95% confidence interval (HR, 95%CI) and two-sided 0.05 as predefined level of significance.

GEICAM/9906 N=1246 → HR+/HER2- N=680 → RNA samples provided to MDACC lab N=647 → $SET_{ER/PR}$ evaluation N=567

$SET_{ER/PR}$ index

$SET_{ER/PR}$ Genes: ABAT, ADCY1, AZGP1, CA12, CD2, CD3D, DNAJC12, ESR1, KCNE4, MAPT, MRPS30, NAT1, NPY1R, PDZK1, QDPR, SCUBE2, SLC39A6, STC2

Reference Genes: AK2, APPBP2, ATP5J2, DARS, LDHA, TRIM2, UBE2Z, UGP2, VDAC2, WIPF2

GEICAM/9906 translational study cohort	FEC arm (N=288)		FEC+P arm (N=279)	
	N	%	N	%
Median age, years (range)	49.8 (27.9–75.7)		50.9 (23.1–76.2)	
Menopausal status at diagnosis				
Premenopausal	165	57.3%	145	52.0%
Postmenopausal	123	42.7%	134	48.0%
Tumor size				
≤ 2 cm	120	41.7%	138	49.4%
> 2 cm and ≤ 5 cm	151	52.4%	128	45.9%
> 5 cm	17	5.9%	13	4.7%
Nodal status				
1-3 positive nodes	173	60.1%	179	64.2%
> 3 positive nodes	115	39.9%	100	35.8%
Histological type				
Infiltrating Ductal Carcinoma	252	87.5%	231	82.8%
Infiltrating Lobular Carcinoma	25	8.7%	36	12.9%
Other	11	3.8%	12	4.3%
Histological grade				
G1	48	16.7%	46	16.5%
G2	138	47.9%	122	43.7%
G3	82	28.5%	84	30.1%
GX	20	6.9%	27	9.7%
ER IHC status				
Negative	9	3.1%	16	5.7%
Positive	268	93.1%	249	89.3%
Unknown	11	3.8%	14	5.0%
PR IHC status				
Negative	47	16.3%	23	8.3%
Positive	229	79·5%	242	86.7%
Unknown	12	4.2%	14	5.0%
Ki67 IHC				
≤ 20%	236	81.9%	219	78.5%
> 20%	38	13.2%	39	14.0%
Unknown	14	4.9%	21	7.5%
$SET_{ER/PR}$, median (range)	1.45 (0-2.73)		1.42 (0-2.85)	
$SET_{ER/PR}$ cutoff point 0·75				
$SET_{ER/PR}$ < 0·75 (Low)	48	16.7%	44	15.8%
$SET_{ER/PR}$ ≥ 0·75 (High)	240	83.3%	235	84.2%

RESULTS

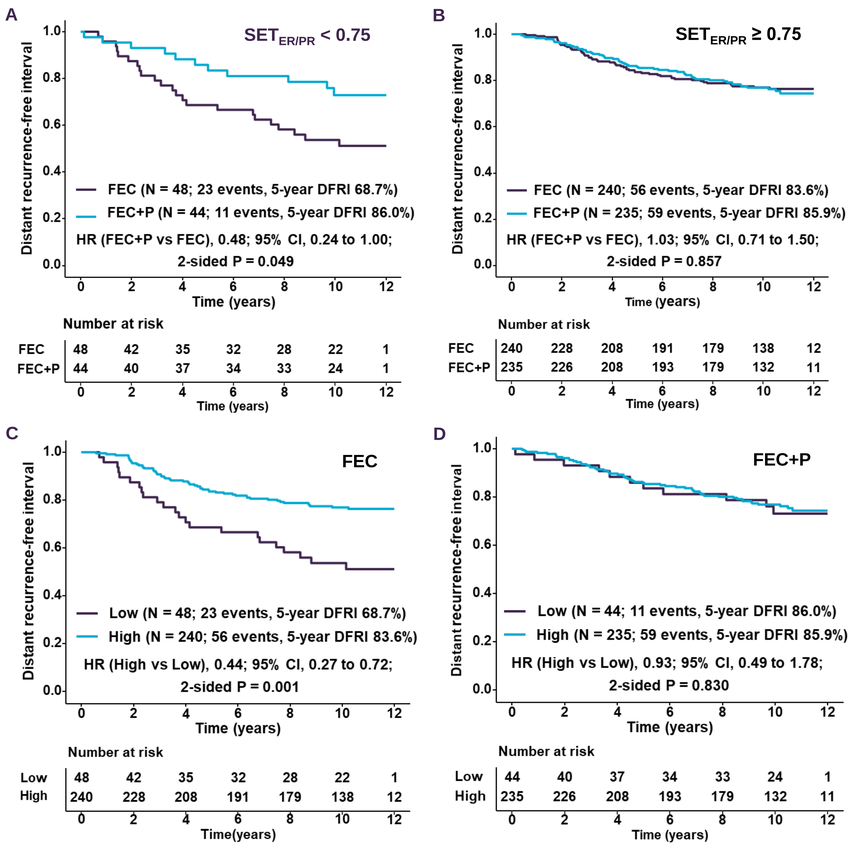
Figure 1. Survival analyses of distant recurrence-free interval (DRFI) between $SET_{ER/PR}$ index and treatment in the GEICAM/9906 translational study cohort. A, $SET_{ER/PR}$ < 0.75 subset, FEC vs FEC-P. B, $SET_{ER/PR}$ ≥ 0.75 subset, FEC vs FEC-P. C, FEC treatment arm subset, $SET_{ER/PR}$ < 0.75 (Low) vs ≥ 0.75 (High). D, FEC+P treatment arm subset, $SET_{ER/PR}$ < 0.75 vs ≥ 0.75.

Exploratory analysis of other $SET_{ER/PR}$ index cutoff points for prediction of distant recurrence-free interval (DRFI) benefit in the GEICAM/9906 translational study cohort

Cutoff point description	Cutoff point range of $SET_{ER/PR}$ range	Interaction p-value
Pre-defined	<0.75 vs ≥0.75	0.046
Arbitrary	<1.00 vs ≥1.00	0.740
Median	≤1.43 vs >1.43	0.418
Interquartile Range	0.99 – 1.78	0.456
Quartiles	≤0.98; 0.99–1.43, 1.44–1.78, >1.78	0.405
None	Continuous	0.665

Multivariate Cox regression analysis of overall survival (OS) for $SET_{ER/PR}$ < 0.75 (Low), $SET_{ER/PR}$ ≥ 0.75 (High), FEC, and FEC-P subsets in the GEICAM/9906 translational study cohort

Cohort subset	HR_{FEC+P} (95% CI)	p-value
$SET_{ER/PR}$ < 0.75	0.61 (0.29 - 1.30)	0.201
$SET_{ER/PR}$ ≥ 0.75	0.84 (0.58 - 1.22)	0.365
Cohort subset	**$HR_{SETER/PR\ Low}$ (95% CI)**	**p-value**
FEC	0.58 (0.34 - 0.97)	0.037
FEC+P	0.83 (0.43 - 1.58)	0.565



CONCLUSIONS

- **In this GEICAM/9906 trial retrospective analysis, patients with node-positive HR+/HER2- breast cancer that has low endocrine transcriptional activity ($SET_{ER/PR}$ index <0.75) benefited from inclusion of weekly paclitaxel in their adjuvant chemotherapy**
- **This result provides independent confirmation that $SET_{ER/PR}$ index predicts benefit from dose-dense paclitaxel-containing chemotherapy in HR+/HER2- breast cancer**

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