Independent validation of the PAM50-based chemoendocrine score (CES) as pathologic complete response and disease-free survival predictor in hormonal receptor positive/HER2-positive breast cancer.

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BACKGROUND

Hormone receptor positive (HR+)/HER2+ breast cancer (BC) is heterogeneous and subgroups with different treatment sensitivities need to be identified to better tailor current and future treatments.

On the other, we previously reported a Chemo-Endocrine Score (CES) based on the PAM50 gene expression-based assay. High CES was associated with endocrine treatment sensitivity and low CES was associated with high chemotherapy sensitivity beyond PAM50 Risk of Relapse (ROR) score and intrinsic subtype (Prat et al. CCR 2016).

Here, we evaluated the association of CES with pCR and DFS following anti-HER2-based therapy in HR-positive/HER2-positive breast cancer across 8 studies, with the two different kinds of backbones (Chemotherapy and hormonotherapy).

METHODS

Intrinsic subtype and clinical-pathological data were obtained from 8 neoadjuvant clinical studies (CherLOB, SOLTI-1002 OptiHER, SOLTI-1114 PAMELA, LPT109096, Institut Catala d' Oncologia-Hospitalet (ICO), Hospital Clínic de Barcelona (HCB) and PerELISA and CALGB 40601).

Intrinsic molecular subtypes from tumor biopsy samples taken at baseline were determined using PAM50 from either RNA-seq data (CALGB40601), microarray (CHER-LOB) and nCounter (the rest of studies).

All evaluable patients were assessed for pathologic complete response (pCR), defined as no residual invasive carcinoma in the breast. Patients from CALGB 40601, CherLOB, ICO and HCB were also assessed for disease-free survival (DFS).

CES was evaluated as a continuous variable, and as group categories (CES-E [endocrine sensitive], CES-U [uncertain] and CES-C [chemo-sensitive]) using the previously reported cutoffs, where we used pre-defined percentiles.

We performed statistical analyses in each dataset individually, and then in a patient-level combined dataset. Univariate and multivariable logistic regressions analyses were used.

RESULTS

Fig 1. CES stratified by Study. The two horizontal lines indicate the cutoffs of each CES group.

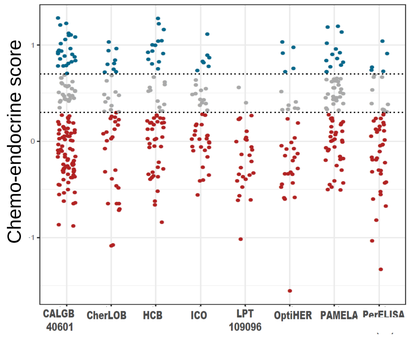


Table 1. Clinical-pathological characteristics and subtypes distribution of the overall study cohort.

Parameter	Parameter Value	Pooled N (%)
Age, years	<50	211 (43.5)
	≥50	245 (50.5)
	missing	29 (6.0)
Stage	I	46 (9.6)
	II	357 (73.6)
	III	81(16.7)
HER2 treatment	Trastuzumab alone	180 (37.1)
	Lapatinib alone	47 (9.7)
	Trastuzumab/Lapatinib	158 (32.6)
	Trastuzumab/Pertuzumab	100 (20.6)
CT/HT	Hormonotherapy	112 (23.2)
	Anthracyclines/Taxanes	215 (44.3)
	Taxanes	158 (32.5)
pCR (ypT0/is)	Yes	185 (38.2)
	No	300 (61.8)
PAM50	Luminal A	110 (46.2)
	Luminal B	114 (23.5)
	Her2-E	244 (50.3)
	Basal-like	17 (3.5)
CES	CES-E	78 (16.1)
	CES-U	107 (22.1)
	CES-C	300 (61.8)

CT: Chemotherapy; HT:Endocrinetherapy

Fig. 2. PAM50-ROR, intrinsic subtype and CES in the combined cohort

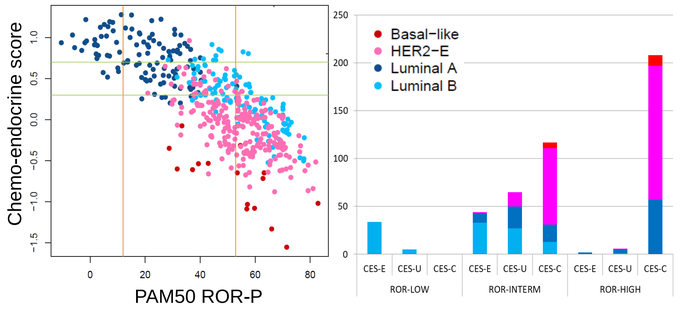
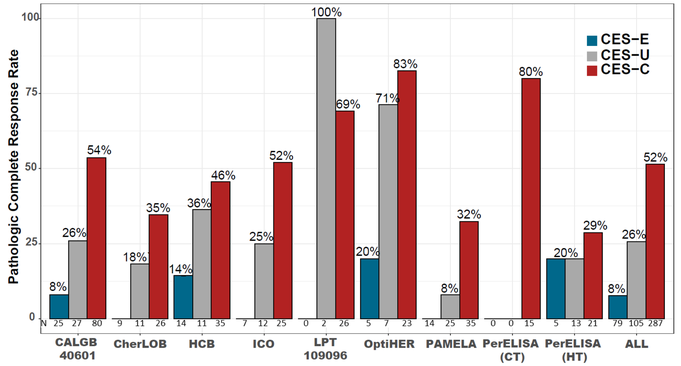


Fig 3. Rates of pathological complete response (pCR) according to the CES group in the 8 neoadjuvant clinical studies and in the all population.



Correlation of CES and pCR

- pCR rates were significantly lower in the CES-E group (8%), compared with CES-U (26%) and CES-C (52%) groups (p<0.001).
- In univariate analysis, neoadjuvant chemotherapy, HER2-E intrinsic subtype, high-ROR, study and low CES (as a continuous variable or as group categories) were statistically significantly associated with pCR.
- In a multivariable model, HER2-E molecular subtype, neoadjuvant chemotherapy and CES remained significantly associated with pCR; the adjusted OR of CES as a continuous variable for achieving pCR was 0.43 (95% CI 0.21–0.86; p=0.016).

Fig. 4. Probability of response (Ki67 relative reduction >20% from baseline) after 2 weeks of letrozole in monotherapy as a function of CES in PerELISA patients

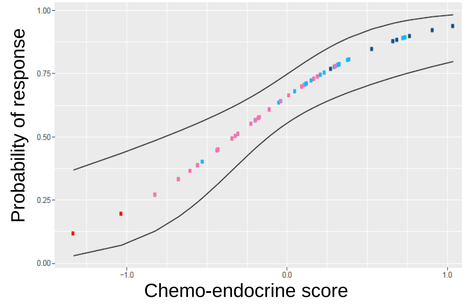
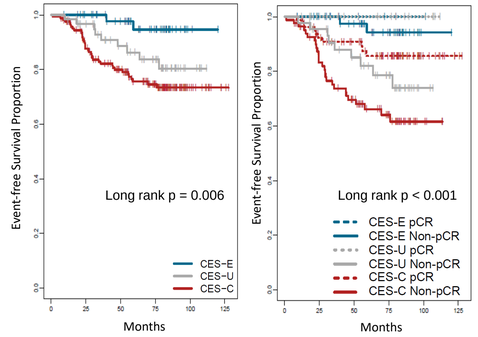


Fig 5. Survival curves in the combined data set. A) DFS according to CES group status. B) DFS according to pCR and CES group status.



CES association with survival outcome

- We pulled together survival data from CALGB 40601, ICO, HCB and CHERLOB (295 primary BC). The median follow-up was 72.7 m.
- CES (as a continuous variable or as group categories) was found significantly associated with DFS. The hazard ratio between the CES-C group vs the CES-E group was 7.02 (95% CI 1.70-28.95, p<0.001).
- In multivariable analysis, only pCR and CES provided independent predictive information for DFS, but intrinsic subtype and ROR did not; the adjusted hazard ratio of CES for DFS was 0.13 (95% CI 0.04–0.41; p=0.002).
- Within patients that achieved a pCR, no variable was found to be significantly associated with DFS.
- Within patients that did not achieve a pCR, CES (as a continuous variable or as group categories) was found to be significantly associated with DFS in univariate and multivariable analyses after adjustment for ROR, PAM50 intrinsic subtypes and the other clinicopathological variables (adjusted hazard ratio 0.14; 95% CI 0.04–0.51.; p=0.003).

CONCLUSIONS

CES at diagnosis provides useful prognostic and predictive information for HR-positive/HER2-positive patients. Further studies are needed to determine the role of CES in treatment decision-making at diagnosis in this population.

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