P2-11-04

Prognostic Contribution of Predicted Sensitivity to Endocrine Therapy (SET) Prior to Neoadjuvant Chemotherapy for Stage II-III Hormone Receptor-positive and HER2-negative (HR+/HER2-) Breast Cancer

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Introduction

The SET2,3 index combines an accurate measure of transcription related to both estrogen and progesterone receptors ($SET_{ER/PR}$ index) with a baseline prognostic index (BPI) derived from c-T Stage, c-N status and molecular subtype by RNA4 (*ESR1*, *PGR*, *ERBB2*, and *AURKA*). SET2,3 index was translated from a microarray-based signature to a customized hybridization assay that yields highly reproducible results from routine pathology tissue sections.

Study Goal

To evaluate the SET2,3 index of predicted sensitivity to endocrine therapy in the context of molecular prognosis and response to neoadjuvant chemotherapy, i.e. residual cancer burden (RCB).

Methods

- Prognostic risk from cT and cN Stage categories were estimated from the published results in the Oxford overview (Pan et al) and refined using subject-level clinical data from the control arms of two adjuvant trials of chemotherapy for Stage II-III HR+/HER2- breast cancer (Project DataSphere).
- The RNA4 classification was developed from published gene expression data sets, using *ESR1*, *PGR*, *ERBB2* and *AURKA*.
- The SET2,3 index was measured from pre-treatment biopsies in the MDACC cohort (N=307), and a cutpoint was defined.
- Blinded independent validation of SET2,3 index in pre-treatment biopsies from the I-SPY2 trial, which evaluates novel therapies added to neoadjuvant taxane-anthracycline chemotherapy in breast cancers that have high-risk MammaPrint test result.
- Evaluation of SET2,3 in contexts of RCB-II and RCB-III, and in prognostic gene expression signatures from U133A microarrays at MDACC, and Agendia'a MammaPrint signature in I-SPY2 trial.

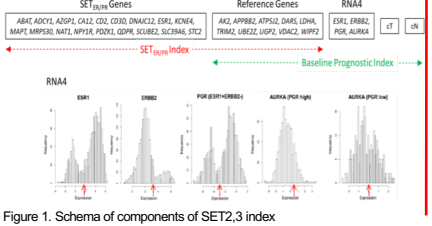

Figure 1. Schema of components of SET2,3 index

Results

Increasing SET2,3 Index Was Associated with Decreased Risk of Distance Relapse in the MDACC Cohort

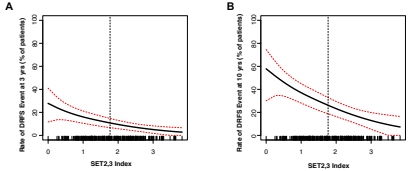

Figure 2. Rate of DRFS event within 3 years (A) and 10 years (B) in MDACC cohort. The cutpoint for high SET2,3 was defined as SET2,3 index > 1.77 units.

SET2,3 Index in the Context of RCB and Genomic Subtype

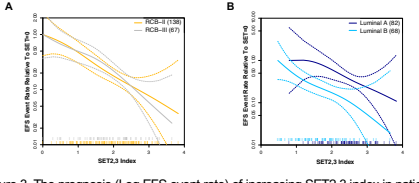

Figure 3. The prognosis (Log EFS event rate) of increasing SET2,3 index in patients with HR+/HER2- cancer who have significant residual disease (RCB-II/III) after neoadjuvant chemotherapy, stratified according to: A) RCB-II (yellow) or RCB-III (grey), and B) PAM50 subtype of Luminal A (dark blue) or Luminal A (light blue).

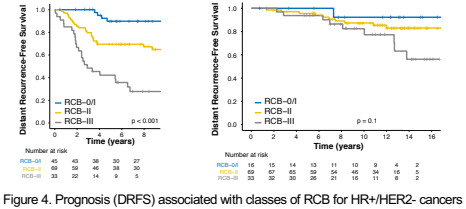

Figure 4. Prognosis (DRFS) associated with classes of RCB for HR+/HER2- cancers with Low (A) or High (B) predicted sensitivity to subsequent adjuvant endocrine therapy, defined from the cutpoint for SET2,3 index in this MDACC cohort.

Baseline Prognostic Index, SET2,3 Index and RCB Add Prognostic Information

Table 1. Multivariate Cox models for the components of residual prognostic risk (DRFS) after chemo-endocrine therapy

	MDACC Cohort		I-SPY2 Trial	
Multivariate: Components of Residual Risk	**HR (95%CI)**	**p**	**HR (95%CI)**	**p**
Baseline Prognostic Index (BPI)	0.55 (0.40, 0.76)	<0.001	1.02 (0.64, 1.63)	0.929
Predicted Endocrine Sensitivity ($SET_{ER/PR}$ Index)	0.56 (0.41, 0.75)	<0.001	0.41 (0.27, 0.62)	<0.001
Residual Cancer Burden after NAC (RCB Index)	2.03 (1.61, 2.54)	<0.001	2.02 (1.57, 2.59)	<0.001
Multivariate: SET2,3 versus RCB	**HR (95%CI)**	**p**	**HR (95%CI)**	**p**
SET2,3 Index	0.23 (0.09, 0.62)	0.004	0.27 (0.08, 0.89)	0.031
RCB Index	1.77 (1.25, 2.50)	< 0.001	1.68 (1.14, 2.45)	0.008
SET2,3 Index * RCB Index	1.19 (0.87, 1.62)	0.257	1.17 (0.81, 1.68)	0.401

SET2,3 Index was Independent from Microarray-derived Prognostic Signatures

Table 2. Prognostic signatures in neoadjuvant treatment cohorts (DRFS). Each signature was initially tested in univariate Cox model, then compared with SET2,3 index in a multivariate Cox model.

Prognostic Signatures	**MDACC Cohort Study (N=307)**						**I-SPY2 Trial (N=268)**					
	Univariate		**Multivariate with SET2,3**				**Univariate**		**Multivariate with SET2,3**			
Analyses of Continuous Scores	**Signature**		**Signature**		**SET2,3 Index**		**Signature**		**Signature**		**SET2,3 Index**	
	HR (95%CI)	**p**	**HR (95%CI)**	**p**	**HR (95%CI)**	**p**	**HR (95%CI)**	**p**	**HR (95%CI)**	**p**	**HR (95%CI)**	**p**
21-gene Recurrence Score (RS)	1.01 (1.00, 1.02)	0.030	0.99 (0.99, 1.00)	0.242	0.49 (0.35, 0.68)	<0.001	-		-		-	
11-gene EndoPredict (EP)	1.07 (1.02, 1.14)	0.012	0.94 (0.86, 1.01)	0.104	0.45 (0.32, 0.64)	<0.001	-		-		-	
70-gene Mammaprint (MP)	10.27 (2.65, 39.91)	0.001	1.34 (0.23, 7.68)	0.741	0.57 (0.42, 0.78)	<0.001	0.54 (0.17-1.72)	0.299	2.82 (0.65-12.74)	0.178	0.39 (0.22-0.71)	0.002

Blinded Independent Validation of SET2,3 Index in the I-SPY2 Trial

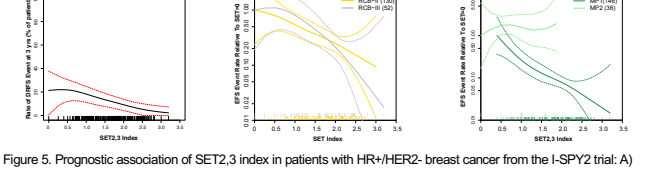

Figure 5. Prognostic association of SET2,3 index in patients with HR+/HER2- breast cancer from the I-SPY2 trial: A) the overall I-SPY2 trial HR+/HER2- population; B) patients with residual disease after neoadjuvant chemotherapy, stratified by residual cancer burden classes RCB-II (yellow) and RCB-III (grey); and C) patients who have significant residual disease (RCB-II/III) after neoadjuvant chemotherapy, stratified by MammaPrint prognostic subgroups of high-risk (MP1, dark green) and very high-risk (MP2, light green).

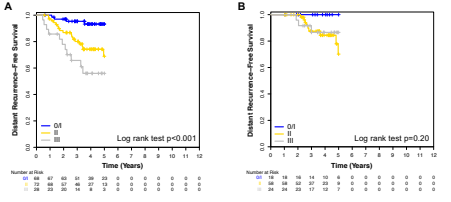

Figure 6. Prognosis (DRFS) associated with classes of RCB in patients with HR+/HER2- cancer with Low (A) or High (B) predicted sensitivity to subsequent adjuvant endocrine therapy defined from the SET2,3 index in the I-SPY2 trial.

Conclusions

- The prognostic performance of SET2,3 index was demonstrated in the MDACC cohort and independently validated in the I-SPY2 clinical trial.
- SET2,3 index added significant prognostic information that was independent from genomic subtype, prognostic score, and response to neoadjuvant chemotherapy (RCB).
- Response to neoadjuvant chemotherapy (RCB class) was highly prognostic if low SET2,3, but not if high SET2,3 index.
- These results suggest that patients with high SET2,3 might be selected for endocrine-based neoadjuvant treatments in clinical trials.

Acknowledgements

Supported in part by research grants from NIH P-01 P0513149 (LE), CPRIT MIRA RP#180712 (WFS), and the Breast Cancer Research Foundation (WFS, LE).

Additional support to I-SPY2 clinical trial related to this analysis from Quantum Leap Healthcare Collaborative, FNIH, NCI (Grant 28XS197 P-0518835), Safeway, an Albertsons Company, William K. Bowes, Jr. Foundation, UCSF, GMU, the Biomarkers Consortium, Salesforce, and Agendia. Sincere thanks to our DSMB, Independent Agent Selection Committee, our patients, advocates and investigators.

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