Combined Gene Signatures Predict Platinum and Taxane Response in the I-SPY2 Breast Cancer Cohort

Abstract title: Taxane and platinum combination as a predictor of pathologic complete response in I-SPY2 by gene expression breast cancer signatures

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BACKGROUND

Carboplatin improves pCR rates in triple-negative breast cancer (TNBC) when added to taxane-based neoadjuvant chemotherapy (NAC), but biomarkers identifying platinum- and taxane-sensitive tumors remain limited.

The **I-SPY2 trial** is a large, multicenter study of high-risk early-stage breast cancer, in which patients were randomized to standard taxane-anthracycline (T-AC) chemotherapy with or without investigational agents. Transcriptomic and clinical data from 987 patients are publicly available and provide a valuable resource for evaluating predictors of chemotherapy response.

In the present study, we evaluated whether two gene expression signatures, a platinum response predictor (**Platin-DRP**) and a **taxane response predictor**, could identify patients more likely to achieve pCR in the veliparib-carboplatin (VC) arm of I-SPY2.

The Platin-DRP has previously been validated in both lung and breast cancer across carboplatin- and cisplatin-based treatments[1,2,3].

The taxane predictor is a machine learning-based model previously validated in six independent neoadjuvant breast cancer cohorts[4,5].

Further evaluation of the taxane predictor is presented in two companion ASCO 2026 posters, including analyses across all I-SPY2 treatment arms and validation in an RNA-sequencing dataset (***see poster boards 82 and 34***).

METHODS

COHORT

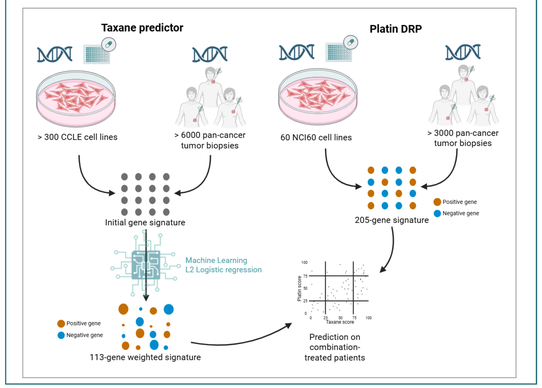
Gene expression data from the I-SPY2 dataset (GSE194040) was analyzed.

- VC arm: 71 HER2-negative patients treated with veliparib + carboplatin + T-AC → **pCR rate = 38%**
- T-AC arm: 179 HER2-negative patients treated with standard T-AC → **pCR rate = 17%**

ANALYSES

- Patients were scored from 0-100 using both predictors
  - 205-gene Platin-DRP signature
  - 113-gene taxane signature
- Logistic regression was used to assess score association with pCR
- Models were adjusted for HR status

Model Development



RESULTS

Combined platinum and taxane prediction

When patients are stratified according to both predictors, clear differences in pCR rates emerge across groups. Patients with high scores for both signatures had the highest likelihood of response, while patients with low scores for both signatures showed poor response. The highest response rate was observed in the high-high group (78%, n=9), whereas no responses were observed in the low-low group (n=8).

Patient cohort characteristics

Characteristic	VC arm (n = 71)	T-AC arm (n = 179)
Age, median (range)	49 (27–70)	47 (24–77)
HR-positive (HR+/HER2-)	32 (45.1%)	94 (52.5%)
Triple-negative	39 (54.9%)	85 (47.5%)
MammaPrint high risk	31 (43.7%)	91 (50.8%)
MammaPrint ultra-high risk	40 (56.3%)	88 (49.2%)
pCR	27 (38.0%)	31 (17.3%)
No pCR	44 (62.0%)	148 (82.7%)

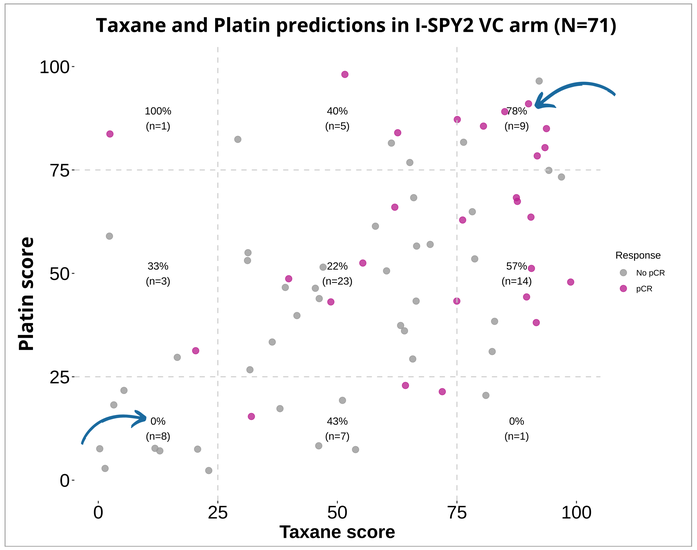


Figure 1. Each point represents an individual patient in the VC arm.

- X-axis: taxane predictor score
- Y-axis: Platin-DRP score
- Points are colored by response (pCR vs no pCR)

Patients are distributed across nine groups defined by splitting the scores using quartile cutoffs at 25 and 75. This shows increasing pCR rates with increasing scores across both predictors.

Both the platinum and taxane predictors were significantly associated with pCR in the VC arm and remained independently predictive after adjustment for HR status.

VC arm n=71

Predictor	OR (50-point increase)	p-value (1-sided)
Platin-DRP	3.4	0.016
Taxane predictor	3.9	0.011

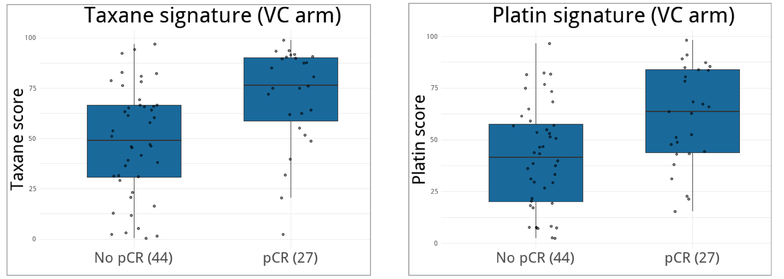


Figure 2: Distribution of predictor scores in patients from the I-SPY2 VC arm (n=71) receiving T-AC + carboplatin + veliparib. For both predictors patients achieving a pCR show consistently higher scores than non responders with an OR of 3.4 and 3.9 for a 50-point increase in score of the Platin-DRP and the taxane predictor, respectively.

T-AC arm n=179

Predictor	OR (50-point)	p-value (2s)
Platin-DRP	1.8	0.12
Taxane predictor	6.1	<0.001

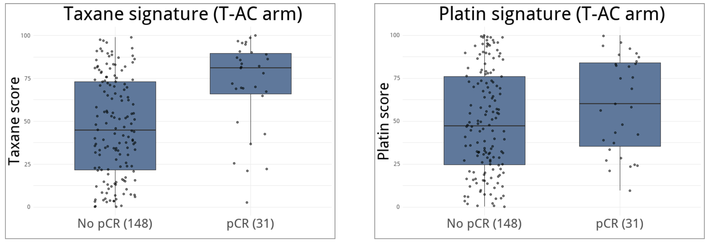


Figure 3: Score distribution of the platinum and taxane predictors in the T-AC arm (n = 179). The taxane predictor shows clear separation between responders and non-responders (results previously presented at SABCS[6]), whereas the Platin-DRP shows no clear association, supporting a platinum-specific effect.

CONCLUSION

Platinum and taxane gene expression signatures were significantly associated with pCR in this cohort of HER2-negative patients treated with T-AC + veliparib-carboplatin in I-SPY2 and remained independently predictive after adjustment for HR status.

Combined use of the two predictors identified subgroups with markedly different response rates, with the highest pCR observed in patients with high scores for both signatures. The **integration of complementary biomarkers** improved stratification of response probability, supporting their use to refine patient selection for platinum- and taxane-containing neoadjuvant chemotherapy.

The platinum and taxane predictors showed moderate correlation (r = 0.53), indicating that they capture complementary, non-overlapping biological information and provide independent predictive value.

Moreover, the Platin-DRP showed a platinum-specific signal, with significant association in the carboplatin arm but not in the T-AC arm.

FUTURE PERSPECTIVES

Future work may explore the use of combined drug-specific predictors to guide patient selection in research settings such as I-SPY2 and to identify patients unlikely to benefit from standard therapies who may be prioritized for experimental treatment approaches.

Additionally, both the platinum and taxane predictors will be further evaluated in the BrighTNess trial cohort.

We are actively seeking collaborators for data sharing to support further validation of the predictors (please contact us for collaboration opportunities).

ACKNOWLEDGEMENTS

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