Correlation of TILs indices generated by visual review and digital computational algorithm with outcomes from preoperative chemotherapy for TNBC in TBCRC 030

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Abstract 555

BACKGROUND

- Predictive biomarkers for response to neoadjuvant chemotherapy (NAC) in early-stage triple negative breast cancer (TNBC) are needed.
- Stromal tumor infiltrating lymphocytes (TILs) are prognostic and predictive in TNBC, typically scored by visual examination (VE) of H&E-stained slides.[1,2]
- Evaluation of image-based surrogate signatures for TILs and complex immune response combining cycle deregulation and proliferative signatures by computational assessment (CA) of slides may offer greater precision and more comprehensive assessment of the immune microenvironment.
- This study was designed to evaluate TILs by VE and CA methods and investigate through blinded assessment the predictive capacity of immune activation.

METHODS

- The phase II study TBCRC 030 (NCT01982448) randomized patients with BRCA1/2-proficient, stage I-III TNBC to cisplatin or paclitaxel NAC, with primary endpoint response at surgery (residual cancer burden – RCB).[3] (**Figure 1**)
- TILs were visually scored on a continuous scale by a single experienced pathologist on digitized H&E images of pre-treatment core needle biopsies (CNB) according to the International TILs Working Group recommendations.[1]
- CA was performed using a hard-coded statistical physics and tumor biology-based algorithm (4D Q-Plasia OncoReader [QPOR]) that generates surrogate biomarkers chosen for specific questions.
- QPOR was used to quantify cell cycle deregulation and microenvironment dynamics including TILs, immune response (IHI), and combined immune response and cell cycle deregulation signature (CmbI) as continuous biomarkers from digitized CNB whole slide images.
- Three CA surrogate biomarkers were derived:
  - **CA TILs**: surrogate biomarker for average immune infiltrates
  - **CA IHI**: immune response scores based on the spatial heterogeneity of immune infiltrates
  - **CA CmbI**: combined IHI, proliferative, and cell cycle G1S deregulation signatures
- Evaluation of TILs by VE and CA were each correlated with response (RCB 0/1) or non-response (RCB 2/3) to NAC.
- VE and CA assessments were performed by investigators who were blinded to the pathologic response.
- Receiver operator characteristic (ROC) curves with area under the curve (AUC) measures and odds ratios (OR) per unit increase with 95% confidence intervals were used to assess the predictive performance of each continuous biomarker.

RESULTS

TBCRC 030: a phase II study of preoperative cisplatin versus paclitaxel in triple-negative breast cancer[3]

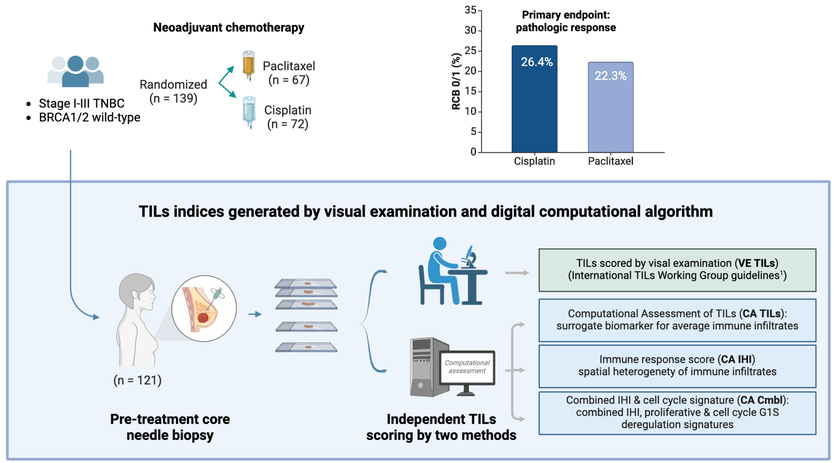

Figure 1: Study design

- Of 139 evaluable patients, 121 had usable data for TILs by both VE and CA (59 received cisplatin, 62 received paclitaxel).
- In the overall population, **VE TILs** and **CA CmbI** were significantly predictive of response (Table 1).
- **VE TILs** had OR 1.86 (95% CI 1.24, 2.87, p=0.031) and AUC 0.69 (95% CI 0.57, 0.80).
- **CA CmbI** had OR 1.54 (95% CI 1.00, 2.42, p=0.053) and AUC 0.62 (95% CI 0.51, 0.73) (Figure 2).
- Neither **CA TILs** nor **CA IHI** were predictive of response.

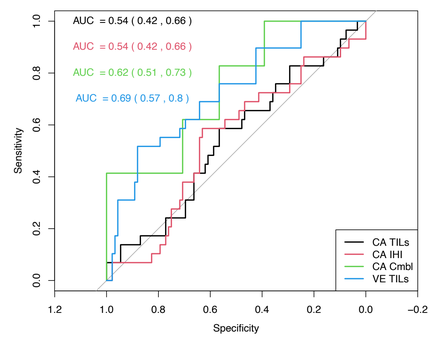

Figure 2: ROC curves for biomarker comparison

- **VE TILs** predicted response to paclitaxel (OR 2.91, 95% CI 1.56, 6.14, p=0.002) but not cisplatin (OR 1.22, 95% CI 0.67, 2.18 p=0.49).
- **CA CmbI** predicted response to paclitaxel (OR 2.70, 95% CI 1.39, 5.95, p= 0.006) but not cisplatin (OR 0.88, 95% CI 0.47, 1.62 p= 0.68).

Table 1: Descriptive statistics for biomarkers by response (RCB 0/1 vs 2/3 or crossover)

Biomarker	RCB (0/1) median (range)	RCB (2/3) median (range)	P value (Wilcoxon test)	OR (95% CI)
Overall population	**N=29**	**N=92**		
VE TILs	**40.0 (0.0,80.0)**	**10.0 (0.0,90.0)**	**0.002**	**1.86 (1.24, 2.87)**
CA TILs	10.2 (1.0,140.3)	8.7 (0.0,122.0)	0.50	1.21 (0.81, 1.78)
CA IHI	403.0 (8.5, 5500.9)	714.8 (-61.3, 4731.4)	0.50	0.99 (0.63, 1.48)
CA CmbI	**0 (-0.75,0.70)**	**-0.05 (-0.75,0.70)**	**0.047**	**1.54 (1.00, 2.42)**
Paclitaxel Arm	**N=15**	**N=47**		
VE TILs	**50.0 (5.0, 80.0)**	**10.0 (0.0, 90.0)**	**<0.001**	**2.91 (1.56, 6.14)**
CA TILs	10.1 (1.0, 32.8)	9.0 (0.0, 81.9)	0.96	0.71 (0.30, 1.33)
CA IHI	319.6 (8.5, 5500.9)	849.8 (8.3, 4731.4)	0.11	0.89 (0.44, 1.59)
CA CmbI	**0.7 (-0.75, 0.70)**	**-0.05 (-0.75, 0.70)**	**0.003**	**2.70 (1.39, 5.95)**
Cisplatin Arm	**N=14**	**N=45**		
VE TILs	15.0 (1.0, 90.0)	10.0 (0.0, 90.0)	0.36	1.22 (0.67, 2.18)
CA TILs	11.0 (2.6, 140.3)	8.6 (2.3, 122.0)	0.33	1.58 (0.91, 2.87)
CA IHI	687.5 (10.9, 2921.0)	548.1 (-61.3, 4461.2)	0.51	1.13 (0.60, 1.99)
CA CmbI	-0.05 (-0.75, 0.70)	0.0 (-0.75, 0.70)	0.65	0.88 (0.47, 1.62)

RCB: residual cancer burden, **OR**: odds ratio, **CI**: confidence interval, **TILs**: tumor infiltrating lymphocytes; **VE TILs**: TILs scored by visual examination; **CA TILs**: TILs scored by computational assessment; **CA IHI**: immune response by computational assessment; **CA CmbI**: combined immune response and cell cycle signature by computational assessment.
The unit increase/decrease of VE TILs and CA TILs is in a scale of 10. The unit increase/decrease of CA IHI is in a scale of 100. The unit increase/decrease of CA CmbI is in a scale of 0.1.

CONCLUSIONS

- **In this analysis of TBCRC 030, VE of baseline TILs and CA CmbI were predictive of response to NAC for TNBC, however CA did not outperform VE.**
- **VE TILs and CA CmbI predicted response to specific chemotherapy.**
- **Automated computational evaluation of TILs or the broader immune microenvironment is an emerging field which may allow accurate and reproducible assessment of these important biomarkers.**

References: 1. Salgado R et al. Ann Oncol 2015; 2. Denkert C et al. Lancet Oncol 2018; 3. Mayer E et al. Ann Oncol 2020.

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