Automated prediction of response to neoadjuvant chemotherapy from digitized H&E slides of pre-treatment core needle biopsies in INFORM (TBCRC 031) patients with low stromal TILs

Stuart J. Schnitt[1,2], Nadine M. Tung[3], Judy Ellen Garber[2] , Satabhisa Mukhopadhyay[4], Tathagata Dasgupta[4], Craig A. Bunnell[2]

1. Brigham and Women's Hospital, Boston, MA; 2. Dana-Farber Cancer Institute, Boston, MA; 3. Beth Israel Deaconess Medical Center, Boston, MA; 4. 4D Path Inc., Newton, MA

Abstract # 611

BACKGROUND

- Previously, an automated analysis (***QPOR™)*** of H&E-stained pre-treatment core needle biopsy (CNB) images from HER2-negative germline BRCA carriers, randomized to neoadjuvant cisplatin vs AC in the INFORM (TBCRC031) [1] study, demonstrated that a digital biomarker of complex immune response (*CmbI*) which combines immune heterogeneity index (***IHI***), proliferative index (*PI*), and cell cycle G1/S deregulation signatures (*G1SI*), was significantly predictive of response (residual cancer burden, RCB 0,1) to neoadjuvant chemotherapy (NAC) in all pts, in sub-cohorts including TNBC, and in both therapy arms [2].
- A lower IHI, indicating less heterogeneity of stromal tumor infiltrating lymphocytes (sTIL), was predictive of a better response to NAC (RCB 0,1), whereas a higher ***IHI***, indicating greater heterogeneity of sTIL was associated with a worse response (RCB 2,3). The predictive performance of ***IHI*** alone was modest compared to *CmbI* but superior to percentage sTIL.
- High sTIL is associated with favorable prognosis for NAC, especially in TNBC. However, the impact of heterogeneity of immune cell distribution on NAC response, particularly in those with low sTIL is unknown. **The current analysis evaluated if *IHI* could augment percentage sTIL assessment by identifying NAC responders in patients with tumors demonstrating low sTIL.**

METHODS

- CNBs scanned at 40x on a Hamamatsu Nanozoomer scanner were evaluated using the 4D QPOR platform to generate ***IHI*** as a continuous index (Figure-1). Among 88 QPOR analyzable pts, 85 had sTIL scores available from prior visual pathologic review.
- Tumors with low sTIL (< 30%, a previously documented clinically significant cut-off [3]) were stratified into low vs high ***IHI*** using median IHI for the population as the cut-off. The relationship between ***IHI*** and response to NAC (RCB 0,1) in the overall cohort, and in the TNBC and ER low (< 10%) sub cohorts were evaluated both for the continuous and dichotomized ***IHI*** using Odds Ratio (OR) with 95% CI, and accuracy, PPV, NPV, Fisher test p-value respectively.
- The immune response signature ***IHI*** computes the intra-slide spatial heterogeneity of immune infiltrates (Figure-1).

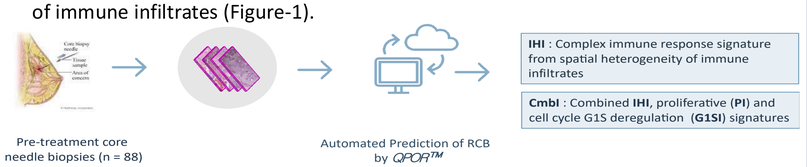


Figure-1: Copies of this poster obtained through Quick Response (QR) Code are for personal use only and may not be reproduced without permission from ASCO® or the author of this poster.

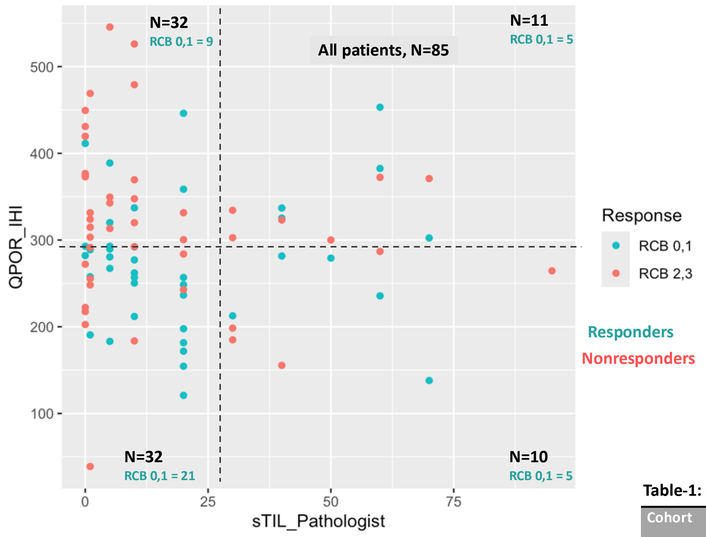


Figure-2: Low IHI was significantly predictive of NAC response (RCB 0,1) in low-sTIL patients in the overall cohort (sTIL<30%, N = 64, OR = 4.75; 95% CI1.50, 16.21), p = 0.005, sensitivity=70%, PPV=66%).

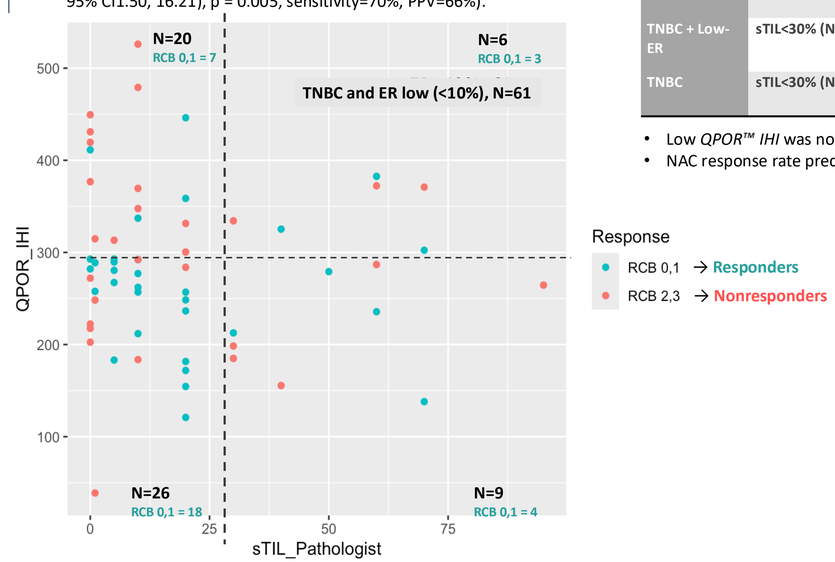
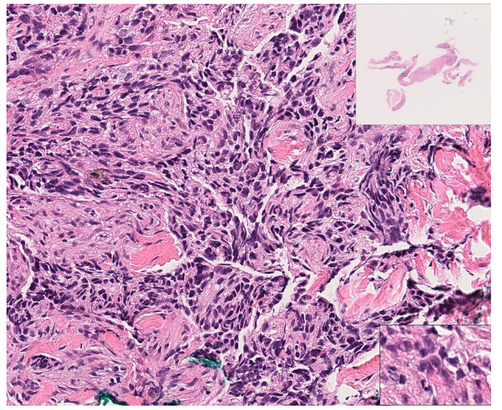
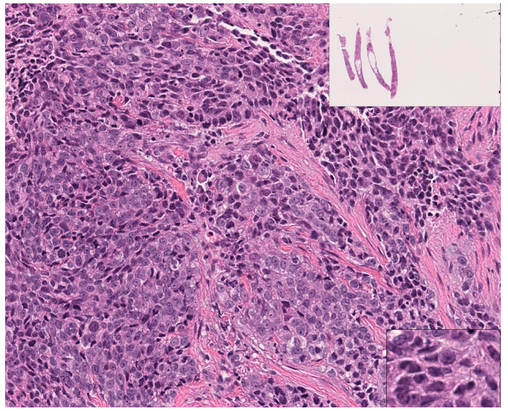


Figure-3: Low IHI was significantly predictive of NAC response (RCB 0,1) in low-sTIL patients in the ER low sub cohort (sTIL<30%, N = 46, OR = 4.04;95% CI 1.04-17.38, p = 0.04, sensitivity=72%, PPV = 69%).

RESULTS



TNBC, 1% sTIL, IHI 277 (low), RCB 0 to Cisplatin



TNBC, 5% sTIL, IHI 546 (high), RCB 3 to Cisplatin

Table-1: Low *QPOR™ IHI* was significantly predictive of NAC response RCB (0,1) in low sTIL HER2- and TNBC patients

Cohort	sTIL status	IHI<median % RCB (0,1)	IHI >= median % RCB (0,1)	Odds ratio (95% CI)	Fisher test p-value	Accuracy	Sensitivity	Specificity	PPV	NPV
Overall	sTIL<30% (N=64)	66% (21/32)	25% (8/32)	4.75 (1.50, 16.21)	0.005	69%	70%	68%	66%	72%
TNBC + Low-ER	sTIL<30% (N=46)	69% (18/26)	35% (7/20)	4.04 (1.04, 17.38)	0.036	68%	72%	62%	69%	65%
TNBC	sTIL<30% (N=41)	74% (17/23)	39% (7/18)	4.28 (0.99, 20.77)	0.031	68%	71%	65%	74%	61%

- Low *QPOR™ IHI* was not predictive of NAC response in tumors with high sTIL.
- NAC response rate predicted by low sTIL and low *QPOR™ IHI* was comparable or better than the NAC response rate measured by high sTIL.

CONCLUSIONS

- **Among germline BRCA carrier HER2- breast cancers with low sTIL there is heterogeneity in the distribution of immune cell infiltrates demonstrating 50% high IHI and 50% low IHI.**
- **The heterogeneity computed by *QPOR™ IHI* was predictive of NAC response in low sTIL tumors. Those with low *IHI* and low sTIL had 66% (21/32) response rate as compared to 25% (8/32) response rate for patients with high *IHI* and low sTIL. Similar response rates were observed for TNBC + ER low patients or TNBC patients alone.**
- **All patients (ER+ and TNBC) with low sTIL and low *IHI* had 66% (21/32) NAC response rate (RCB 0/1) compared to 48% (10/21) NAC response rate in patients with high sTIL.**
- **TNBC patients with low sTIL and low *IHI* had 74% (17/23) NAC response rate (RCB 0/1) compared to 50% (6/12) NAC response rate in patients with high sTIL.**
- **Low IHI was a better predictor of response to NAC than percentage of sTILs in all subtypes.**

References: 1. Tung, N. et al. J Clin Oncol 2020, May 10;38(14):1539-1548.
2. Tung, N. et al. J Clin Oncol 2024 Volume 42, Number 16_suppl https://doi.org/10.1200/JCO.2024.42.16_suppl.605
3. Jong, V. MT et. al, Clin Oncol 2022 Mar 30; 40(21):2361–2374.

Corresponding author: Stuart J. Schnitt, MD
Contact: sschnitt@bwh.harvard.edu

Special Thanks to …
… for their support of the TBCRC

Special thank you to the patients, families, providers and study staff who participated in this trial!!