OXFORD

JNCI: Journal of the National Cancer Institute, 2025, **00(00)**, 1–6

https://doi.org/10.1093/jnci/djaf162
Advance Access Publication Date: July 2, 2025
Brief Communications

Stromal tumor infiltrating lymphocytes and TNBC-DX provide complementary prognostic information in triple-negative breast cancer

Shane R. Stecklein, MD, PhD*[,1,2,3,4,5], Miguel Martín, MD, PhD[6,7,8,9], Guillermo Villacampa, MSc[10,11,12,13], María del Monte-Millan, BSc[6,7,8], Rachel Yoder, MS[4], Harsh Pathak, PhD[2], Sandra Cobo, PhD[12], Fara Brasó-Maristany, PhD[12,13], Enrique L. Álvarez, MSc[6,7], Isabel Echavarría, MD, PhD[6,7,8], Coralia Bueno-Muiño, MD[14], Yolanda Jerez, MD, PhD[6,7,8], María Cebollero, MD, PhD[6,7], Oscar Bueno, MD[6,7], José Á. García-Saenz, MD, PhD[9,15], Fernando Moreno, MD, PhD[9,15], Henry L. Gómez, MD, PhD[16], Tatiana Massarrah, BSN[6,7,8], Blanca Herrero, MD[6,7,9], Laia Paré, PhD[13], Mercedes Marín-Aguilera, PhD[13], Wesley Buckingham, BSci[13], Sara López-Tarruella, MD, PhD[6,7,8,9,10], Patricia Villagrasa, PhD[13], Andrew K. Godwin, PhD[2,4,17], Roberto Salgado, MD, PhD[18,19], Aleix Prat, MD, PhD[12,13,20,21,22], Priyanka Sharma, MD[4,23]

[1]Department of Radiation Oncology, University of Kansas Medical Center, Kansas City, KS, United States
[2]Department of Pathology & Laboratory Medicine, University of Kansas Medical Center, Kansas City, KS, United States
[3]Department of Cancer Biology, University of Kansas Medical Center, Kansas City, KS, United States
[4]The University of Kansas Cancer Center, Kansas City, KS, United States
[5]Department of Breast Radiation Oncology, MD Anderson Cancer Center, Houston, TX, United States
[6]Hospital General Universitario Gregorio Marañón, Madrid, Spain
[7]Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain
[8]Centro de Investigación Biomédica en Red de Cáncer, Madrid, Spain
[9]Grupo Español de Investigación en Cáncer de Mama, Madrid, Spain
[10]SOLTI Cancer Research Group, Barcelona, Spain
[11]Statistics Unit, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain
[12]Translational Genomics and Targeted Therapies in Solid Tumors, August Pi I Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain
[13]Reveal Genomics, Barcelona, Spain
[14]Hospital Infanta Cristina (Parla), Madrid, Spain
[15]Instituto de Investigación Sanitaria Hospital Clínico San Carlos (IdISSC), Madrid, Spain
[16]Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru
[17]Kansas Institute for Precision Medicine, University of Kansas Medical Center, Kansas City, KS, United States
[18]Department of Pathology, GZA-ZNA Hospitals, Antwerp, Belgium
[19]Division of Research, Peter MacCallum Cancer Centre, Melbourne, Australia
[20]Cancer and Blood Disorders Institute, Hospital Clínic Barcelona, Barcelona, Spain
[21]Department of Medicine, University of Barcelona, Barcelona, Spain
[22]Breast Cancer Unit, IOB-QuirónSalud, Barcelona, Spain
[23]Division of Medical Oncology, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, KS, United States

*Corresponding author: Shane Stecklein, MD, PhD, Department of Radiation Oncology, University of Kansas Medical Center, 4001 Rainbow Blvd, Kansas City, KS 66160, United States (sstecklein@kumc.edu)

Abstract

Patients with triple-negative breast cancer (TNBC) who achieve pathologic complete response (pCR) to neoadjuvant systemic therapy have favorable survival, while those with residual disease have high recurrence risk. Stromal tumor infiltrating lymphocytes (sTILs) and TNBC-DX both predict pCR in TNBC. Whether these 2 biomarkers provide complementary information has not been tested. We evaluated sTILs and TNBC-DX in TNBC patients treated with docetaxel-carboplatin (TCb) on the MMJ-CAR-2014-01 study (NCT01560663) or TCb plus pembrolizumab (TCb+Pem) on the NeoPACT trial (NCT03639948). sTILs and TNBC-DX independently predicted pCR in patients treated with TCb+Pem. Patients with sTILs ≥ 30% and a TNBC-DX pCR-high genomic score achieved a pCR rate of 91.3% with TCb+Pem. An integrated classification incorporating sTILs and TNBC-DX identified approximately 40% of the NeoPACT cohort with a pCR rate exceeding 85%. The integrated classification was prognostic for event-free survival in patients treated with TCb+Pem. Integrating sTILs and TNBC-DX may facilitate chemoimmunotherapy escalation and de-escalation trials.

Neoadjuvant systemic therapy (NAST) is the standard-of-care for patients with early-stage high-risk triple-negative breast cancer (TNBC)[1] and response to NAST predicts long-term survival.[2,3] Immunologic enrichment, defined by either high levels of stromal tumor infiltrating lymphocytes (sTILs) or various gene expression-based biomarkers of immunologic enrichment, is a

Received: March 11, 2025. **Revised:** May 19, 2025. **Accepted:** June 13, 2025
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Table 1. Univariate and multivariate analysis of pCR.

	MMJ-CAR-2014-01		NeoPACT	
	OR (95% CI)	P	OR (95% CI)	P
Univariate model				
Nodal status				
Negative	Ref	—	Ref	—
Positive	0.68 (0.42 to 1.09)	.105	0.42 (0.19 to 0.93)	.033
sTILs (each 10% increment)	1.16 (1.06 to 1.26)	.001	1.27 (1.11 to 1.46)	.001
sTILs				
Low (<5%)	Ref	—	Ref	—
Medium (5%-29%)	1.70 (0.95 to 3.02)	.073	1.60 (0.56 to 4.62)	.382
High (≥30%)	3.13 (1.74 to 5.62)	<.001	5.61 (2.10 to 15.03)	.001
TNBC-DX pCR score (each 10-percentile increment)	1.35 (1.22 to 1.50)	<.001	1.46 (1.17 to 1.82)	.001
TNBC-DX pCR				
Low	Ref	—	Ref	—
Medium	3.94 (2.16 to 7.19)	<.001	3.39 (1.28 to 8.97)	.014
High	5.53 (2.90 to 10.53)	<.001	7.25 (2.55 to 20.62)	<.001
Multivariate model (continuous variables)				
Nodal status				
Negative	Ref	—	Ref	—
Positive	1.02 (0.60 to 1.75)	.932	0.44 (0.17 to 1.13)	.087
sTILs (each 10% increment)	1.03 (0.93 to 1.14)	.521	1.26 (1.09 to 1.46)	.002
TNBC-DX pCR Score (each 10-percentile increment)	1.33 (1.18 to 1.49)	<.001	1.28 (1.03 to 1.61)	.029
Multivariate model (categorical variables)				
Nodal status				
Negative	Ref	—	Ref	—
Positive	0.94 (0.55 to 1.60)	.817	0.47 (0.17 to 1.31)	.149
sTILs				
Low (<5%)	Ref	—	Ref	—
Medium (5%-29%)	1.28 (0.69 to 2.39)	.438	0.96 (0.29 to 3.20)	.949
High (≥30%)	1.67 (0.85 to 3.29)	.141	4.04 (1.25 to 13.02)	.019
TNBC-DX pCR				
Low	Ref	—	Ref	—
Medium	3.63 (1.90 to 6.95)	<.001	1.97 (0.64 to 6.05)	.237
High	4.11 (1.95 to 8.68)	<.001	3.76 (1.05 to 13.41)	.041

known predictor of response to NAST.[4-7] TNBC-DX is a 15-gene test which integrates a 10-gene core immune module (*CD274*, *CD79A*, *CXCR6*, *IRF4*, *LAX1*, *PDCD1*, *PIM2*, *POU2AF1*, *SLAMF1*, and *TNFRSF17*), a 4-gene tumor cell proliferation module (*EXO1*, *ASPM*, *NEK2*, and *KIF23*) and *ERBB2*, with tumor size (T1, T2, and T3-4 categories) and nodal involvement (N0, N1, and N2-3 categories); it has been validated as a reliable predictor of pathologic complete response (pCR) in multiple cohorts of TNBC patients treated with NAST with or without immunotherapy.[8] We previously showed that while sTILs were prognostic on univariate analysis in TNBC treated without neoadjuvant immunotherapy, sTILs were not independently prognostic in multivariate models that included TNBC-DX pCR.[8] Whether sTILs and TNBC-DX pCR provide complementary prognostic information in TNBC receiving neoadjuvant chemoimmunotherapy remains uncertain.

We analyzed sTILs and TNBC-DX pCR in 280 patients with TNBC treated with neoadjuvant carboplatin plus docetaxel (TCb) on the MMJ-CAR-2014-01 study (NCT01560663)[9] and 108 patients with TNBC treated with neoadjuvant TCb plus pembrolizumab (TCb+Pem) on the NeoPACT trial (NCT03639948).[10] All research was conducted in accordance with ethical standards of the Helsinki Declaration, and both studies were approved by the relevant institutional review board. sTILs were centrally evaluated by a single expert pathologist (R.S.) according to international consensus guidelines.[11] Tumors were categorized as sTIL-low (<5%), sTIL-medium (5%-29%), or sTIL-high (≥30%). The ≥30% threshold was chosen to define sTIL-high as it has been shown to be prognostic in multiple studies, exhibits good pathologist interrater reliability, and is being used in ongoing prospective trials to assign treatment.[10,12-14] The TNBC-DX genomic score was calculated and pre-established cut-offs defined TNBC-DX pCR-low, -medium, and -high groups. Absolute rates of pCR were calculated for groups defined by both sTILs and TNBC-DX pCR groups. Binary logistic regression models were used to assess the association between sTILs, TNBC-DX pCR, and pCR. $P < .05$ defined statistical significance, and all statistical tests were 2-sided.

Patient and tumor characteristics for patients from both cohorts have been previously reported.[9,10,14] Patients treated on MMJ-CAR-2014-01 (TCb) were older, less likely to be Black, had a higher presenting clinical TNM stage, and lower levels of sTIL infiltration compared to patients treated on NeoPACT (TCb+Pem). The overall pCR rate in MMJ-CAR-2014-01 and NeoPACT was 51% (95% CI = 45% to 57%) and 58% (95% CI = 49% to 68%), respectively. As continuous variables, sTILs and TNBC-DX pCR were moderately correlated (Spearman $\rho = 0.46$, $P < .001$). On univariate analysis, sTILs and TNBC-DX pCR were associated with pCR as both continuous and categorical variables in patients treated with TCb and TCb+Pem (Table 1). On multivariate analysis including nodal status and TNBC-DX pCR, sTILs were not prognostic in patients treated with TCb but were prognostic in patients treated with TCb+Pem (Table 1).

Patients in both treatment cohorts were classified according to sTILs and TNBC-DX pCR categories (Figure 1, A and B) and pCR rates were calculated for each group (Figure 1, C and D). In the TCb+Pem-treated cohort with sTILs ≥ 30% and a TNBC-DX pCR-high genomic score, the pCR rate was 91.3% (Figure 1, D). Since sTILs and TNBC-DX pCR were independently prognostic among patients treated with TCb+Pem, we designated integrated-low

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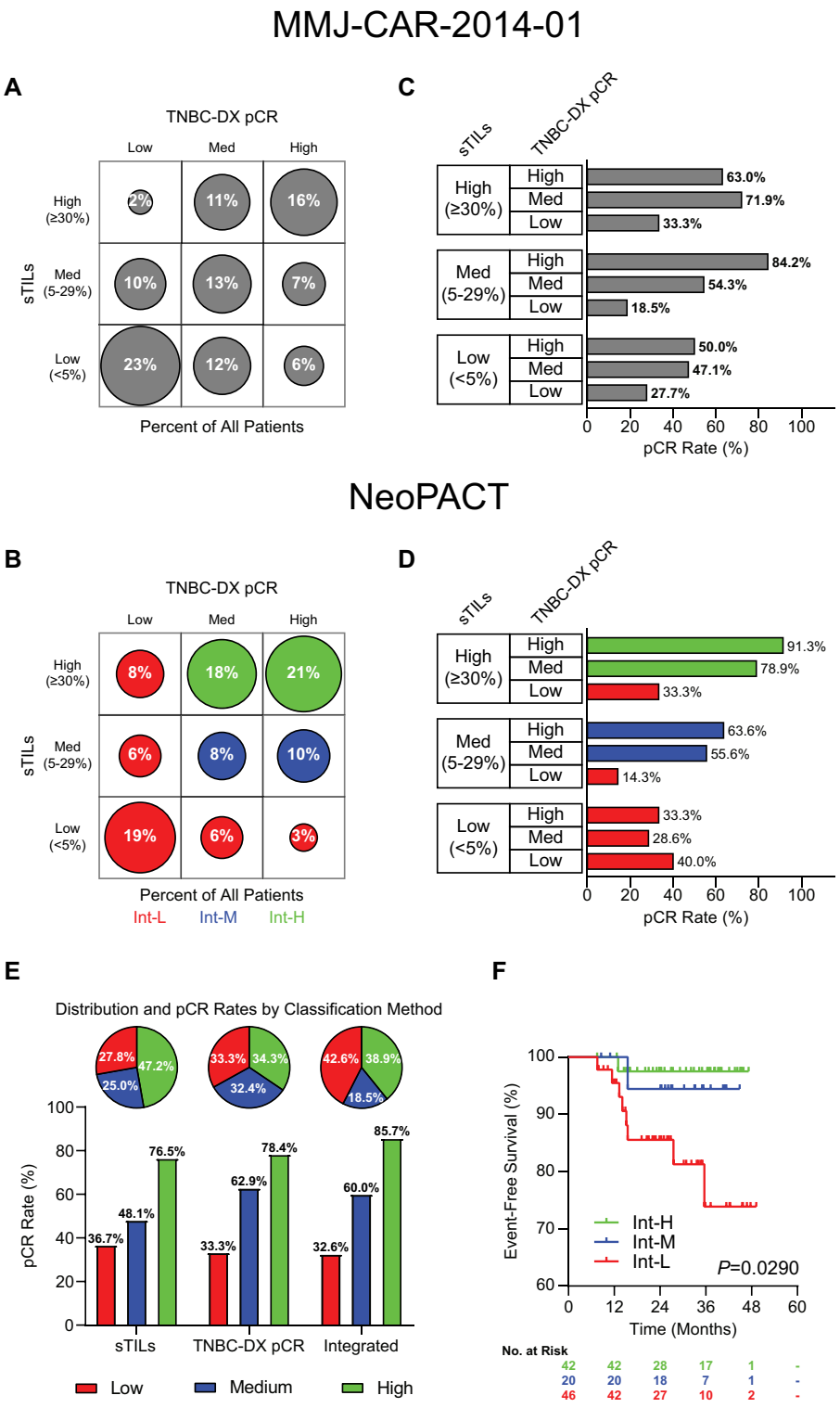

Figure 1. Classification and Prognostication of TNBC by sTILs and TNBC-DX pCR. Classification of patients on MMJ-CAR-2014-01 (**A**) and NeoPACT (**B**) based on categorical sTIL and TNBC-DX pCR classification. Size of circle and value represent percent of all patients within each study with that dual classification. In (**B**), red denotes Int-L, blue denotes Int-M, and green denotes Int-H integrated classification incorporating sTILs and TNBC-DX pCR. pCR rates within each sTIL and TNBC-DX pCR classification in MMJ-CAR-2014-01 (**C**) and NeoPACT (**D**). (**E**) Pie charts show the distribution of patients by classification method and bar graphs show pCR rates by sTILs, TNBC-DX pCR, and the integrated classification in NeoPACT. (**F**) Event-free survival within Int-L, Int-M, and Int-H integrated classification groups for NeoPACT. *P* is log-rank statistic.

(Int-L; low sTILs and/or low TNBC-DX pCR), integrated-medium (Int-M; medium sTILs and medium/high TNBC-DX pCR), and integrated-high (Int-H; high sTILs and medium/high TNBC-DX pCR) groups within the NeoPACT cohort (Figure 1, B). We then calculated the distribution of patients based on sTILs, TNBC-DX pCR, and the integrated classification (Figure 1, E). Use of the integrated classification gave the broadest discrimination in pCR rates between the 3 risk groups while also partitioning the most

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patients into discrete low- or high-pCR groups (81.5% for integrated vs 67.6% for TNBC-DX pCR vs 75.0% for sTILs) (Figure 1, E). The integrated classification also improved discrimination performance in predicting pCR compared to categorical sTILs alone and categorical TNBC-DX pCR alone (C-statistics 0.693 [sTILs], 0.707 [TNBC-DX pCR], and 0.763 [integrated classification]). Notably, the Int-H group accounts for nearly 40% of the NeoPACT cohort, and the pCR rate among this group of patients exceeded 85% (Figure 1, E). The integrated classification was prognostic for event-free survival in patients treated with TCb+Pem (Figure 1, F). In NeoPACT, compared to the Int-L group, the Int-M group had numerically higher EFS (94% vs 74%; HR = 0.26, 95% CI = 0.03 to 2.05, $P = .20$) and the Int-H group had significantly higher EFS (98% vs 74%; HR = 0.12, 95% CI = 0.02 to 0.94, $P = .04$). The integrated classification was not associated with EFS within pCR ($P = .23$) and no pCR ($P = .74$) groups, though this analysis is limited by low event numbers within subgroups.

In summary, we show that sTILs and the TNBC-DX genomic classifier independently predict pCR in TNBC treated with neoadjuvant docetaxel-carboplatin chemotherapy plus pembrolizumab, suggesting that gene expression and sTILs provide distinct and potentially complementary information. To our knowledge, this is the first analysis of prospectively treated TNBC patients that shows independent prognostic utility of sTILs and a validated genomic assay. Among patients with sTILs ≥ 30% and a TNBC-DX pCR-high genomic score who received chemoimmunotherapy, the pCR rate was 91.3%. To our knowledge, a biomarker-selected TNBC subgroup predicted to achieve a pCR rate of >90% has not been identified to date. Moreover, the subgroup we defined as Int-H accounted for approximately 40% of patients treated with chemoimmunotherapy, and the pCR rate in this group still exceeded 85%. Patients with a TNBC-DX pCR-low score and/or sTILs <5% also accounted for approximately 40% of patients treated with chemoimmunotherapy, and only one-third of these patients achieved a pCR with chemoimmunotherapy, which is substantially below the pCR rate observed in unselected TNBC patients treated with chemoimmunotherapy.[10,15] Use of an integrated classification system with both biomarkers was associated with event-free survival in the TCb+Pem-treated cohort. Limitations of our current analysis include the low number of EFS events within NeoPACT, lack of a validation cohort of patients treated with chemoimmunotherapy, and limitations in making inferences about subgroups given the relatively small number of patients in each category. There are notable differences in disease burden between the MMJ-CAR-2014-01 and NeoPACT cohorts that may confound comparisons between these studies. Although the MMJ-CAR-2014-01 cohort had a larger proportion of patients with higher T stage and nodal involvement, these 2 variables are incorporated into the TNBC-DX score, which allows for interstudy comparison of the assay between the 2 cohorts. Although T stage and nodal involvement are incorporated into TNBC-DX, other differences between MMJ-CAR-2014-01 and NeoPACT could impact the validity of interstudy comparisons and the generalizability of our findings to other populations. Validation of TNBC-DX is planned in our ongoing NeoTRACT trial (NCT05645380), which is prospectively assessing chemoimmunotherapy de-escalation based on sTILs and radiographic response. Integrated analysis of sTILs and TNBC-DX may be of use to identify patients suitable for future chemoimmunotherapy de-escalation and escalation trials. Specifically, we posit that patients with an Int-L biomarker profile are high-risk and could be ideal candidates for studies evaluating intensification of neoadjuvant therapy, while patients with an Int-H biomarker profile might be suitable for trials that are examining personalized de-escalation of neoadjuvant systemic therapy.

Author contributions

Shane R. Stecklein (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Visualization, Writing—original draft, Writing—review & editing), Miguel Martín (Conceptualization, Data curation, Formal analysis, Writing—original draft, Writing—review & editing), Guillermo Villacampa (Data curation, Formal analysis, Writing—original draft, Writing—review & editing), María del Monte-Millan (Data curation, Writing—review & editing), Rachel Yoder (Data curation, Formal analysis, Project administration, Writing—review & editing), Harsh Pathak (Data curation, Methodology, Writing—review & editing), Sandra Cobo (Data curation, Project administration, Writing—review & editing), Fara Brasó-Maristany (Data curation, Methodology, Writing—review & editing), Enrique L. Álvarez (Data curation, Formal analysis, Writing—review & editing), Isabel Echavarría (Data curation, Writing—review & editing), Coralia Bueno-Muiño (Data curation, Writing—review & editing), Yolanda Jerez (Data curation, Writing—review & editing), María Cebollero (Data curation, Writing—review & editing), Oscar Bueno (Data curation, Writing—review & editing), José Á García-Saenz (Data curation, Writing—review & editing), Fernando Moreno (Data curation, Writing—review & editing), Henry L Gómez (Data curation, Writing—review & editing), Tatiana Massarrah (Data curation, Writing—review & editing), Blanca Herrero (Data curation, Writing—review & editing), Laia Paré (Data curation, Formal analysis, Investigation, Writing—review & editing), Mercedes Marín-Aguilera (Data curation, Methodology, Writing—review & editing), Wesley Buckingham (Data curation, Methodology, Writing—review & editing), Sara López-Tarruella (Data curation, Writing—review & editing), Patricia Villagrasa (Data curation, Methodology, Writing—review & editing), Andrew K. Godwin (Data curation, Funding acquisition, Project administration, Resources, Writing—review & editing), Roberto Salgado (Data curation, Formal analysis, Methodology, Resources, Writing—review & editing), Aleix Prat (Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing—original draft, Writing—review & editing), and Priyanka Sharma (Conceptualization, Data curation, Funding acquisition, Project administration, Resources, Writing—original draft, Writing—review & editing).

Funding

This work was supported by Reveal Genomics; the European Union's Horizon 2020 Research and Innovation Programme under the Marie Skłodowska–Curie grant (955951); Fundación CRIS contra el cáncer (PR_EX_2021-14); Agència de Gestó d'Ajuts Universitaris i de Recerca (2021 SGR 01156); Fundación Fero BECA (ONCOXXI21); Instituto de Salud Carlos III and co-funded by the European Union (PI22/01017, PI18/01775, PI22/01346); Asociación Cáncer de Mama Metastásico IV Premios M. Chiara Giorgetti, Breast Cancer Research Foundation (BCRF-22-198); Asociación Beca Marta Santamaria; RESCUER; the European Union's Horizon 2020 Research and Innovation Programme (847912); Fundación Científica AECC Ayudas Investigador AECC 2021

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(INVES21943BRAS); and Fundación Contigo (HIMALAIA). The NeoPACT trial was supported by The University of Kansas Cancer Center (KUCC); the National Institutes of Health Cancer Center Support Grant to KUCC (P30 CA168524) and the National Institute of General Medical Sciences to the KUCC Biospecimen Repository Core Facility (P20 GM130423); the KUCC ACS-IRG Pilot award; University of Kansas Medical Center Research Institute (Lied Pilot award); The Kansas Institute for Precision Medicine (P20 GM130423); National Institutes of Health KL2 award (KL2TR002367-05); Congressionally Directed Medical Research Programs Breast Cancer Research Program (W81XWH-22-1-0322, W81XWH-22-1-0323); Team Michelle; and by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Conflicts of interest

M.M.: Speaker fee: AstraZeneca, Amgen, Roche/Genentech, Novartis, Daiichi Sankyo, Pfizer; Consultant fee: AstraZeneca, Amgen, Taiho Oncology, Roche/Genentech, Novartis, PharmaMar, Eli Lilly, PUMA, Pfizer; Research support: Roche, Novartis, PUMA. G.V.: Speaker fee: Pfizer, MSD, GSK, Pierre Fabrer; Advisory role: AstraZeneca; Consultant fee: Reveal Genomics I.E.: Speaker fee: Pfizer, Roche, Novartis, Lilly, Gilead, Daiichi Sankyo, Pierre Fabre, AstraZeneca; Advisory role: Lilly AstraZeneca, Daiichi Sankyo; Travel support: Pfizer, Roche, Novartis, Lilly, Gilead, Daiichi Sankyo, AstraZeneca. C.B.M.: Speaker fee: Roche, Novartis, Lilly, Pfizer, MSD, Daiichi Zankyo, AstraZeneca; Travel Support: Roche, Novartis, Daiichi Sankyo, AstraZeneca, Pfizer. Y.J.: Speaker fee: Roche, Novartis, Lilly, Daiichi Sankyo, AstraZeneca; Travel and training support: Roche, Novartis, Pfizer, Daiichi Sankyo, Gilead, Lilly. J.A.G.S.: Speaker fee: Lilly, MSD, Exact Sciences, Tecnofarma, Nolver (Adium), Asofarma, Roche; Advisory role: Seagen, AstraZeneca, Daiichi Sankyo, Novartis, Gilead, Menarini; Research support: AstraZeneca; Travel support: Gilead, AstraZeneca, Daiichi Sankyo. F.M.: Advisory role: Seagen, MSD, Roche, Daiichi Sankyo, Pfizer, Gilead, Menarini; Research support: Pfizer; Travel support: Gilead, Pfizer, Lilly. B.H.: Speaker fee: Roche, Novartis, PharmaMar, Eisai, Pfizer, Teva, Kyowa Kirin, AstraZeneca, GSK, Daiichi Sankyo, Gilead, MSD; Advisory role: Daiichi Sankyo, AstraZeneca; Research support: Daiichi Sankyo, AstraZeneca; Travel and training support: Roche, Pfizer, Novartis, Merck. L.P.: Employee of Reveal Genomics; Patents: EP23383369, EP23382703, PCT/EP2021/070788, PCT/EP2024/068197. M.M.A.: Employee of Reveal Genomics. W.B.: Employee of Reveal Genomics. S.L.T.: Speaker fee: Lilly; Advisory role: AstraZeneca, Daiichi Sankyo, Gebro Pharma, Gilead, GSK, Lilly, Menarini Stemline, MSD, Novartis, Pfizer, Pierre Fabre, Roche, Seagen, Veracyte. P.V.: Employee of Reveal Genomics; Patents: PCT/EP2021/086493, PCT/EP2023/060810. A.P.: Speaker fee: AstraZeneca, Roche, Novartis, Daiichi Sankyo; Advisory role: AstraZeneca, Roche, Pfizer, Novartis, Daiichi Sankyo, Peptomyc; Research support: AstraZeneca, Novartis, Roche, Daiichi Sankyo; Stockholder and employee of Reveal Genomics; Patents: PCT/EP2016/080056, PCT/EP2022/086493, PCT/EP2023/060810, EP23382703, and EP23383369. P.S.: Advisory role: Merck, Gilead, Genzyme Corporation (Sanofi), Novartis, AstraZeneca, GSK, Pfizer, Exact Sciences, Lilly, Menarini Stemline. S.R.S., M.D.M.M., R.Y., H.P., S. C., F.B.M., E.L.A., M.C., O.B., H.L.G., T.M., A.K.G., R.S. have declared no conflict of interest.

The statistical analysis in this manuscript was independently performed by investigators not affiliated with Reveal Genomics.

Data availability

Any requests for anonymized trial data or supporting material will be reviewed on a case-by-case basis. Only requests that have scientifically and methodologically sound proposals will be considered, and the usage of the shared trial data or supporting material will be limited to the approved proposal. The final decision as to whether data or supporting material might be shared and the exact data or supporting material to be shared will be made between the trial team and the principal investigators. Proposals should be directed to the corresponding author.

Acknowledgments

The funders did not play a role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. This work was presented in part at the 2024 San Antonio Breast Cancer Symposium.

References

1. Schmid P, Cortes J, Dent R, et al. KEYNOTE-522 Investigators. Overall survival with pembrolizumab in early-stage triple-negative breast cancer. *N Engl J Med*. 2024;391:1981-1991.
2. Spring LM, Fell G, Arfe A, et al. Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: a comprehensive meta-analysis. *Clin Cancer Res*. 2020;26:2838-2848.
3. Yau C, Osdoit M, van der Noordaa M, et al. I-SPY 2 Trial Consortium. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. *Lancet Oncol*. 2022;23:149-160.
4. Loi S, Drubay D, Adams S, et al. Tumor-infiltrating lymphocytes and prognosis: a pooled individual patient analysis of early-stage triple-negative breast cancers. *J Clin Oncol*. 2019;37:559-569.
5. Dugo M, Huang CS, Egle D, et al. The immune-related 27-gene signature DetermaIO predicts response to neoadjuvant atezolizumab plus chemotherapy in triple-negative breast cancer. *Clin Cancer Res*. 2024;30:4900-4909.
6. Shepherd JH, Ballman K, Polley MC, et al. CALGB 40603 (Alliance): long-term outcomes and genomic correlates of response and survival after neoadjuvant chemotherapy with or without carboplatin and bevacizumab in triple-negative breast cancer. *J Clin Oncol*. 2022;40:1323-1334.
7. Sinn BV, Loibl S, Hanusch CA, et al. Immune-related gene expression predicts response to neoadjuvant chemotherapy but not additional benefit from PD-L1 inhibition in women with early triple-negative breast cancer. *Clin Cancer Res*. 2021;27:2584-2591.
8. Martin M, Stecklein SR, Gluz O, et al. TNBC-DX genomic test in early-stage triple-negative breast cancer treated with neoadjuvant taxane-based therapy. *Ann Oncol*. 2025;36:158-171.
9. Echavarria I, Lopez-Tarruella S, Picornell A, et al. Pathological response in a triple-negative breast cancer cohort treated with neoadjuvant carboplatin and docetaxel according to Lehmann's refined classification. *Clin Cancer Res*. 2018;24:1845-1852.
10. Sharma P, Stecklein SR, Yoder R, et al. Clinical and biomarker findings of neoadjuvant pembrolizumab and carboplatin plus

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docetaxel in triple-negative breast cancer: NeoPACT Phase 2 Clinical Trial. *JAMA Oncol*. 2024;10:227-235.
11. Salgado R, Denkert C, Demaria S, et al. International TILs Working Group 2014. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. *Ann Oncol*. 2015;26:259-271.
12. de Jong VMT, Wang Y, Ter Hoeve ND, et al. Prognostic value of stromal tumor-infiltrating lymphocytes in young, node-negative, triple-negative breast cancer patients who did not receive (neo) adjuvant systemic therapy. *J Clin Oncol*. 2022;40:2361-2374.
13. Leon-Ferre RA, Jonas SF, Salgado R, et al. International Immuno-Oncology Biomarker Working Group. Tumor-infiltrating lymphocytes in triple-negative breast cancer. *JAMA*. 2024;331:1135-1144.
14. Martin M, Yoder R, Salgado R, et al. Tumor-infiltrating lymphocytes refine outcomes in triple-negative breast cancer treated with anthracycline-free neoadjuvant chemotherapy. *Clin Cancer Res*. 2024;30:2160-2169.
15. Schmid P, Cortes J, Pusztai L, et al. KEYNOTE-522 Investigators. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382:810-821.

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JNCI: Journal of the National Cancer Institute, 2025, 00, 1–6
https://doi.org/10.1093/jnci/djaf162
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