

TROP2 Expression and Therapeutic Opportunities in Inflammatory Breast Cancer

Shayla Murray[1,2], Azadeh Nasrazadani[2,3], Clinton Yam[2], Angela Alexander[2,3], Oleg Baranov[5], Daria Goncharova[5], Francesca Paradiso[5], Michael Hensley[5], The MDACC IBC Team[3], Wendy A. Woodward[3,4], Bora Lim[2,3]

[1] Drexel University College of Medicine; [2] Breast Medical Oncology; [3] Morgan Welch IBC Research and Clinic Program; [4] Breast Radiation Oncology; [5] BostonGene Corporation

Abstract

RNA-seq data were analyzed using the BostonGene transcriptomic platform. Tumor samples were obtained from the Morgan Welch IBC Registry and related MD Anderson protocols under IRB approval. TROP2 expression was quantified and classified as high, medium, or low. A total of 71 IBC samples were compared with 631 non-IBC tumors, including no-special-type (NST), TNBC, and PAM50-matched subtypes (basal-like, luminal, and HER2-enriched). Univariate analyses assessed expression differences across groups, and progression-free survival (PFS) was evaluated in a subset of 11 IBC patients treated with SG. No statistically significant difference in overall TROP2 expression was observed between IBC and non-IBC tumors. In subtype-matched analyses, 15 of 22 basal-like IBC cases had TROP2 expression above the median of basal-like non-IBC, though this was not significant. TROP2 levels did not differ between HR+ and TNBC IBC subtypes (p = 0.67). Among SG-treated patients, higher TROP2 expression trended toward longer PFS (mean 1142 vs. 983 days for high vs. low expressors), but the correlation was minimal (r = 0.084).

Introduction

- Inflammatory Breast Cancer (IBC) is characterized by rapid onset, dermal lymphatic tumor emboli, and high rates of nodal and distant metastasis, reflecting a uniquely inflammatory and immune-evasive tumor microenvironment (TME).
- Antibody–drug conjugates (ADCs) have emerged as effective therapeutic options in hard-to-treat breast cancers, notably sacituzumab govitecan (SG), which delivers SN-38 via TROP2 (TACSTD2) targeting.
- TROP2 is a transmembrane glycoprotein overexpressed in multiple epithelial malignancies and associated with cell proliferation, migration, and poor prognosis.
- Early data from metastatic TNBC and HR+/HER2– trials (ASCENT, TROPiCS-02) support TROP2 as a clinically validated target, but its expression profile and spatial distribution in IBC remain poorly characterized.

Based on this, we aim to:
1) Establish the consistency and spatial localization of TACSTD2/ **TROP2 expression** in IBC across molecular subtypes (TNBC, HR+/HER2–, HER2+).
2) Correlate **TROP2 expression** intensity and pattern with clinical–pathologic variables, including response to neoadjuvant therapy and presence of residual disease.

Methods and Materials

- Cohorts: IBC and non-IBC tumors were collected through the Morgan Welch IBC Program and related MD Anderson registries under IRB-approved protocols.
- RNA-seq Profiling: Transcriptomic data were analyzed using the BostonGene platform, applying standardized normalization and subtype classification.
- TROP2 Quantification: TACSTD2 (TROP2) expression was categorized as high, medium, or low based on normalized RNA-seq values.
- Comparative Groups: 71 IBC samples were compared with 631 non-IBC cases, including NST, TNBC, and PAM50-matched subtypes (basal-like, luminal, HER2-enriched).
- Statistical Analyses: Univariate tests evaluated differences in TROP2 expression across groups.
- Clinical Correlation: In a subset of 11 IBC patients treated with sacituzumab govitecan (SG), progression-free survival (PFS) was analyzed relative to TROP2 levels.
- Goal: To define the pattern and clinical relevance of TROP2 expression in IBC and its potential as a predictive biomarker for ADC therapy.

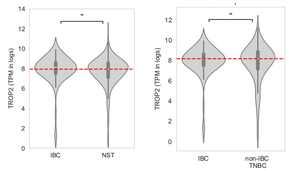


Figure 1. TROP2 level Violin plots show A) comparable TROP2 (TACSTD2) transcript expression between IBC and non-IBC tumors (NST). Red dashed line indicates cohort median. B) same comparison between IBC and no-IBC triple negative breast cancers (TNBCs). TROP2 is broadly expressed across both groups, suggesting its stability as a surface target in aggressive breast cancers.

Table 1. TROP2 levels per transcriptomic measurement and PFS in IBC patients, treated with Anti-TROP2 antibody drug conjugate, SG. TROP2 expression was called as low, medium, high using median expression among TNBC tumors.

Subject	TROP2 expression compared to TNBC NST (Low/Med/High)	PFS (days)	HR vs TN-IBC
1	Med	958	TN-IBC
2	Med	862	TN-IBC
3	Med	1023	TN-IBC
4	High	1180	TN-IBC
5	High	1074	TN-IBC
6	Low	991	HR+IBC
7	Med	1128	HR+IBC
8	Low	975	TN-IBC
9	Med	1130	HR+IBC
10	Low	682	HR+IBC
11	High	1210	HR+IBC

Results

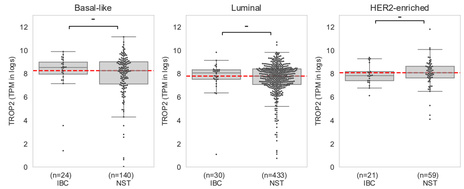


Figure 2. TROP2 expression level per molecular subtypes, A) basal-like IBC vs NST showed numerically higher level in IBC compared to NST ; while luminal IBC had numerically higher but not statistically significant. C) The HER2 enriched subtype had numerically lower level of TROP2 but not statistically significant. None of levels showed difference. The TROP2 level in IBC appear to be more homogeneous compared to NST.

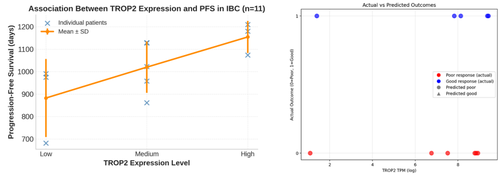


Figure 3. TROP2 expression level and the correlation with response prediction. *Association between TROP2 expression and PFS in SG-treated IBC.* Scatter plot with mean ± SD (orange line) shows a mild, non-significant trend toward longer progression-free survival (PFS) with increasing TROP2 expression. Transcript-level expression alone did not predict SG benefit, indicating that TROP2 may be necessary but not sufficient as a response biomarker. B) *Comparison of actual vs. predicted outcomes in SG-treated IBC.*. observed versus predicted outcomes highlight limited predictive value of TROP2 transcript levels for therapeutic response, reinforcing the need for integrated, multivariate modeling.

- TROP2 is consistently expressed across both IBC and non-IBC tumors, supporting its potential as a therapeutic target in aggressive breast cancer.
- No strong correlation was observed between TROP2 expression levels and sacituzumab govitecan (SG) response.
- Transcript-level expression alone may be insufficient as a predictive biomarker, particularly within the biologically homogeneous IBC cohort, where TROP2 levels are uniformly high.
- Despite this, TROP2-directed strategies may retain therapeutic value in HER2-negative IBC, offering an additional targeted approach in a population with limited options.

Discussion

- Within IBC, TROP2 transcript levels alone did not predict response to SG, suggesting that while target expression is necessary for ADC delivery, it is not sufficient to determine benefit, likely reflecting the complex tumor immune microenvironment (TiME) of IBC. We observed contribution of TiME in response/clinical outcome in other studies.
- The uniformly high TROP2 expression seen in IBC may reflect a ceiling effect, reducing discriminatory power in predicting SG outcomes, particularly in a relatively homogeneous cohort – yet providing new therapeutic opportunity integrating TROP2 targeting as part of induction therapy as example.
- Basal-like IBC cases demonstrated slightly higher expression relative to non-IBC counterparts, supporting the rationale for HER2-negative, basal-enriched IBC subsets as potential candidates for TROP2-targeted strategies.
- The modest PFS trend in high expressors indicates that ADC efficacy may depend on factors beyond expression, including drug internalization, payload sensitivity, or microenvironmental resistance mechanisms.

Conclusions

- Transcript-level TROP2 expression did not predict sacituzumab govitecan (SG) benefit, suggesting that expression alone may be insufficient as a biomarker—particularly within the relatively homogeneous HER2 negative IBC cohort, where TROP2 expression appears uniformly high.
- Future multivariate and spatial transcriptomic analyses are warranted to clarify how TROP2 integrates with immune and stromal features, potentially improving patient selection for TROP2-targeted ADCs in aggressive breast cancer subtypes.
- We plan to evaluate TROP2 as a potential biomarker for ADC eligibility and a therapeutic target to improve outcomes in aggressive IBC subtypes using larger dataset.

Acknowledgement

- The transcriptomic analyses were performed via collaboration with BostonGene and Morgan Welch IBC program.
- Morgan Welch IBC Research and Clinic Program is funded by the State of Texas Rare and Aggressive Breast Cancer Grant.
- SM was supported by the Medical Students Summer in Oncology at Anderson Research (SOAR) Program, funded by R25CA265800-01A1.

Contact Bora Lim, MD; Breast Medical Oncology, The UT MD Anderson Cancer Center
Email: Blim@mdanderson.org

The MDACC-IBC team author list
Rachel Layman[1], Bora Lim[1], Azadeh Nasrazadani[1], Sadia Saleem[1], Vicente Valero[1], Michael C. Stauder[2], Wendy A. Woodward[2], Anthony Lucci[3], Susie X. Sun[3], Gary J. Whitman[4], Miral Patel[4], Huong Le-Petross[4], Yang Lu[4], Angela Marx[1], Angela Alexander[1], Chasity Yajima[1], Megumi Kai[1], Lily Villarreal[1], Heather Lopez[1].
1. Department of Breast Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
2. Department of Breast Radiation Oncology, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
3. Department of Breast Surgical Oncology, Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA
4. Department of Breast Imaging, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

References

1. Dawood S, Ueno NT, Valero V, et al. Differences in outcomes among patients with stage III inflammatory and noninflammatory locally advanced breast cancer treated with neoadjuvant chemotherapy. Cancer. 2011;117(12):2749–2754.
2. Cristofanilli M, Buzdar AU, Hortobagyi GN. Update on the management of inflammatory breast cancer. Oncology (Williston Park). 2003;17(11):1513–1522.
3. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. N Engl J Med. 2021;384:1529–1541.
4. Rugo HS, Bardia A, Tolaney SM, et al. Sacituzumab govitecan in hormone receptor–positive/HER2– metastatic breast cancer. J Clin Oncol. 2023;41(12):2123–2134.
5. Goldenberg DM, Stein R, Sharkey RM. The emergence of TROP-2 as a therapeutic target in solid cancers. Clin Cancer Res. 2018;24(3):533–539.
6. Zeng P, Sun S, Li R, et al. TROP2: A promising therapeutic target for cancers resistant to antibody–drug conjugates. Cancer Sci. 2023;114(3):876–885.
7. Lim B, Ueno NT, Krishnamurthy S, et al. Translational landscape of inflammatory breast cancer: Molecular, immunologic, and stromal determinants of poor prognosis. NPJ Breast Cancer. 2022;8(1):64.
8. BostonGene Corporation. Comprehensive transcriptomic profiling and analytic methodology. Internal technical white paper; 2023.

This presentation is the intellectual property of the author/presenter. Contact them at Blim@mdanderson.org for permission to reprint and/or distribute.

© Poster Template by Genigraphics® 1.800.790.4001 www.genigraphics.com