# Prevalence of genomic alterations in Xerna tumor microenvironment subtypes in triple negative breast cancer patients

San Antonio Breast Cancer Symposium
December 5-9, 2023
Poster # PO2-06-10

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## Introduction

Immune checkpoint inhibitors (ICI) are an important therapeutic option for patients with triple negative breast cancer (TNBC). However, identification of patients most likely to respond is challenging.

PD-L1 positivity by immunohistochemistry is the standard biomarker used for ICI therapy selection in TNBC. However, other biomarkers, such as analysis of the tumor microenvironment (TME) may be more accurate in predicting response.

The Xerna™ TME Panel uses RNA sequencing data and machine learning to analyze the TME, utilizing the angiogenic and immunogenic biology of the TME to classify tumors into four TME subtypes (*Figure 1*).

In this study, the distribution of Xerna TME subtypes and associated genomic alterations in TNBC were investigated for their potential use in therapy selection.

## Methods

A total of 203 TNBC patient samples underwent tumor-normal whole-exome, whole-transcriptome sequencing testing with the OncoExTra™ assay.

Expression data from whole-transcriptome sequencing were analyzed with the Xerna TME Panel to assign each sample to one of four subtypes:

**Immune Active (IA),**

**Immune Suppressed (IS),**

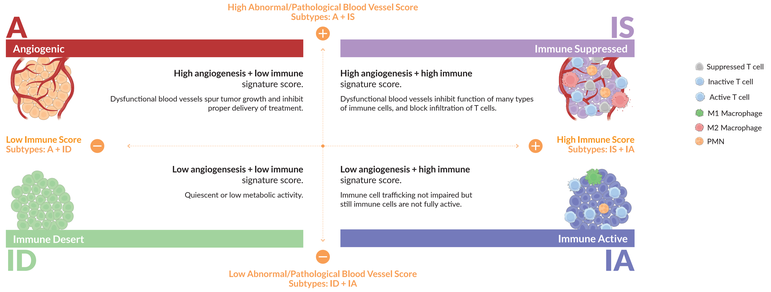
**Immune Desert (ID), and**

**Angiogenic (A).**

Actionable alterations, defined as those with FDA-approved matched therapies in any cancer, with matched clinical trials, or with evidence in cancer guidelines or the literature for possible matched therapies, were also identified and associations across Xerna subtypes were explored.

▼ ***Figure 1.***

*The machine learning-based Xerna score is obtained from RNA gene expression levels of ~100 genes. The score reflects the dominant cellular micro-environment of the tumor, along immune and angiogenic axes, and may be useful for predicting response to particular therapies, thus informing therapy decisions. [1]*




## Results

Approximately half (100 of 203; 49.3%) of the patient samples had high (IA+IS) immune subtypes (*Table 1*). Targetable alterations associated with an FDA-approved therapy were present in 114 (56.2%) patients.

No biomarkers were significantly associated ($p<0.05$) with high (IA+IS) versus low (ID+A) immune scores (*Table 2*).

Biomarkers associated with ICI response, namely mismatch repair gene alterations (*MSH2/3/6*, *MLH1/3*, *PMS1/2*), high tumor mutational burden (TMB-high) and microsatellite instability were detected in only 6 (3.0%), 3 (1.5%) and 1 (0.5%) patient samples respectively, and all but 1, an *MSH6* alteration, were in high immune subtype samples (*Table 2*).

▼ ***Table 1.***

*Patient characteristics and Xerna tumor microenvironment subtype / immune group.*

| | | Xerna subtype | | | | Immune group | |
|---|---|---|---|---|---|---|---|
| **Variable** | **All Samples** | **A** | **IA** | **ID** | **IS** | **High (IA/IS)** | **Low (A/ID)** |
| **N** | **203** | **48** | **51** | **55** | **49** | **100** | **103** |
| **Age (years)** | | | | | | | |
| **Mean (SD)** | 56.6 (13.30) | 60.6 (10.68) | 53.1 (13.00) | 54.7 (13.24) | 58.6 (14.90) | 55.8 (14.16) | 57.5 (12.41) |
| **Sex** | | | | | | | |
| **Female** | 202 (99.5%) | 47 (97.9%) | 51 (100.0%) | 55 (100.0%) | 49 (100.0%) | 100 (100.0%) | 102 (99.0%) |
| **Male** | 1 (0.5%) | 1 (2.1%) | (%) | (%) | (%) | (%) | 1 (1.0%) |
| **Actionable Alterations per Sample** | | | | | | | |
| **Mean (SD)** | 2.6 (2.03) | 2.4 (1.62) | 2.7 (2.48) | 3.4 (2.28) | 2.0 (1.17) | 2.3 (1.97) | 2.9 (2.05) |
| **Median** | 2.0 | 2.0 | 2.0 | 3.0 | 2.0 | 2.0 | 2.0 |
| **Q1-Q3** | 1 - 3 | 1 - 3 | 1 - 3 | 2 - 5 | 1 - 3 | 1 - 3 | 2 - 4 |
| **Min, Max** | 0, 16 | 0, 7 | 1, 16 | 1, 11 | 1, 5 | 1, 16 | 0, 11 |

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▼ ***Table 2.***

*Frequency of the 6 actionable biomarkers that were present at least 10 TNBC samples as well as 6 biomarkers associated with ICI response. No correction for multiple comparisons was employed. N is the number of patient samples.*

| | | Xerna subtype | | | | Immune group | | |
|---|---|---|---|---|---|---|---|---|
| **Biomarker** | **Total (n=203)** | **A (n=48)** | **IA (n=51)** | **ID (n=55)** | **IS (n=49)** | **High (IA/IS) (n=100)** | **Low (A/ID) (n=103)** | **p-value** |
| *TP53* | 173 (85.2%) | 36 (75.0%) | 48 (94.1%) | 49 (89.1%) | 40 (81.6%) | 88 (88.0%) | 85 (82.5%) | 0.32 |
| *PIK3CA* | 34 (16.7%) | 8 (16.7%) | 9 (17.6%) | 9 (16.4%) | 8 (16.3%) | 17 (17.0%) | 17 (16.5%) | 1.00 |
| *PTEN* | 17 (8.4%) | 5 (10.4%) | 1 (2.0%) | 5 (9.1%) | 6 (12.2%) | 7 (7.0%) | 10 (9.7%) | 0.61 |
| *BRCA1* | 16 (7.9%) | 3 (6.3%) | 4 (7.8%) | 6 (10.9%) | 3 (6.1%) | 7 (7.0%) | 9 (8.7%) | 0.80 |
| *MYC* | 12 (5.9%) | 0 (0.0%) | 4 (7.8%) | 7 (12.7%) | 1 (2.0%) | 5 (5.0%) | 7 (6.8%) | 0.77 |
| *RB1* | 12 (5.9%) | 5 (10.4%) | 3 (5.9%) | 1 (1.8%) | 3 (6.1%) | 6 (6.0%) | 6 (5.8%) | 1.00 |
| Biomarkers relevant to ICI therapy | | | | | | | | |
| *MSH6* | 5 (2.5%) | 0 (0.0%) | 2 (3.9%) | 1 (1.8%) | 2 (4.1%) | 4 (4.0%) | 1 (1.0%) | 0.21 |
| *MLH1* | 1 (0.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (2.0%) | 1 (1.0%) | 0 (0.0%) | 0.49 |
| *PMS2* | 1 (0.5%) | 0 (0.0%) | 1 (2.0%) | 0 (0.0%) | 0 (0.0%) | 1 (1.0%) | 0 (0.0%) | 0.49 |
| TMB-high | 3 (1.5%) | 0 (0.0%) | 2 (3.9%) | 0 (0.0%) | 1 (2.0%) | 3 (3.0%) | 0 (0.0%) | 0.12 |
| MSI-high | 1 (0.5%) | 0 (0.0%) | 1 (2.0%) | 0 (0.0%) | 0 (0.0%) | 1 (1.0%) | 0 (0.0%) | 0.49 |

## Conclusions

- **The Xerna TME Panel classified 49.3% of TNBC patient tumors to IA or IS, suggesting they may respond to ICI therapy.**
- **Many (56.2%) patient tumors harbored alterations associated with potential targeted therapies (e.g., *PIK3CA* and *PTEN* with PI3K/mTOR inhibitors and *BRCA1* with PARP inhibitors), which might be considered for novel combination therapies.**
- **These findings warrant further study and clinical validation in TNBC patients treated with ICI therapy.**

**References**

1. Uhlik M, Pointing D, Iyer S, Ausec L, Štajdohar M, Cvitković R, Žganec M, Culm K, Santos VC, Pytowski B, Malafa M, Liu H, Krieg AM, Lee J, Rosengarten R, Benjamin L. Xerna™ TME Panel is a machine learning-based transcriptomic biomarker designed to predict therapeutic response in multiple cancers. Front Oncol. 2023 May 12;13:1158345. doi: 10.3389/fonc.2023.1158345. PMID: 37251949; PMCID: PMC10213262.

**Acknowledgements**

The study was funded by Exact Sciences. Special thanks to Karen White for assistance in poster preparation.