# Genomic and Immunologic Landscape of *ERBB2*/*ERBB3* Alterations in Gastroesophageal Adenocarcinoma

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## INTRODUCTION

***HER2/ERBB2***
Known therapeutic target

***HER3/ERBB3***
Less known emerging therapeutic target

**Gastroesophageal Adenocarcinoma (GEAC)**

We aimed to gather Insights into the **genomic and immunologic landscape of *ERBB2/ERBB3* alterations** (*ERBB2/3*-alt) to develop treatments

## METHODS

GEAC Patients (N = 2050) + Molecular profiling with Tempus xT assay*

Retrospective review of De-identified patient data

Bivariate analyses were performed to compare:
- **Demographics**
- **Immune Biomarkers**
- **Co-mutations between *ERBB2*/3-alt groups**
- **Locally advanced at sample collection (i.e. stage 2B onward)**

*Tempus xT assay - DNA-seq of 648 genes at 500x coverage, full transcriptome RNA-seq

Groups defined as follows:
- *ERBB2* CN amp=*ERBB2* copy number (CN) amplification (CN >=8)
- *ERBB2* other=*ERBB2* pathogenic/likely pathogenic mutation or CN loss
- *ERBB3* CN amp=*ERBB3* CN amplification (CN >=8)
- *ERBB2*/*ERBB3* WT=no pathogenic/likely pathogenic mutation or CN amplification in *ERBB2*/*ERBB3*
- No CN losses in the *ERBB3* other group, so it is truly pathogenic/likely pathogenic mutations

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## RESULTS

**Cohort Characteristics**

| Characteristic | *ERBB2* CN amp, N = 252[1] | *ERBB2* other, N = 71[1] | *ERBB3* CN amp, N = 17[1] | *ERBB3* other, N = 22[1] | *ERBB2*/*ERBB3* WT, N = 1,685[1] | p-value[2] |
|---|---|---|---|---|---|---|
| **Age at Diagnosis** | 64 (57, 71) | 66 (59, 74) | 66 (58, 72) | 58 (46, 79) | 64 (56, 71) | **0.5** |
| Unknown | 10 | 3 | 1 | 1 | 81 | |
| **Gender** | | | | | | **0.002** |
| Female | 47 (19%) | 26 (37%) | 6 (35%) | 10 (45%) | 391 (23%) | |
| Unknown | 0 | 0 | 0 | 0 | 2 | |
| **Primary Cancer Site** | | | | | | **<0.001** |
| Esophagus | 142 (56%) | 33 (46%) | 5 (29%) | 8 (36%) | 666 (40%) | |
| Stomach | 54 (21%) | 28 (39%) | 5 (29%) | 12 (55%) | 565 (34%) | |
| Cardia | 56 (22%) | 10 (14%) | 7 (41%) | 2 (9.1%) | 454 (27%) | |

[1] Median (IQR); n (%), [2] Kruskal-Wallis rank sum test; Fisher's exact test

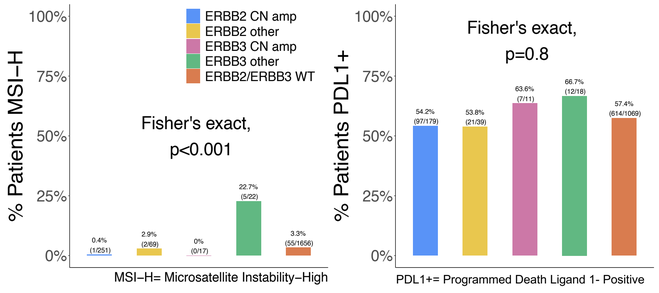


**Figure 1 -** Comparisons of percentage patients MSI-H and percentage patients PDL1+ between *ERBB2*/*ERBB3* groups. *ERBB3* other patients demonstrated significantly increased MSI-H compared to other groups.

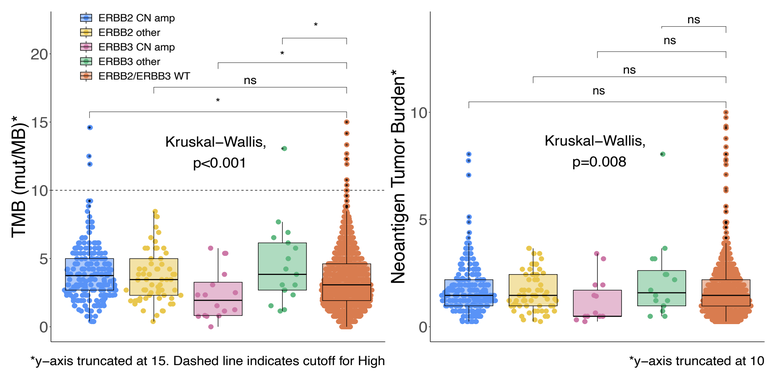


**Figure 2 -** Comparisons of TMB (Tumor Mutational Burden) and Neoantigen Tumor Burden between *ERBB2*/*ERBB3* groups. Global significance was detected for each metric, with *ERBB3* CN amp patients demonstrating the lowest median TMB and Neoantigen Tumor Burden

**Immune Biomarkers**

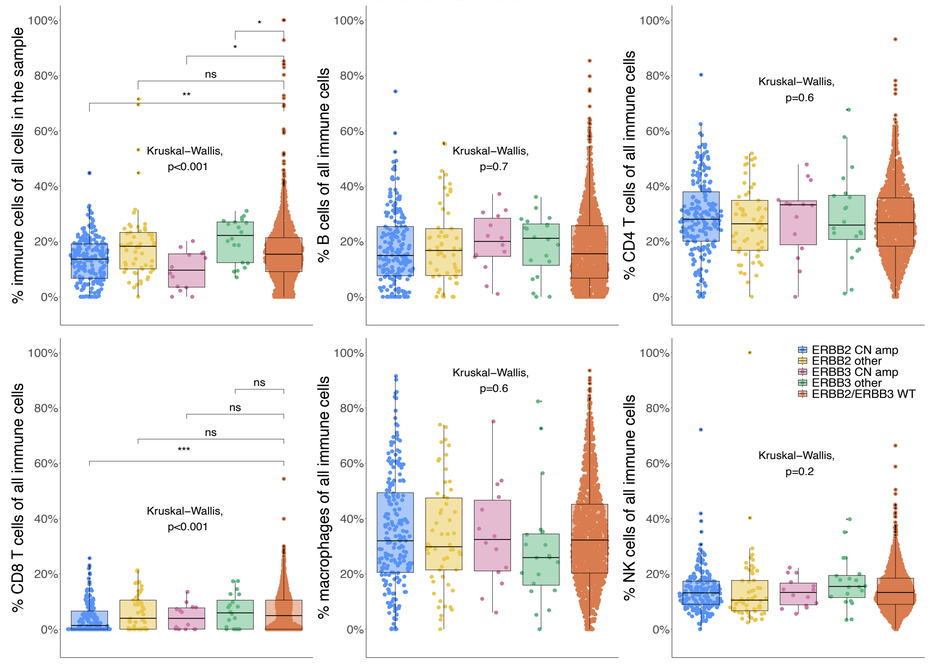


**Figure 3 -** Comparisons of immune cell compositions between *ERBB2*/*ERBB3* groups. Global significance we detected for both the % makeup of immune cells amongst all cells in the sample and the % makeup of CD8 T cells out of all immune cells. Notably, *ERBB3* CN amp patients (median 10% immune cells of all cells) demonstrated significantly decreased % immune cells compared to *ERBB2*/*ERBB3* WT patients (median 15%) while *ERBB3* other patients demonstrated significantly increased % immune cells (22%).

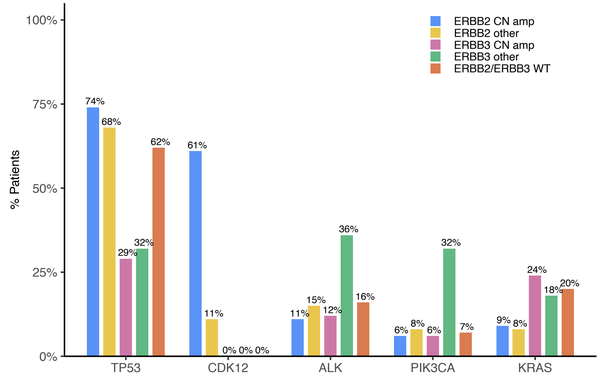


**Figure 4 -** Comparisons of individual gene somatic alterations between *ERBB2*/*ERBB3* groups. Somatic alterations were defined as either a pathogenic or likely pathogenic short variant, copy number loss, or copy number amplification. Genes of interest are shown; all reached significance after false-discovery adjustment aside from ALK (q-value=0.064) and CDK12 (incalculable due to 0 cell counts).

## SUMMARY

- ***ERBB2*/*ERBB3*-alt** are associated with **significant changes** in the **tumor microenvironment** in **GEAC**.
- Co-occurring genetic or immunologic alterations can be exploited to develop effective targeted or immune therapies.