# Genomic landscape and prognostic impact of HER2 low-expressing tumors

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## Background

- There is evolving evidence that HER2 low-expressing (1+/2+ IHC) tumors may respond to novel anti-HER2-based therapies.
- We evaluated the frequency and prognostic impact of HER2 expression and its association with ERBB2 genomic alterations in a large database of molecularly profiled tumors from real-world patients (pts).

## Methods

- A wide range of tumor types (N = 88,535) underwent HER2 immunohistochemistry (IHC; 4B5 antibody), next-gen sequencing (NGS) of DNA (592-gene or whole exome) and RNA (whole transcriptome) at Caris Life Sciences (Phoenix, AZ).
- ERBB2 copy number amplification was determined by calculating the average depth of sample & sequencing depth of each exon in comparison to a pre-calibrated reference value.
- Copy number >6 was classified as amplified (amp).
- ERBB2 variants (SNV/indels) were classified according to the American College of Medical Genetics and Genomics (ACMG) standards.
- Cohorts were stratified by IHC HER2 values of 0 (non-expressors), 1+, 2+, or 3+ and compared with ERBB2 alterations using $\chi^2$ where applicable.

## Results

**Figure 1 –** (A) Pan-cancer distribution of HER2 IHC stain intensities. (B) Distribution of HER2 IHC stain intensities across all cancers.

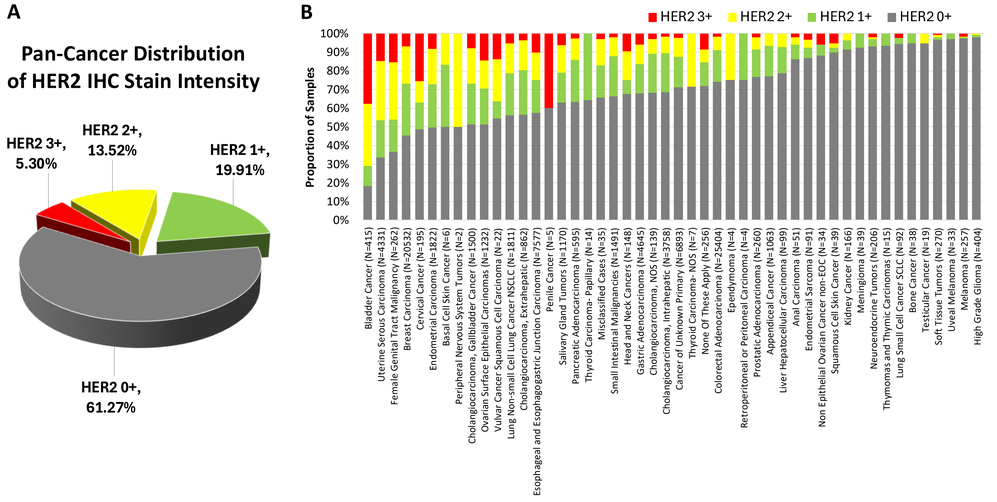



**Figure 2 –** (A) Proportion of samples with HER2 amplification among samples with varying HER2 IHC stain intensity. (B) Proportion of samples with HER2 mutations (pathogenic/likely pathogenic single nucleotide variant or nucleotide insertion/deletion) among samples with varying HER2 IHC stain intensity.

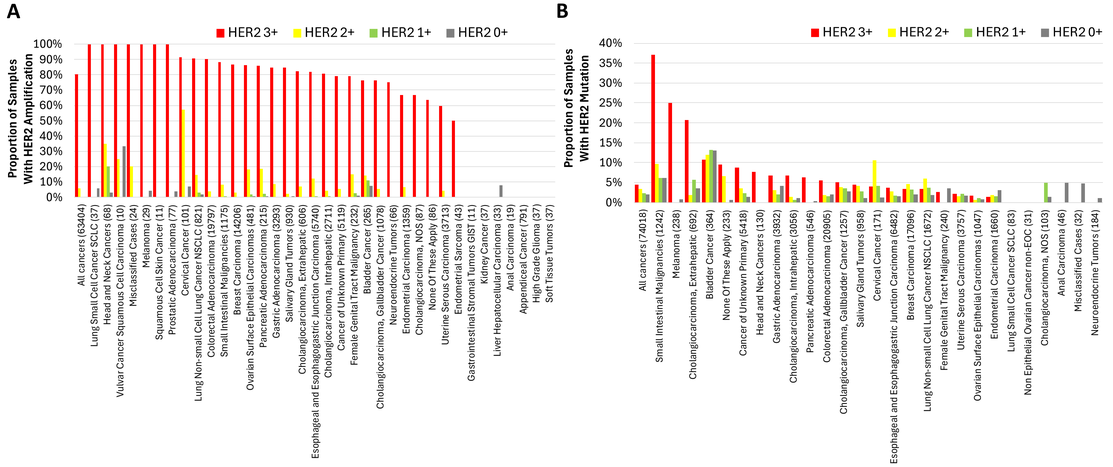



**Figure 3 –** ERBB2 expression (in transcript per million, TPM) by HER2 IHC stain intensity across all cancers.

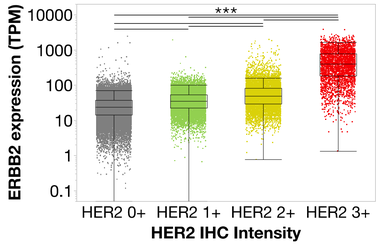
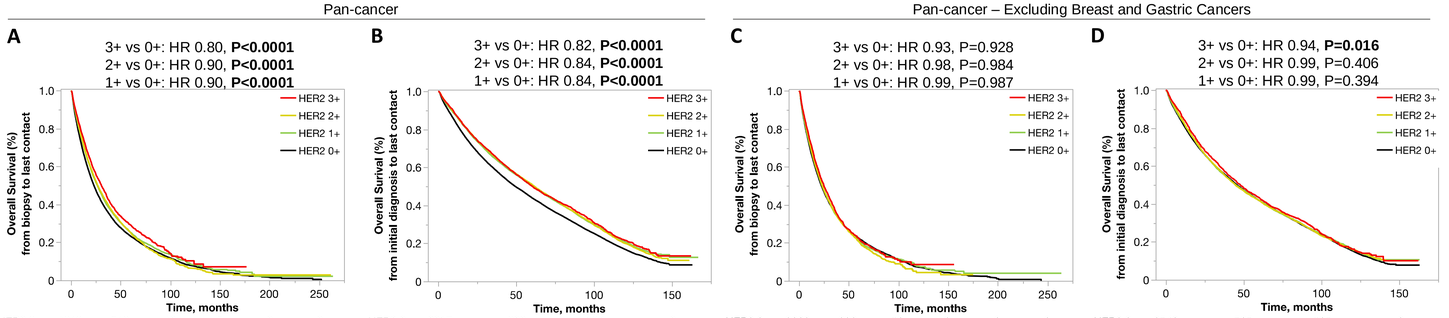



**Figure 4 –** Pan-cancer analysis of overall survival from the date of biopsy collection to last contact (A) or from initial diagnosis to last contact (B) among patients stratified by HER2 IHC intensity. Excluding breast and gastric cancers, pan-cancer analysis of overall survival from the date of biopsy collection to last contact (C) or from initial diagnosis to last contact (D) among patients stratified by HER2 IHC intensity.




| | A | | | | | |
|---|---|---|---|---|---|---|
| HER2 3+ | 4648 | 540 | 43 | 5 | 0 | 0 |
| HER2 2+ | 11844 | 1132 | 75 | 8 | 2 | 1 |
| HER2 1+ | 17380 | 1727 | 162 | 20 | 2 | 1 |
| HER2 0+ | 53497 | 5127 | 590 | 62 | 10 | 2 |

| | B | | | | |
|---|---|---|---|---|---|
| HER2 3+ | 2317 | 693 | 193 | 0 | |
| HER2 2+ | 9459 | 3368 | 1023 | 5 | |
| HER2 1+ | 15161 | 5610 | 1703 | 10 | |
| HER2 0+ | 48023 | 15727 | 4391 | 11 | |

| | C | | | | | |
|---|---|---|---|---|---|---|
| HER2 3+ | 3003 | 232 | 18 | 2 | 0 | 0 |
| HER2 2+ | 7319 | 481 | 23 | 3 | 1 | 0 |
| HER2 1+ | 11024 | 836 | 68 | 11 | 2 | 1 |
| HER2 0+ | 41182 | 3526 | 420 | 36 | 4 | 0 |

| | D | | | |
|---|---|---|---|---|
| HER2 3+ | 2743 | 787 | 197 | 3 |
| HER2 2+ | 6697 | 1808 | 478 | 4 |
| HER2 1+ | 10040 | 2834 | 737 | 4 |
| HER2 0+ | 37535 | 11124 | 2936 | 6 |

## Conclusions

- Significant associations between ERBB2 alterations and HER2 low-expressing tumors were observed.
- High prevalence of ERBB2 alterations was observed in some uncommonly tested tumors.
- Median OS of HER2 low-expressors was better than non-expressors in this heterogenous group, however, there was no significant difference after excluding breast and gastric cancers.

## Contact Info

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