Impact of HER2 and PD-L1 co-expression in Claudin18.2-positive resectable gastroesophageal cancers


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Background

- CLDN18.2, HER2, and PD-L1 are targetable biomarkers in gastroesophageal adenocarcinoma (GEA).
- Tailored treatments have shown efficacy in the unresectable space.1
- Prevalence and significance of their co-expression in the resectable stages remain unclear.

Methods

- CLDN18.2, HER2, and PD-L1 were assessed by immunohistochemistry (IHC) on adjacent slides from FFPE tumour samples in a cohort of resectable GEA with paired clinical and WGS data (Figure 1).
- Copy number alterations were inferred via ASCAT using read counts at germline heterozygous positions inferred by GATK HaplotypeCaller.
- Tumour mutational burden (TMB) was calculated as the number of non-synonymous somatic mutations per mega-base from WGS.
- Fisher’s exact test/Mann-Whitney test were used to compare clinicopathological characteristics and log-rank test to compare survival curves, with statistical significance set at p=0.05 (two-sided).

Results

Eighty-four patients with resected GEA were evaluated.
- CLDN18.2 was expressed in 20% (17/84), HER2 in 19% (16/84), and PD-L1 in 32% (27/84) of the cases.
- Co-expression of HER2 and PD-L1 occurred in 23% (4/17) and 41% (7/17) of CLDN18.2+ve cases, respectively (Figure 1).
- Across biomarkers subgroups there were similar:
  - Clinicopathological characteristics, except for younger age (OR:5.0, p=0.007) and more stage IV at diagnosis (OR:4.5, p=0.03) in HER2+ve disease (Table 1).
  - Response to neoadjuvant chemotherapy (TRG2-3 vs TRG4-5 and survival) (Figure 2).
- Compared to CLDN18.2+ve only, CLDN18.2+ve/HER2+ve tumours had significantly higher TMB (10.46 vs 5.51, p=0.03), and HER2 gene copy numbers (1.39 vs 0.8, p=0.0008) (Figure 3). Of note, CLDN18.2+ve/HER2+ve cases were all MSS.
- In CLDN18.2+ve subgroup, TMB was not significantly different by PD-L1 nor between CLDN18.2+ve and HER2+ve cases.

Conclusions

- Biomarker co-expression may be frequent in the CLDN18.2+ve subset.
- CLDN18.2+ve/HER2+ve may reveal a genomically more complex subgroup.
- Evaluation in larger datasets is required to understand its biological significance and potential therapeutic implications.

Table 1. Clinicopathological characteristics in the entire cohort and by biomarkers.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=84)</th>
<th>CLDN18.2+ve (n=67)</th>
<th>HER2+ve (n=68)</th>
<th>PD-L1+ve (n=68)</th>
<th>HER2+ve (n=68)</th>
<th>CLDN18.2+ve (n=67)</th>
<th>PD-L1+ve (n=68)</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>64.8±10.8</td>
<td>68.7±11.8</td>
<td>64.8±10.4</td>
<td>67.5±9.8</td>
<td>60.2±10.4</td>
<td>71.5±9.6</td>
<td>68.5±10.8</td>
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<tr>
<td>Gender (m/f)</td>
<td>54/30</td>
<td>41/26</td>
<td>40/28</td>
<td>42/26</td>
<td>35/33</td>
<td>40/28</td>
<td>42/26</td>
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<tr>
<td>T-stage</td>
<td>1/73/0</td>
<td>12/52/0</td>
<td>1/72/0</td>
<td>1/72/0</td>
<td>1/71/0</td>
<td>1/71/0</td>
<td>1/72/0</td>
</tr>
</tbody>
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Figure 1. A) Patterns of biomarkers co-expression in operative GEA. Percentages and ratios display co-expression rates in CLDN18.2+ve subgroup. B) Panel of IHC/TIM174/adjacent slides with CLDN18.2 and HER2 co-expression. C) Summary of scoring criteria.

Figure 2. A) Pathological response rates (Mandard classification) and B) overall survival across biomarkers subgroups.

Figure 3. Comparison of TMB and gene copy numbers in the CLDN18.2+ve subgroups.

COIs

No.

References