Tumor profiling of gastric and esophageal carcinoma reveal different treatment options

**Background**: NCCN guidelines state that chemotherapies for esophageal and gastric cancers may be used interchangeably. We interrogated biomarkers from a large cohort of gastroesophageal cancer patients to identify similar and distinct alterations with therapeutic implications for gastric and esophageal cancers.

**Methods**: 666 gastric adenocarcinoma (GA) and 640 esophageal squamous cell carcinoma (ES) were evaluated by a combination of sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH/ISH).

**Results**: In the complete cohort of 1,306 patients, 30 of 45 (66%) genes tested had mutations, with the highest rates seen in TP53 (54%), APC (50%), SMAD4 (5%), Kras (5%) and PIK3CA (5%). Elevated IHC of TOPO2A was seen in 76% of cases, TOP2A in 51% and SPARC in 25%; decreased IHC of ERCC1 was seen in 65%, ERBB2 in 32%, TGF in 61% and MGMT in 45%, indicating benefits from spizoblin, irinotecan, nab-paclitaxel, platinum, gemcitabine, SPUA/caspasepide, and temozolomide, respectively. In the HER2 positive cases, additional alterations were seen including low T5 (50%), ERCC1 (65%), RRM1 (ES) and high TOP2A (53%), indicating potential benefits from combining trastuzumab with SPUA/caspasepide, cisplatin, gemcitabine and irinotecan, respectively. When comparing GA to EA, select biomarkers showed a differential pattern between cancer types (Table 1), suggesting potential variability in efficacy of available therapeutic agents.

**Conclusions**: A multiplatform biomarker analysis identified common actionable targets in gastric and esophageal cancer as well as significant biomarker differences in EA and GA. This indicates the potential clinical impact of molecular profiling and highlights the need for the separation of two cancer entities for therapeutic target development.

**Abstract**

- GC and EC tissue samples were submitted to Caris Life Sciences (Phoenix, AZ) for tumor profiling analysis aimed to provide therapeutic information.
- Retrospective biomarker analysis performed on samples submitted from 2000-2013.
- Diagnoses were collected from referring physicians and classified at intake based on pathology, clinical history, case-specific testing performed per physician request and included a combination of sequencing (Sanger, NGS or sequencing), protein expression (IHC or CISH) and gene amplification (CISH or FISH).
- A total of 1,306 samples were evaluated: 666 gastric adenocarcinoma (GA) and 640 esophageal squamous cell carcinoma (ES).

**Background**

Emergence of molecular profiling has enabled clinicians to measure the activity of potential genetic targets in tumors for which systemic therapy agents are already available.

**Methods**

- Overall prognosis for gastro-esophageal tumors remains poor.
- Despite improved outcomes with multidrug therapies, tumor response rates to cytotoxic therapy continues to be sub-optimal (40-50%).
- Aggressive nature of gastric (GC) and esophageal (EC) cancer makes selecting the optimal systemic chemotherapy regimen critical when attempting to prolong survival.
- Tumor genomics has been used to identify genetic markers that can guide treatment.
- Genomic profiling of tumors reveals specific genetic mutations, which can aid in determining which patients will benefit from which therapies.

**Results**

- Genes that are targets of NCCN treatment for gastro-esophageal cancers:
  - Blue: Agents that are on NCCN compendium
  - Green: Agents that are off NCCN compendium

**Table 1: Biomarker comparison of gastric and esophageal adenocarcinoma**

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Target Biomarker</th>
<th>GA (%)</th>
<th>EA (%)</th>
<th>p-value</th>
</tr>
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<tbody>
<tr>
<td>PI3K/AKT</td>
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<td>53</td>
<td>46</td>
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<td>JAK2</td>
<td>JAK2</td>
<td>36</td>
<td>33</td>
<td>&lt;0.01</td>
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<tr>
<td>ERBB2</td>
<td>HER2</td>
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<tr>
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<td>EGFR</td>
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<td>45</td>
<td>&lt;0.01</td>
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<tr>
<td>CDH1</td>
<td>E-cadherin</td>
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<td>45</td>
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<tr>
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<td>RB1</td>
<td>55</td>
<td>45</td>
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<td>STK11</td>
<td>LATS</td>
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<td>&lt;0.01</td>
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<tr>
<td>PIK3CA</td>
<td>PIK3CA</td>
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<td>20</td>
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<tr>
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<td>Trak2</td>
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<td>29</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FGFR2</td>
<td>FGFR2</td>
<td>55</td>
<td>45</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Conclusions**

- A multiplatform profiling of over 2,920 gastric and esophageal cancer patients identified effective treatments in both cancer types.
- Interrogation of tumor biomarkers by IHC, FISH, and NGS analysis demonstrated significant differences in expression patterns between GC and EC, suggesting potential variation in tumor responsiveness to associated therapies.
- HER2 and SMARCC1 are significantly more prevalent in EA while PIK3CA mutation is more prevalent in GA, indicating differential responses to trastuzumab, sub-paclitaxel and PI3K/mTOR inhibitors.
- HER2-positive esophageal adenocarcinomas demonstrate a potential sensitivity to combination therapies with platinum agents, irinotecan or fluoropyrimidines. Highlighting IHC and IHC as possible diagnostic adjunct to further optimize systemic therapies.
- Prospective controlled studies are needed to validate the role of biomarkers in identifying effective systemic agents for gastric and esophageal cancer.

**References**

1. NCCN Clinical Practice Guidelines in Oncology Version 2, 2013
3. Caris Life Sciences, 2016, 25.3.1-4877-83

**Figure 1: Overall actionable targets by IHC and FISH analysis and associated therapies**

**Figure 2: Gene mutations and associated clinical trials in gastro-esophageal cancers**

**Figure 3: Actionable biomarker targets by IHC and FISH analysis among Her2+ gastro-esophageal tumors:** IHC and FISH tests identify combination therapy with trastuzumab in Her2+ cohorts.