**NRG1 Fusions**

- **Neuregulin-1 (NRG1)** gene fusions are rare oncogenic drivers found in 0.2% of solid tumors, including pancreatic, gallbladder, colorectal, lung, breast, ovarian, neuroendocrine, and sarcomas.
- Patients with tumors bearing NRG1 fusions have limited responses to standard current therapies, as well as poorer disease-free and overall survival than patients without NRG1 fusions.

**NRG1 fusion proteins predominantly retain an active EGF domain, which drives tumorigenesis and proliferation through aberrant HER3 activation** (Figure 1). Importantly, NRG1 fusions and other known driver alterations are often mutually exclusive.

**Figure 1. NRG1 fusion activation of HER3 and downstream pathways**

**NRG1 Fusions in Gastrointestinal Cancers**

- NRG1 fusions are enriched in pancreatic ductal adenocarcinoma (PDAC), where the incidence may be as high as 6%.
- Published clinical case reports of gastrointestinal cancers harboring NRG1 fusion suggest that significant responses can be achieved through inhibition of ERBB family members (Table 1).

**Table 1. Clinical case reports of responses in NRG1 fusion-positive gastrointestinal cancers**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>NRG1 fusion</th>
<th>Response</th>
<th>DoR (mths)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS wt Stage IV with liver metastases, PDAC</td>
<td>APP–NRG1</td>
<td>PR (7+, ongoing)</td>
<td>[9]</td>
</tr>
<tr>
<td>KRAS wt Stage IV with liver metastases, PDAC</td>
<td>ATP1B1–NRG1</td>
<td>PR (5.5)</td>
<td>[8]</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>ATP1B1 (E2)–NRG1 (E2)</td>
<td>PR (8)</td>
<td>[10]</td>
</tr>
<tr>
<td>KRAS wt, Stage IV</td>
<td>ATP1B1–NRG1</td>
<td>PR (&lt;5)</td>
<td>[8]</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>POMK–NRG1</td>
<td>SD (9+, ongoing)</td>
<td>[9]</td>
</tr>
<tr>
<td>NRG1 fusion</td>
<td>POMK–NRG1</td>
<td>SD (16)</td>
<td>[11]</td>
</tr>
</tbody>
</table>

**Seribantumab**

- Seribantumab is a fully human immunoglobulin G2 (IgG2) monoclonal antibody (mAb) against HER3.
- Seribantumab inhibits NRG1-dependent activation of HER3, HER3-HER2 dimerization, phosphorylation, and signaling with EGFRI, HER2, and HER4, and downstream signaling through the phosphoinositide 3-kinases (PI3K/AKT) and mitogen-activated protein kinase (MAPK) pathways in preclinical models in vitro and in vivo (Figure 2).
- Seribantumab inhibited growth, induced pro-apoptotic proteins, and activated caspase 3/7 in NRG1 fusion-positive long and breast cancer cell lines.

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**REFERENCES**

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- MEB served as a consultant for Pointcare Genomics, Strata Oncology, and Novartis, and has patents for an implantable/localize drug delivery device and a method to detect recombination events
- SJK served as a consultant/Speakers’ Bureau for Lilly, Boston Biomedical, Astellas Pharma, Foundation Medicine, Bristol-Myers Squibb, Pieris Pharmaceuticals, and Merck, received funds from Natera, holds stock with Turning Points Therapeutics, and other with NCCN
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