Novel EGFR<sup>WT</sup>-Sparing, HER2 Selective Inhibitors for the Treatment of HER2 Exon 20 Insertion Driven Tumors Address a Clear Unmet Medical Need

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Introduction

- Activating mutations in ERBB receptors act as oncogenes in NSCLC.
- Besides the more prevalent EGFR activating mutations, oncogenic variants in HER2 occur in 2-3% of NSCLC patients. Oncogenic mutations in HER2 in NSCLC predominantly affect the tyrosine kinase domains of HER2 and cluster in exon 20 of the ERBB2 gene. Clinically approved and currently tested tyrosine kinase inhibitors are not sufficiently efficacious in these patients, as they are limited by EGFR wild-type mediated dose limiting toxicity. 1, 12
- An EGFR wild-type sparing HER2 inhibitor with sufficient potency on HER2 exon 20 mutations constitutes an interesting therapeutic strategy for HER2 exon-20 mutant cancers.

Objectives

- Identification of potent HER2 exon 20 mutation TKIs which bind oncogenic HER2 while sparing EGFR wild-type, thus enabling efficacious dosing.
- Pre-clinical validation of therapeutic concept.

Cell Line Engineering

- Generation of a HER2 YVMA mechanistic model, as tumor cell lines carrying this mutation do not exist.
- CRISPR-based engineering of EGFR<sup>WT</sup> or HER2 wild type dependent cell lines.
- Modification of endogenous locus (HG-H2170) or overexpression of HER2 YVMA and isolated of endogenous EGFR (PC-9).
- CRISPR engineered cells serve as pre-clinical mechanistic models to guide compound optimization.

Medicinal Chemistry

- Cell based screen of ~12,000 compounds
- ~900 compounds followed-up with full dose response curves on HER2<sup>WT</sup> and EGFR<sup>WT</sup> expressing HEK cells
- ~35 compounds showed a >5-fold selectivity between the inhibition of HER2 phosphorylation and EGFR phosphorylation.

- Medicinal Chemistry optimization yielded covalent HER2 inhibitors with excellent potency, EGFR wild-type selectivity, and favorable pharmacokinetic profile in mice.

- X-ray crystal structure of BI-4142 bound to HER2
  - resolution 1.77Å
  - binding site as ATP binding site
  - X-ray structure demonstrates covalent bond between acrylamide warhead and Cys805

Table 1. in vitro Data of BI-1022 and BI-4142

<table>
<thead>
<tr>
<th></th>
<th>BI-1022</th>
<th>BI-4142</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt; (± SEM)</td>
<td>7.6±0.9</td>
<td>7.6±0.9</td>
</tr>
<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt; 1000nM</td>
<td>3.0±0.6</td>
<td>2.0±0.6</td>
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<tr>
<td>IC&lt;sub&gt;50&lt;/sub&gt; 100nM</td>
<td>2.0±0.8</td>
<td>1.5±0.8</td>
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<tr>
<td>PPB range (± SEM)</td>
<td>8±9</td>
<td>8±9</td>
</tr>
<tr>
<td>Mouse liver microsomes (Cl&lt;sub&gt;p&lt;/cl&gt;), 15µM</td>
<td>&lt;14.2±4.2</td>
<td>&lt;14.2±4.2</td>
</tr>
<tr>
<td>CYP1A1/2A/3a percent inhibitory effects</td>
<td>0.0% ± 0.0%</td>
<td>0.0% ± 0.0%</td>
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Chemical Activity

In vitro potency and selectivity
- BI-4142 and BI-1022 display excellent HER2 on target activity.

In vivo efficacy in mechanistic models
- BI-4142 induces tumor regression in HER2<sup>WT</sup> mutant models.
- No body weight change or toxicity observed for BI-4142
- >10% body weight reduction and EGFR wild-type associated toxicity observed for Poziotinib<br>

Key findings and conclusions

- Medicinal Chemistry based identification and optimization of chemical series with HER2 inhibitory and EGFR wild-type sparing activity.
- BI-4142 and BI-1022 show high selectivity.
- Excellent tolerability and efficacy in mice.
- Pre-clinical data suggest improved efficacy and tolerability in comparison to the pan-ERBB blocker Poziotinib.
- Current preclinical data warrant evaluation of this chemical series in NSCLC patients with HER2 mutations.

References


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