BLU-667 is a Potent and Highly Selective RET Inhibitor Being Developed for RET-Driven Cancers

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**RET Kinase is Oncogenic in Diverse Cancer Subtypes**

Rearranged during transfection (RET) is a highly conserved receptor tyrosine kinase that transduces signaling from the GDNF family of neurotrophic factors. Activating RET mutations are observed in sporadic medullary thyroid cancer (MTC) and multiple endocrine neoplasia type 2 (MEN2). In other tumor types, chromosomal translocations oncogeneically activate RET by fusing the kinase domain to a dimerization domain of another gene, creating RET fusion proteins with constitutive activity. Although RET kinase inhibitors were initially identified in papillary thyroid cancer (PTC), recent genomic analyses of diverse tumor types identified RET fusions in normal cell lung cancer (NSCLC), colon, breast, ovary, and hematologic malignancies.

**Frequency of Oncogenic RET Alterations in Solid Tumors**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>RET Alteration</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>Fusions</td>
<td>50%</td>
</tr>
<tr>
<td>RCC</td>
<td>Fusions</td>
<td>10%</td>
</tr>
<tr>
<td>PTC</td>
<td>Fusions</td>
<td>10%</td>
</tr>
<tr>
<td>Other solid tumors</td>
<td>Fusions</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

**RET-Altered Cancer Patients Have High Medical Need**

Multikinase inhibitors (mKIs), currently being tested in RET-altered NSCLC patients, were not designed to selectively target RET and exhibit:

- Broad kinase activity, often with potent inhibition of VEGFR-2
- Off-target related dose limiting toxicities that hinder their ability to fully inhibit RET
- Dramatically lower ORR and duration of response in NSCLC compared to selective kinase inhibitors targeting other kinase drivers

**BLU-667 is Designed to Transform Treatment of RET-Altered Cancers**

- CRAFTed to target oncogenic RET fusions and activating mutations
- Highly active against activating and resistance mutations at the gatekeeper (V804) residue
- Kinase selectivity allowing full in vivo RET Inhibition at well tolerated doses

**BLU-667 is a sub-nanomolar RET inhibitor with >90% selectivity fully overexpressing VEGFR-2**

Kineses Inhibited by BLU-667

- RET
- VEGFR-2
- PDGFRα
- KIT
- NGF P75
- CDK4
- PRKCH
- BTK
- IKK
- MET
- Raf kinase
- SRC
- Sprk
- ALK
- DDR1
- DDR2
- DDR3
- PDGFRβ
- FGFRs
- FGFR1
- FGFR3
- FGFR4
- FGFR7
- EphA2
- EphA3
- EphA4
- EphA5
- EphA6
- EphA7
- EphA9
- EphB2
- EphB3
- EphB4

**BLU-667 is a Highly Potent RET Inhibitor that exhibits ≥100X selectivity for RET over 96% of kinases tested**