BLU-667 is a potent and highly selective RET inhibitor in development for RET-driven thyroid cancers

Rami Rahal, PhD
Blueprint Medicines
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Employee and shareholder of Blueprint Medicines

BLU-667 is an investigational agent currently in development by Blueprint Medicines
- Receptor tyrosine kinase that transduces signals from GDNF-family ligands

- One of the first oncogenic kinase fusions cloned from an epithelial tumor
**RET Kinase Fusions and Mutations are Oncogenic**

### RET fusions
- **~10% of papillary thyroid cancer patients**
- **1-2% of NSCLC patients**
- **<1% of patients with colon, ovary, breast, or hematological cancer**

### RET mutations
- **~60% of medullary thyroid cancer (MTC) patients harbor oncogenic RET mutations**
- **M918T is the most prevalent RET mutation**
Kinase Inhibitors Approved for Treating MTC were Not Designed to Selectively Inhibit RET

- Broad kinome activity with potent inhibition of VEGFR-2
- Off-target related dose limiting toxicities hamper ability to inhibit fully RET

<table>
<thead>
<tr>
<th>Compound (Trade Name)</th>
<th>Intended Target(s)</th>
<th>VEGFR-2 Biochem. IC₅₀ (nM)</th>
<th>RET Biochem. IC₅₀ (nM)</th>
<th>Serious adverse events</th>
<th>Overall Response Rate in MTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib (Cometriq)</td>
<td>VEGFR-2 / MET</td>
<td>2</td>
<td>11</td>
<td>Perforations and fistulas; hemorrhage</td>
<td>27%</td>
</tr>
<tr>
<td>Vandetanib (Calpresa*)</td>
<td>VEGFR-2 / EGFR</td>
<td>4</td>
<td>4</td>
<td>QT prolongation; Torsades de pointes; sudden death</td>
<td>44%</td>
</tr>
</tbody>
</table>

*Only available through Calpresa REMS due to safety concerns
BLU-667: a Highly Potent and Selective RET Inhibitor

1. Potently inhibit RET wild-type fusions (PTC, NSCLC & other cancers)
2. Potently inhibit oncogenic RET mutants (MTC)
3. Spare VEGFR-2 in a kinome-selective manner
4. *Potently inhibit resistance mutations to existing multi-kinase inhibitors*

<table>
<thead>
<tr>
<th></th>
<th>RET (nM)</th>
<th>VEGFR-2 (nM)</th>
<th>VEGFR-2 / RET ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLU-667</td>
<td>0.4</td>
<td>35</td>
<td>88x</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>11</td>
<td>2</td>
<td>0.2x</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>4</td>
<td>4</td>
<td>1x</td>
</tr>
</tbody>
</table>

• Greater than 100-fold selective over 95% of the kinome

BLU-667 is currently being evaluated in a phase 1 trial for patients with MTC and other advanced solid tumors harboring oncogenic RET alterations
BLU-667 inhibits RET signaling and RET-driven proliferation of thyroid cancer cell lines

**TT Cells**

*RET(C634W)*

<table>
<thead>
<tr>
<th>nM Compound</th>
<th>BLU-667</th>
<th>Cabozantinib</th>
<th>Vandetanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
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<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
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<tr>
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<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td><img src="image9" alt="Image" /></td>
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<tr>
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<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
</tr>
</tbody>
</table>

**MZ-CRC-1 Cells**

*RET(M918T)*

<table>
<thead>
<tr>
<th>nM Compound</th>
<th>BLU-667</th>
<th>Cabozantinib</th>
<th>Vandetanib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
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<tr>
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<td><img src="image17" alt="Image" /></td>
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<tr>
<td>100</td>
<td><img src="image19" alt="Image" /></td>
<td><img src="image20" alt="Image" /></td>
<td><img src="image21" alt="Image" /></td>
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<tr>
<td>1000</td>
<td><img src="image22" alt="Image" /></td>
<td><img src="image23" alt="Image" /></td>
<td><img src="image24" alt="Image" /></td>
</tr>
</tbody>
</table>

**TT (MTC)**

*RET(C634W)*

% Inhibition vs. log[compound], nM

**MZ-CRC-1 (MTC)**

*RET(M918T)*

% Inhibition vs. log[compound], nM

**TPC-1 (PTC)**

*CCDC6-RET*

% Inhibition vs. log[compound], nM

**LC2/ad (NSCLC)**

*CCDC6-RET*

% Inhibition vs. log[compound], nM

- BLU-667
- Cabozantinib
- Vandetanib
BLU-667 suppresses tumor growth and inhibits RET signaling in RET-altered thyroid and NSCLC tumors.

**MTC Xenograft RET(C634W)**

**BLU-667 suppresses tumor growth and inhibits RET signaling in RET-altered thyroid and NSCLC tumors**

**Effects of BLU-667 and cabozantinib on VEGFR-2 in vivo?**

**NSCLC PDX KIF5B-RET**

**BLU-667**

- 60mg/kg QD
- 3mg/kg BID
- 10mg/kg BID
- 30mg/kg BID
- 60mg/kg QD

**Phospho-Ret**

**Phospho-Shc**

**Total Ret**

**KIF5B-RET NSCLC PDX tumor lysates**
Clinical biomarkers of VEGFR-2 pathway inhibition

<table>
<thead>
<tr>
<th>Drug</th>
<th>VEGF-A</th>
<th>sVEGFR-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Axitinib</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Telatinib</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Brivanib</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Motesanib</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Cediranib</td>
<td>↑</td>
<td>↓</td>
</tr>
</tbody>
</table>

Class effect of VEGFR-2 inhibitors:

- increased VEGF-A
- decreased sVEGFR-2

Adapted from Ebos et al, PNAS (2007)
Murukesh et al, British Journal of Cancer (2010)
Tolaney et al, The Oncologist (2017)
BLU-667 suppresses tumor growth without significantly impacting VEGFR-2

**MTC Xenograft**

RET(C634W)

**Biomarkers of VEGFR-2 inhibition:**

- increased VEGF-A
- decreased sVEGFR-2

**NSCLC PDX**

KIF5B-RET

**Relative Level**

- VEGF-A
  - Vehicle: 3.85
  - BLU-667 3 mg/kg BID: above MTD
  - BLU-667 10 mg/kg BID: 7.2
  - Cabozantinib 60 mg/kg QD: 3.85

**Relative Level**

- VEGF-A
  - Vehicle: 3.85
  - BLU-667 3 mg/kg BID: above MTD
  - BLU-667 10 mg/kg BID: 7.2
  - Cabozantinib 60 mg/kg QD: 3.85
Anticipating On-Target Resistance

- On-target resistance remains an issue for targeted therapies

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Tyrosine Kinase Inhibitor</th>
<th>Drug-Resistant Mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR-ABL</td>
<td>Imatinib, Dasatinib, Nilotinib</td>
<td>T315I</td>
</tr>
<tr>
<td>ALK</td>
<td>Crizotinib</td>
<td>L1152R, C1156Y, <strong>V1196M</strong>, G1202R, G1269A</td>
</tr>
<tr>
<td>EGFR</td>
<td>Gefitinib, Erlotinib, Osimertinib</td>
<td><strong>T790M</strong>, C797S</td>
</tr>
<tr>
<td>KIT</td>
<td>Imatinib</td>
<td>V654A, <strong>T670I</strong>, N822K, D816V</td>
</tr>
<tr>
<td>NTRK</td>
<td>Entrectinib</td>
<td>G595R, G667C,</td>
</tr>
</tbody>
</table>

*Gatekeeper*
BLU-667 Prevents RET Resistance Mutants in Preclinical Studies

Selective and potent inhibition of RET with BLU-667 decreases the frequency of resistance

<table>
<thead>
<tr>
<th>Cell Number (ATP)</th>
<th>V804E</th>
<th>V804M</th>
<th>V804L</th>
<th>Y806C</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10k</td>
<td>480</td>
<td>480</td>
<td>480</td>
<td>480</td>
</tr>
<tr>
<td>10k - 100k</td>
<td>480</td>
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</tr>
<tr>
<td>100k - 1000k</td>
<td>480</td>
<td>480</td>
<td>480</td>
<td>480</td>
</tr>
<tr>
<td>&gt;1000k</td>
<td>480</td>
<td>480</td>
<td>480</td>
<td>480</td>
</tr>
</tbody>
</table>

16x IC50 Cabozantinib

No wells harbored resistant clones

~30% wells harbor resistant clones

8x IC50 BLU-667

Selective and potent inhibition of RET with BLU-667 decreases the frequency of resistance.

<table>
<thead>
<tr>
<th>Ba/F3 KIF5B-RET (RET-driven cell line)</th>
<th>ENU (mutagen)</th>
<th>8x - 64x IC50 (Cabo or BLU-667)</th>
<th>Cell Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>ENU (mutagen)</td>
<td>8x - 64x IC50 (Cabo or BLU-667)</td>
<td>Cell Number (ATP)</td>
<td></td>
</tr>
</tbody>
</table>

Cell Number (ATP)
BLU-667 Induces Dose Dependent Regression and 
pRET Inhibition in \textit{RET} V804L-Driven Allograft

\textbf{KIF5B-RET Ba/F3}

\begin{itemize}
  \item Vehicle QD
  \item Cabozantinib 60 mg/kg QD
  \item BLU-667 3 mg/kg BID
  \item BLU-667 10 mg/kg BID
  \item BLU-667 30 mg/kg BID
  \item BLU-667 60 mg/kg QD
\end{itemize}

Days after start of treatment

\textbf{KIF5B-RET(V804L) Ba/F3}

\begin{itemize}
  \item 3 mpk BLU667 BID
  \item 10 mpk BLU667 BID
  \item 30 mpk BLU667 BID
  \item 20 mpk BLU667 QD
\end{itemize}

Days after start of treatment

\textbf{KIF5B-RET(V804L) Ba/F3 Lysates}

\begin{itemize}
  \item RET
  \item SHC
  \item ERK
  \item Proliferation
\end{itemize}
BLU-667 Phase 1 study (NCT03037385) in RET-driven MTC, NSCLC, and other advanced solid tumors

**Phase 1 study initiated and first patient enrolled in March, 2017**

<table>
<thead>
<tr>
<th>Part 1: Dose escalation <em>Enrolling</em></th>
<th>Part 2: Dose expansion <em>Planned</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Escalation</td>
<td>NSCLC with RET fusion, prior TKI that inhibits RET, N= ~20</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>NSCLC with RET fusion, no prior TKI that inhibits RET, N= ~20</td>
</tr>
<tr>
<td>MGH</td>
<td>Medullary thyroid cancer, N= ~20</td>
</tr>
<tr>
<td>OHSU</td>
<td>RET-altered solid tumors other than NSCLC and MTC, N= ~20</td>
</tr>
<tr>
<td>UC Irvine</td>
<td>Additional sites planned</td>
</tr>
<tr>
<td>U Pennsylvania</td>
<td></td>
</tr>
</tbody>
</table>

**KEY OBJECTIVES**

- **Part 1**: MTD and RP2D, anti-tumor activity, pharmacokinetics, pharmacodynamics
- **Part 2**: Response rate, duration of response, RET gene status in plasma and tumor tissue
BLU-667 has the potential to be a transformative medicine for patients with RET-driven malignancies

- In preclinical studies, BLU-667:
  - Potently inhibits RET wild-type fusions & oncogenic RET mutants
  - Spare VEGFR-2 in a kinome-selective manner
  - Prevents on-target resistance mutations
  - Induces robust tumor growth inhibition in multiple in vivo models of MTC and NSCLC

- BLU-667 is currently being evaluated in a phase 1 trial for patients with MTC, NSCLC and other advanced solid tumors harboring oncogenic RET alterations
RET project team members

- Terri Alvarez-Diez
- Jim Baker
- Andy Boral
- Natasja Brooijmans
- David Brower
- Jason Brubaker
- Elizabeth Burke
- Fong Cao
- Corinne Clifford
- Lucian DiPietro
- Alex Gardino
- Erica Evans
- Paul Fleming
- Tim Guzi
- Wei Hu
- Vic Kadambi
- Joe Kim
- Tim LaBranche
- Debra Mazaik
- Patrick McNamara
- Michelle Maynard
- Stephen Miller
- Michael Nest
- Michael Palmer
- Rami Rahal
- Sherwin Sattarzadeh
- Hongliang Shi
- Grace Silva
- Teghi Singh
- Dawna Smith
- Nico Stransky
- Mike Sheets
- Csani Varga
- Joshua Waetzig
- Weifan Weng
- Steve Wenglowsky
- Gordon Wilkie
- Doug Wilson
- Kevin Wilson
- Ben Wolf
- Yulian Zhang