BLU-701 is a highly potent, brain-penetrant and WT-sparing next-generation EGFR TKI for the treatment of sensitizing (ex19del, L858R) and C797S resistance mutations in metastatic NSCLC

Background

Lung cancer is the leading cause of cancer death globally. The sensitizing activating EGFR-exon 19 deletion (ex19del) and L858R mutations are the oncogenic drivers in ~17% of patients with lung adenocarcinoma, the most common form of non-small cell lung cancer (NSCLC). First- and third-generation (3G) EGFR inhibitors such as gefitinib and osimertinib, respectively, have improved treatment outcomes for patients with EGFR-driven NSCLC, but resistance inevitably emerges, leading to disease progression often with central nervous system (CNS) metastases. Toxicities driven by inhibition of wild-type (WT) EGFR are frequently reported with 1G inhibitors. The 7T99M and C797S mutations are the most common on-target resistance mechanisms to 1G and 3G inhibitors, respectively.

There are no approved therapies for patients with disease progression following treatment with a first-line 3G inhibitor, following disease relapse with free EGFR and second-line 3G inhibitors. BLU-701 and BLU-945 are fourth-generation (4G) investigational EGFR inhibitors designed for use as monotherapy or combination therapies (together or with other agents) to potently suppress activating and in-target resistance EGFR mutants and spare WT EGFR, with potential to treat or prevent CNS metastases (Lim SM et al. AACR 2020 - Abstract 1416). BLU-701 is a highly selective and potent investigational inhibitor of double-mutant EGFR harboring the ex19del or L858R activating mutations and the C797S resistance mutation.

Here we provide further preclinical data to support the clinical development of BLU-701 in patients with EGFR-driven NSCLC.

Methods

• BLU-701 activity was tested in biochemical assays for EGFR mutants and WT EGFR

• Cellular activity was evaluated by a phosphorylation-specific EGFR AlphaLISA assay in WT cell lines and in cell lines expressing EGFR mutations

• The in vivo antitumor activity of BLU-701 was assessed in a PDX ex19del cell line derived xenograft (CDX) tumor model and in tumors grown from Ba/F3 cells expressing EGFR C797S

Results

Table 1: BLU-701 is a WT-sparing potent inhibitor of activating mutant EGFRs and double mutant EGFRm/C797S

<table>
<thead>
<tr>
<th>Compound</th>
<th>WT ex19del</th>
<th>L858R ex19del/C797S</th>
<th>L858R/C797S</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLU-701</td>
<td>54.4 ± 0.5</td>
<td>2.6 ± 0.5</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>11.5 ± 0.5</td>
<td>1.0 ± 0.5</td>
<td>0.7 ± 0.7</td>
</tr>
</tbody>
</table>

Table 2: BLU-701 potently inhibits EGFR autophosphorylation in EGFRm and EGFRm/C797S-driven cell lines

<table>
<thead>
<tr>
<th>Compound</th>
<th>WT ex19del</th>
<th>L858R ex19del/C797S</th>
<th>L858R/C797S</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLU-701</td>
<td>107.2 ± 3.7</td>
<td>3.3 ± 0.3</td>
<td>3.3 ± 0.3</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>21.3 ± 2.1</td>
<td>4.2 ± 0.5</td>
<td>4.2 ± 0.5</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>113.5 ± 1.8</td>
<td>5.0 ± 10.3</td>
<td>&gt;1000</td>
</tr>
</tbody>
</table>

Figure 1: BLU-701 and BLU-945 are optimized for single agent and combination therapy.

Figure 2: BLU-701 selectively inhibits EGFR autophosphorylation in mutant compared with WT cell lines.

Figure 3: BLU-701 strongly inhibits EGFR autophosphorylation in vivo at exposures that spare WT EGFR.

Figure 4: BLU-701 has durable antitumor activity in an EGFR ex19del-driven cancer cell line at doses that spare WT EGFR.

Figure 5: BLU-701 inhibits EGFR autophosphorylation in Ba/F3 CDX models expressing EGFRm/C797S double mutations.

Figure 6: BLU-701 has dose-dependent anti-tumor activity on Ba/F3 CDX models expressing EGFRm/C797S double mutants.

Figure 7: BLU-701 plasma concentrations are comparable to brain concentrations, suggesting significant brain penetration.

Conclusions

• BLU-701 is a potent both-in-class, selective, potent, fourth-generation EGFR TKI with activity against EGFR ex19del/L858R activating mutations and the EGFRm/C797S double mutant

• BLU-701 shows strong inhibition of EGFR autophosphorylation and inhibition of tumor growth at doses that spare WT EGFR

• BLU-701 indicated CNS penetration with potential to treat and prevent CNS metastases in patients with EGFR-driven tumors

• AS BLU-701 has activity against the activating EGFR mutants, these pre-clinical data support the clinical development of BLU-701 in EGFR-driven NSCLC

References

1Carroll JS, John Campbell, Rich Weissman, Jian Guo, Yoar Tinsiel, Maria Fox, Scott Wardwell, Alison Davies, Sharon Chicklas, John Hsieh, Meredith Enol, Omar Ahmad, Dilme Fernandso, Kevin Barvian, Joseph Kim, Steven Kazmirska, Emanuela Persoiu, Tom Dineen, Victoria Brown, Timothy Guizzi, Aggipoo Down, Paul Davoll, Carlin Lott, Claire Mordendonk, Robert Melin,man, Marion Dorsch, Kristin Hendricks. BLU-701 Activity in Biochemical Assays for EGFR Mutants and WT EGFR. Presented at AACR 2021, April 9-14, 2021, Virtual Format. Please contact medinfo@blueprintmedicines.com for permission to reprint and/or distribute.

2Medical writing support was provided by Natasha Tracey, PhD, and editorial support was provided by Travis Taylor, BA, all of Paragon, Knutsford, UK.

3AppTec oncology and immunology department (Shanghai, China) contributed to the study.

4Blueprint Medicines Corporation, Cambridge, Massachusetts, USA