Clinical activity of BLU-667, a highly selective RET inhibitor, in advanced RET-altered thyroid cancers: updated results from the phase 1 ARROW study

Mimi I. Hu, Matthew Taylor, Lori Wirth, Viola Zhu, Robert Doebele, Dae Ho Lee, Ignacio Matos, Christina Baik, Marcia Brose, Giuseppe Curigliano, Gilberto de Lima Lopes, Dong-Wan Kim, Daniel Tan, Chia-Chi Lin, Michael Palmer, Meera Tugnait, Hui Zhang, Brenton Mar, Corinne Clifford, Beni Wolf, Elena Garralda, Sai-Hong Ignatius Ou, Vivek Subbiah, Justin Gainor

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I have the following financial relationships to disclose:

- **Research support**: Sanofi-Genzyme
- **Consultant**: Blueprint Medicines Corporation
- **Advisory board**: Loxo Oncology
BLU-667 is designed to treat *RET*-altered cancers

BLU-667 potently inhibits RET alterations and resistance mutants while sparing VEGFR2

<table>
<thead>
<tr>
<th></th>
<th>RET M918T</th>
<th>RET V804M</th>
<th>CCDC6-RET</th>
<th>VEGFR2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RET M918T</strong></td>
<td>Most common in MTC</td>
<td>Gatekeeper resistance in MTC</td>
<td>Occurs in PTC</td>
<td></td>
</tr>
<tr>
<td>BLU-667</td>
<td>0.4</td>
<td>0.4</td>
<td>0.4</td>
<td>35</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>8</td>
<td>45</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Vandetinib</td>
<td>7</td>
<td>3597</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>23</td>
<td>32</td>
<td>ND</td>
<td>21</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>3</td>
<td>360</td>
<td>4</td>
<td>0.7</td>
</tr>
</tbody>
</table>

VEGFR, vascular endothelial growth factor receptor; IC50, half maximal inhibitory concentration; MTC, medullary thyroid cancer; CCDC6, coiled-coil domain containing 6; PTC, papillary thyroid cancer; ND, not determined. Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and the authors and Blueprint Medicines are not responsible for its content.

PHASE 1, PART 1: PROOF OF CONCEPT

Hu et al. International Thyroid Oncology Group (ITOG) 2018
Subbiah et al. American Association for Cancer Research (AACR) 2018 (clinical trials plenary presentation)
Subbiah et al. Precision Targeted Therapy with BLU-667 for RET-Driven Cancers. Cancer Discovery, July 2018
ARROW trial: first-in-human study with BLU-667

**PART 1: Dose escalation – complete**

**Objective:** Determine MTD/RP2D

*Proof of concept*

**BOIN design**
Advanced MTC, NSCLC*, or other solid tumor*

- MTD/RP2D
  - 400 mg PO daily

*All NSCLC and other solid tumors were RET-altered in cohorts higher than 30 mg QD

**Part 1:** 62 patients treated
- 53 treated at 30 – 600 mg QD
- 9 treated at 200 – 300 mg divided BID dosing

**PART 2: Dose expansion – ongoing**

**Objective:** Determine Overall Response Rate

- **RET-altered NSCLC with prior MKI**
- **RET-altered NSCLC with no prior MKI**
- **MTC with prior MKI**
- **MTC with no prior MKI**
- **Other RET-altered solid tumors (including PTC)**
- **RET-altered solid tumors with prior selective RET TKI**

MTD, maximum tolerated dose; RP2D, recommended Part 2 dose; BOIN, Bayesian optimal interval; MTC, medullary thyroid cancer; NSCLC, non–small cell lung cancer; QD, once daily; BID, twice daily; PO, orally; ORR, overall response rate; MKI, multikinase inhibitor; PTC, papillary thyroid cancer; TKI, tyrosine kinase inhibitor. NCT03037385

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018
Patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total (N=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>57 (19-85)</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>42 (61)</td>
</tr>
<tr>
<td>ECOG, PS, n (%)</td>
<td>26 (38)</td>
</tr>
<tr>
<td>ECOG, PS, n (%) 1-2</td>
<td>43 (62)</td>
</tr>
<tr>
<td>Metastatic disease, n (%)</td>
<td>65 (94)</td>
</tr>
<tr>
<td>Prior systemic therapy, n (%)</td>
<td>51 (74)</td>
</tr>
<tr>
<td>Multikinase inhibitor</td>
<td>21 (30)</td>
</tr>
<tr>
<td>Number of prior regimen, median (range)</td>
<td>1 (0-8)</td>
</tr>
<tr>
<td>Tumor type, n (%)</td>
<td></td>
</tr>
<tr>
<td>Medullary thyroid cancer</td>
<td>37 (54)</td>
</tr>
<tr>
<td>RET fusion papillary thyroid cancer</td>
<td>5 (7)</td>
</tr>
<tr>
<td>RET fusion non–small cell lung cancer</td>
<td>23 (33)</td>
</tr>
<tr>
<td>RET fusion intrahepatic bile duct carcinoma</td>
<td>1 (1)</td>
</tr>
<tr>
<td>RET mutation retroperitoneal paraganglioma</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Non-RET altered solid tumors</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; PS, performance status; MKI, multikinase inhibitor; MTC, medullary thyroid cancer; PTC, papillary thyroid cancer; NSCLC, non–small cell lung cancer; CCDC6, coiled-coil domain containing 6; NCOA4, nuclear receptor coactivator 4.

MTC (N=37)

- RET M918T (70%)
- RET V804M (3%)
- RET C634R/S/W (11%)
- > 1 RET Mutation (5%)
- Other RET (11%)

RET Fusion PTC (N=5)

- NCOA4 (N=3)
- CCDC6 (N=2)

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018
BLU-667 has profound activity in RET-altered thyroid cancer

90% of evaluable RET-altered thyroid cancer patients had tumor shrinkage

Responses seen regardless of RET alteration, including RET V804M, or prior treatment

NCO4A, nuclear receptor coactivator 4; CCDC6, coiled-coil domain containing 6; M, prior MKI therapy; C, prior chemotherapy; O, other therapy; I, prior immunotherapy; PD, progressive disease; SD, stable disease; PR, partial response.

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018
Response rate in MTC patients increases with dose and duration of therapy

### MTC Response Evaluateable Patients

<table>
<thead>
<tr>
<th>Best response, (%)</th>
<th>Total All doses All cycles (N=35)</th>
<th>300/400 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At 8 weeks (N=17)</td>
<td>At 16 weeks (N=16)</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td>17 (49)</td>
<td>6 (35)</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td>1 (3)</td>
<td>1 (6)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>16 (46)</td>
<td>5 (29)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>18 (51)</td>
<td>10 (59)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Pending confirmation: 2 PR, 1 CR, 5 PR

### Results

- **ORR**: 8 (62%) at 24+ weeks in MTC at 300/400 mg QD
- **Response Rate**: 62% at 24+ weeks in MTC at 300/400 mg QD

#Evaluable patients at a specific week considers only post baseline assessments up to at that week of therapy (based on cycle start), or those that discontinued therapy or progressed prior to that.

MTC, medullary thyroid cancer; QD, once daily; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors. Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018.
High ORR in MTC patients treated with BLU-667 regardless of prior MKI Treatment

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Total (n=35) n (%)</th>
<th>No prior MKI (n=18) n (%)</th>
<th>Prior MKI (n=17) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (CR+PR)</td>
<td>17 (49)</td>
<td>9 (50)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>CR</td>
<td>1 (3)</td>
<td>1 (6)</td>
<td>-</td>
</tr>
<tr>
<td>PR*</td>
<td>16 (46)</td>
<td>8 (44)</td>
<td>8 (47)</td>
</tr>
<tr>
<td>SD</td>
<td>18 (51)</td>
<td>9 (50)</td>
<td>9 (53)</td>
</tr>
</tbody>
</table>

MKI, multikinase inhibitor; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria in Solid Tumors.

*2 PRs pending confirmation

Evaluable patients at all cycles include all dosed patients with RECIST target lesions with 1 or more post-baseline assessments or progressed or ended therapy for any reason.
BLU-667 shows durable responses in thyroid cancer patients

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

- Patients remain on treatment for more than 15 months
- Overall, 35 of 42 (83%) patients remain on treatment
- 14 of 14 (100%) treated at 400 mg QD remain on treatment
- 19 of 19 (100%) of responders remain on treatment
- Responses increase over time

PD, progressive disease.
* Patients were allowed to continue on treatment following progressive disease if there was continued clinical benefit.
Significant declines in MTC tumor markers

Carcinoembryonic Antigen (CEA)
23 of 28 (82%) decrease ≥50%

Calcitonin
34 of 37 (92%) decrease ≥50%

MTC, medullary thyroid cancer; CEA, carcinoembryonic antigen.
*Tumor marker normalized.

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018
BLU-667 demonstrates potent activity in germline \textit{RET} V804M mutant MTC

- 52-year-old male gastroenterologist with MTC (germline \textit{RET} V804M gatekeeper mutation) with metastases to neck and mediastinal lymph nodes, lungs, liver and bone
- Progressive disease in liver on sunitinib (AE’s: anorexia, weight loss, diarrhea, hand/foot syndrome, fatigue)
- Initiated BLU-667 at 100 mg BID and escalated to 400 mg QD at C3D1
- By C5D1, showed -41% (PR) reduction in liver metastases; gaining weight (BMI increased from 18.9 to 23.5), no diarrhea
- Remains on treatment in Cycle 7 with continued PR

MTC, medullary thyroid cancer; BSL, baseline; PD, progressive disease; AE, adverse event; BID, twice daily; QD, once daily; PR, partial response; BMI, body mass index. Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018
23-year-old woman with PTC, sclerosing variant (CCDC6-RET fusion) who presented 6 years ago with symptomatic diffuse lung metastases requiring supplemental oxygen \( (O_2) \) since diagnosis; treated with I-131 (total activity 351 mCi) with subsequent fibrosis.

- Progressed on sorafenib and early this year on lenvatinib (increasing \( O_2 \) needs, pleural effusions and intubated 3 times over 6 wks)
- Initiated BLU-667 at 400 mg once daily → RECIST SD (no target lesion/non-target lymphangitic lung metastases)
- Symptomatic response: \( O_2 \) weaned monthly to room air within 5 months, baseline BMI 14.8 steadily increased to 22.3 after 6 mos
- Remains on treatment at Cycle 8 and plans to start college and get her driver’s license this Fall.

**BLU-667 induced dramatic improvement in young PTC patient**
## Safety - BLU-667 is well tolerated

All doses and patients, N=69

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Any event n (%)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>24 (35)</td>
<td>22 (32)</td>
<td>2 (3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>23 (33)</td>
<td>20 (29)</td>
<td>3 (4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>21 (30)</td>
<td>8 (12)</td>
<td>7 (10)</td>
<td>6 (9)</td>
<td>-</td>
<td>4 (6)</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (30)</td>
<td>5 (7)</td>
<td>5 (7)</td>
<td>11 (16)</td>
<td>-</td>
<td>6 (9)</td>
<td>-</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>20 (29)</td>
<td>7 (10)</td>
<td>10 (15)</td>
<td>3 (4)</td>
<td>-</td>
<td>3 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19 (28)</td>
<td>11 (16)</td>
<td>3 (4)</td>
<td>5 (7)</td>
<td>-</td>
<td>4 (6)</td>
<td>-</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19 (28)</td>
<td>5 (7)</td>
<td>5 (7)</td>
<td>6 (9)</td>
<td>3 (4)</td>
<td>5 (7)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>17 (25)</td>
<td>16 (23)</td>
<td>-</td>
<td>1 (1)</td>
<td>-</td>
<td>1 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>16 (23)</td>
<td>15 (28)</td>
<td>1 (1)</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (19)</td>
<td>9 (13)</td>
<td>3 (4)</td>
<td>1 (1)</td>
<td>-</td>
<td>1 (1)</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>12 (17)</td>
<td>9 (13)</td>
<td>2 (3)</td>
<td>1 (1)</td>
<td>-</td>
<td>1 (1)</td>
<td>-</td>
</tr>
</tbody>
</table>

Most AEs were Grade 1

Only 2 discontinuations for related AEs*

AE, adverse event; ALT, alanine aminotransferase.  
*Discontinuations for related AEs: ↑ALT (gr3) and pneumonitis (gr2)

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018
Conclusions

• **BLU-667** has demonstrated:
  – Responses across *RET* genotypes, which increase with dose and time on treatment
    ▪ **Durable and high ORR of 62%** at 300/400 mg QD in patients with MTC at 24+ weeks
    ▪ **100%** of MTC patients treated at 400 mg daily remain on treatment
    ▪ **ORR of ~50%** in MTC patient regardless of prior MKI treatment
    ▪ Patients remain on treatment for more than 15 months
    ▪ **100%** of responders remain on treatment

• BLU-667 is well tolerated at efficacious doses in MTC and PTC patients

• Results warrant further clinical development in MTC and PTC

• **ARROW** trial Part 2 dose expansion is open and enrolling globally in the United States, Europe, and Asia

ORR, overall response rate; QD, once daily; MTC, medullary thyroid cancer; MKI, multikinase inhibitor; PTC, papillary thyroid cancer. Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018
Acknowledgments

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  - Massachusetts General Hospital Cancer Center, Boston, MA, United States
  - Chao Family Comprehensive Cancer Center University of California Irvine Medical Center, Irvine, CA, United States
  - University of Colorado, Aurora, CO, United States
  - University of Miami, Miami, FL, United States
  - University of Washington, Seattle Cancer Care Alliance, Seattle, WA, United States
  - Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, United States
  - Asan Medical Center, Seoul, Republic of Korea
  - Vall d'Hebron University Hospital, Barcelona, Spain
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  - Seoul National University Hospital, Seoul, Republic of Korea
  - National Cancer Centre Singapore, Singapore, Singapore
  - National Taiwan University Hospital, Taipei, Taiwan