Clinical Activity and Tolerability of BLU-667, a Highly Potent and Selective RET Inhibitor, in Patients with Advanced RET-Fusion+ Non-small Cell Lung Cancer

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Disclosures

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BLU-667 is an investigational agent discovered by and currently in development by Blueprint Medicines Corporation (Blueprint Medicines)
RET Alterations: Diverse Oncogenic Drivers Lacking Targeted Therapeutic Approach

Non-small cell lung cancer: ~1-2% RET fusions\(^1,2\)

Advanced medullary thyroid cancer: ~90% RET mutations\(^3\)

Papillary thyroid cancer: ~20% RET fusions\(^4\)

Multiple other tumor types including esophageal, breast, melanoma, colorectal, and leukemia: <1% RET-altered\(^5,6\)

NSCLC patients with RET fusions have not significantly benefited from existing therapy

- Chemotherapy: nonspecific, low response rates, significant toxicity
- Checkpoint inhibition: Preliminary evidence for lack of benefit in RET-altered NSCLC\(^7\)
- Multikinase inhibitors: ↓ activity, ↑ off-target toxicity\(^8,9\)

No selective RET inhibitors are approved
**BLU-667 Potently and Selectively Inhibits RET Alterations and Resistance Mutants**

**BLU-667: High kinome selectivity for RET\(^a\)**

BLU-667 vs. pharmacologically relevant kinases:
- ~90-fold more selective for RET than VEGFR2
- 20-fold more selective for RET than JAK1

**BLU-667 Cellular activity in KIF5B-RET\(^2\)**

<table>
<thead>
<tr>
<th></th>
<th>KIF5B-RET</th>
<th>KIF5B-RET V804L</th>
<th>KIF5B-RET V804M</th>
<th>KIF5B-RET V804E</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLU-667</td>
<td>10.1 nM (1x)</td>
<td>8.1 nM (0.8x)</td>
<td>14.1 nM (1.4x)</td>
<td>8.1 nM (0.8x)</td>
</tr>
</tbody>
</table>

**KIF5B-RET**

- Vehicle QD
- Cabozantinib 60 mg/kg QD
- BLU-667 3 mg/kg BID
- BLU-667 10 mg/kg BID
- BLU-667 30 mg/kg BID

**Cabozantinib-resistant KIF5B-RET(V804L)**

- Vehicle QD
- Cabozantinib 60 mg/kg QD
- BLU-667 3 mg/kg BID
- BLU-667 10 mg/kg BID
- BLU-667 30 mg/kg BID

*In vivo models of implanted, engineered Ba/F3 cells\(^1\)*

**Notes:**
- Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content. BLU-667 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines). 1. Subbiah, et al. Cancer Discovery 2018; 2. Blueprint internal data

\(\textit{a}\) Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content. BLU-667 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines).
ARROW: BLU-667 Dose-Escalation and Expansion Study

Part 1:
Dose-Escalation (N=62; Complete)\(^1\)

- RET-altered advanced solid tumors
- BLU-667: 30-600 mg by daily oral administration (QD or BID)

Phase 2 dose determined (400 mg QD)

ARROW is registered with clinicaltrials.gov (NCT03037385)

Part 2:
Expansion Cohorts (Ongoing)

**BLU-667 400 mg QD**
- Unresectable, advanced solid tumor
- RET alteration status by local tumor testing
- No additional driver mutation
- ECOG PS 0-1
- Asymptomatic brain metastases allowed
- Progressive disease or intolerant to SOC therapy, or not a candidate

**Primary objectives:**
Overall response rate (RECIST 1.1)
Safety

**RET fusion+ NSCLC, prior platinum (n=80)**

**RET fusion+ NSCLC, platinum naïve (n=40)**

**MTC, prior cabozantinib or vandetanib (n=60)**

**MTC, no prior cabozantinib or vandetanib (n=40)**

**Other RET fusion+ tumors (n=40)**

**Other RET-mutated tumors (n=40)**

**RET-altered, prior selective RET inhibitor (n=20)**

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## Baseline Characteristics

### RET Fusion+ Advanced NSCLC Patients

**ECOG PS, Eastern Cooperative Oncology Group Performance Status.**

- **Smoking history is unknown for one patient.**
- **Includes RET fusion+ by fluorescence in situ hybridization (FISH); RET fusion partner to be determined via central analysis. Data cut-off date: 28 Apr 2019.**

### RET Fusion Partner

- **KIF5B**: 66%
- **CCDC6**: 13%
- **Fusion partner unknown**: 19%
- **Other (DOCK1, EML4)**: 2%

### Table: RET-Fusion+ Advanced NSCLC

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (N=120)</th>
<th>Prior Platinum (N=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (range)</td>
<td>60 (28-87)</td>
<td>60 (28-85)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>59 (49)</td>
<td>45 (49)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>46 (38)</td>
<td>33 (36)</td>
</tr>
<tr>
<td>1-2</td>
<td>74 (62)</td>
<td>58 (64)</td>
</tr>
<tr>
<td>Brain metastases, n (%)</td>
<td>48 (40)</td>
<td>36 (40)</td>
</tr>
<tr>
<td>Prior systemic regimens, median (range)</td>
<td>2 (0-11)</td>
<td>2 (1-11)</td>
</tr>
<tr>
<td>Any prior anticancer treatment</td>
<td>101 (84)</td>
<td>91 (100)</td>
</tr>
<tr>
<td>Chemotherapy, n (%)</td>
<td>92 (77)</td>
<td>91 (100)</td>
</tr>
<tr>
<td>PD-1 or PD-L1 inhibitor, n (%)</td>
<td>47 (39)</td>
<td>41 (45)</td>
</tr>
<tr>
<td>Chemotherapy + PD-(L)1 combination, n (%)</td>
<td>41 (34)</td>
<td>41 (45)</td>
</tr>
<tr>
<td>Multikinase inhibitor, n (%)</td>
<td>21 (18)</td>
<td>20 (22)</td>
</tr>
<tr>
<td>Smoking historya</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current/Prior</td>
<td>41 (34)</td>
<td>33 (36)</td>
</tr>
<tr>
<td>Never</td>
<td>78 (65)</td>
<td>57 (63)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>114 (95)</td>
<td>87 (96)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (5)</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

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*ECOG PS, Eastern Cooperative Oncology Group Performance Status.*

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*Includes RET fusion+ by fluorescence in situ hybridization (FISH); RET fusion partner to be determined via central analysis. Data cut-off date: 28 Apr 2019.*

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*Smoking history is unknown for one patient.*

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*Presented by: Justin F. Gainor*
BLU-667 is Well Tolerated by Patients with RET Fusion+ Advanced NSCLC

Among 120 pts with advanced NSCLC receiving BLU-667 starting dose of 400 mg QD:

- Treatment-related toxicity is generally low-grade and reversible
- 7% discontinued BLU-667 due to treatment-related toxicity*  
  - Pneumonitis, respiratory distress/hypoxemia, mucositis/colitis, myelosuppression, gait disturbance, anemia

### Treatment-Emergent and Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>All</th>
<th>Grade ≥3</th>
<th>All</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>30%</td>
<td>2%</td>
<td>17%</td>
<td>2%</td>
</tr>
<tr>
<td>Neutropeniaa</td>
<td>26%</td>
<td>13%</td>
<td>26%</td>
<td>13%</td>
</tr>
<tr>
<td>AST increased</td>
<td>24%</td>
<td>5%</td>
<td>20%</td>
<td>2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21%</td>
<td>3%</td>
<td>13%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20%</td>
<td>13%</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Anemia</td>
<td>18%</td>
<td>7%</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18%</td>
<td>2%</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18%</td>
<td>-</td>
<td>2%</td>
<td>-</td>
</tr>
<tr>
<td>ALT increased</td>
<td>17%</td>
<td>3%</td>
<td>13%</td>
<td>2%</td>
</tr>
<tr>
<td>Cough</td>
<td>17%</td>
<td>-</td>
<td>3%</td>
<td>-</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>17%</td>
<td>-</td>
<td>12%</td>
<td>-</td>
</tr>
</tbody>
</table>

Additional grade ≥3 treatment related AEs (≥2%): increased CPK (3%), leukopeniab (3%).

* Across the entire study (n=276), rate of discontinuation due to treatment-related toxicity is 4%.

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a Combined term including decreased neutrophils and neutropenia.

b Combined term including leukopenia and white blood cell count decreased.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase. Data cut-off date: 28 Apr 2019.
BLU-667 Demonstrates Substantial Antitumor Activity in RET Fusion+ Advanced NSCLC

BLU-667 Starting Dose 400 mg QD

<table>
<thead>
<tr>
<th>Best Response</th>
<th>All (N=48)</th>
<th>Prior Platinum (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>58% (43–72)</td>
<td>60% (42–76)</td>
</tr>
<tr>
<td>CR*</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PR*</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>SD</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>DCR (95% CI)</td>
<td>96% (86–99)</td>
<td>100% (90–100)</td>
</tr>
</tbody>
</table>

* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

- 5/7 (71%) treatment-naïve patients had confirmed PR

CI, confidence interval; CR, complete response; DCR, disease control rate (best response of SD or better); ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease. Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19. Response-evaluable population includes patients with measurable disease at baseline and ≥1 evaluable post-treatment disease assessment, and excludes 4 patients who previously received >1 cycle of a selective RET inhibitor.
BLU-667 Induces Rapid and Durable Responses in RET Fusion+ Advanced NSCLC

- Most responses occur at the first scan (week 8)
- 82% of responding patients remain on treatment as of the data cut-off
- Median duration of response not yet reached
- Patients have been on treatment up to 24 months (including dose-escalation and regardless of starting dose)
BLU-667 is Active Regardless of Prior Checkpoint Treatment

BLU-667 Starting Dose 400 mg QD

Prior PD-1 or PD-L1 inhibitor
PD-1 and PD-L1 inhibitor naïve

Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.
BLU-667 is Active Across RET Fusion Genotypes

BLU-667 Starting Dose 400 mg QD

Maximum % Reduction from Baseline
Sum of Diameters of Target Lesions

-100 -80 -60 -40 -20 0 20 40

-100 -80 -60 -40 -20 0 20 40

CCDC6
KIF5B
Other/unknown

Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.
BLU-667 is Active Regardless of CNS Involvement

BLU-667 Starting Dose 400 mg QD

- Maximum % Reduction from Baseline
- Sum of Diameters of Target Lesions

- CNS involvement
- No CNS involvement

Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.
BLU-667 is Active Against Intracranial Metastases

- 7 of 9 (78%) patients had shrinkage of measurable brain metastases
- No patients at 400 mg QD starting dose had progression due to new CNS involvement

Data shown for 9 patients with brain lesion(s) identified as RECIST 1.1 target lesions at baseline.
Data cut-off date: 28 Apr 2019.
BLU-667 is Active Against Intracranial Metastases

- 52-year-old woman, RET fusion+ NSCLC, prior platinum and checkpoint inhibitor
- Near-complete resolution of previously untreated target brain metastasis after two months of BLU-667 400 mg QD
- Continues to receive treatment with ongoing confirmed PR (70% shrinkage) at ~6 months

- 59-year-old man, RET fusion+ NSCLC, prior platinum and checkpoint inhibitor
- Complete resolution of previously untreated nontarget brain metastasis after two months of BLU-667 400 mg QD
- Continues to receive treatment with ongoing confirmed PR (67% shrinkage) at ~6 months

Images courtesy of Dr. Stephen Liu, Georgetown University, Washington, D.C.

Data cut-off 28 Apr 19.
Among patients receiving a BLU-667 starting dose of 400 mg QD:

- 18/20 (90%) with detectable RET fusion ctDNA at baseline had complete clearance within the first cycle

- Clearance of genomic driver variants ctDNA has been associated with improved cancer outcomes\(^1\)–\(^3\)

BLU-667 has Activity in Other RET Fusion+ Malignancies

- PR in 2/2 patients with metastatic pancreatic cancer
  - 67 yo male, CCDC6-RET fusion, continues with confirmed PR (53% shrinkage) at ~6 months
  - 31 yo male, TRIM33-RET and JMJD1C-RET fusions, continues treatment after PR (41% shrinkage) at first response assessment

- PR in a patient with intrahepatic bile duct carcinoma
  - 51 yo female, NCOA4-RET fusion, continues with confirmed PR (67% shrinkage) at ~15 months

- ORR 83% (5/6)* in RET-fusion PTC (Abstract 6018 presented June 1, 2019)

- Safety profile similar to what was seen in RET fusion+ NSCLC

* Confirmation of response is pending for two patients. Data cut-off date: 28 Apr 2019.
Conclusions

- BLU-667 demonstrates broad and durable antitumor activity in patients with RET fusion+ advanced NSCLC
  - 60% ORR and 100% DCR in patients previously treated with platinum chemotherapy, and 58% ORR in all RET fusion+ patients
  - Responses observed regardless of treatment history, RET fusion partner or CNS involvement
  - Active against intracranial metastases
  - Well tolerated at 400 mg QD with most AEs grade 1/2

- BLU-667 has FDA breakthrough therapy designation in RET fusion+ NSCLC that progressed following platinum based chemotherapy

- Data support expansion of ARROW trial in treatment-naïve NSCLC patients and continued enrollment of other RET-altered solid tumor groups
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  - Universitätsklinikum Essen, Essen, Germany
  - Pius-Hospital Oldenberg, Oldenberg, Germany
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