Highly potent and selective RET inhibitor, BLU-667, achieves proof of concept in ARROW, a phase 1 study of advanced, RET-altered solid tumors

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BLU-667 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines)
Receptor tyrosine kinase, *RE*arranged during *Transfection* (*RET*)

Organ development and tissue homeostasis
Receptor tyrosine kinase, **REarranged during Transfection (RET)**

Organ development and tissue homeostasis

Normal RET signaling

- GDNF ligand
- RET Proto-oncogene

Oncogenic RET signaling

- Activating RET mutations*
- C620/C634
- V804L/M
- M918T
- Dimeric RET fusions
  - KIF5B-, CCDC6-, NCOA4,
  - TRIM-33- and more partners

Normal RET signaling

- ✓
- RAS/RAF/MEK/ERK
- Tumorigenesis

**GFRα1**, **TK1**, **TK2**
RET is a rare driver of multiple, diverse tumor types\textsuperscript{1,2}

- Medullary thyroid cancer >60% RET-mutations
- Papillary thyroid cancer ~10% RET-fusions
- Non-small cell lung cancer ~1-2% RET-fusions
- Colorectal cancer
- Breast cancer
- Melanoma
- Esophageal cancer
- Leukemia
- Other tumor types ≤1% RET-altered

Patients with *RET*-alterations have not benefited from precision oncology

**Precision oncology**

Non-small cell lung cancer

- **EGFR mutation**
- **ALK-fusion**
- **ROS-fusion**

Selective RTK inhibitors¹

↑Activity and ↓off-target toxicity

- Typical ORR >60%
- Typical PFS >9 months
- Favorable tolerability

MKI, multikinase inhibitors; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival; RTK, receptor tyrosine kinase

Patients with \textit{RET}-alterations have not benefited from precision oncology.

**Precision oncology**

Non-small cell lung cancer

- \textit{EGFR} mutation
- \textit{ALK}-fusion
- \textit{ROS}-fusion

Selective RTK inhibitors\(^1\)

\textarrow{↑Activity and ↓off-target toxicity}

Typical ORR >60%
Typical PFS >9 months
Favorable tolerability

**Current “non-targeted” paradigms for RET**

NSCLC

- \textit{RET}-fusion

  - Chemotherapy
  - Immunotherapy
  - Multikinase inhibitors

  Multikinase Inhibitors\(^2\)

  \textarrow{↓Activity and ↑off-target toxicity}

  NSCLC
  
  Typical ORR <30%
  
  Typical PFS ~4.6–7.3 months
  
  MKI have frequent dose reduction/interruption for treatment related toxicity

MTC

- \textit{RET}-mutation

  Multikinase inhibitors

- \textit{RET}-fusion

  No standard of care

MTC

Typical ORR 25-45%
Typical PFS ~11-30 months

NSCLC

Typical ORR <30%
Typical PFS ~4.6–7.3 months

MKI, multikinase inhibitors; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer;
ORR, overall response rate; PFS, progression-free survival; RTK, receptor tyrosine kinase

BLU-667 was designed to treat RET-altered cancers

Subnanomolar potency\(^1\)

<table>
<thead>
<tr>
<th>Variant</th>
<th>Biochemical IC(_{50}) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RET wildtype</td>
<td>0.4</td>
</tr>
<tr>
<td>RET V804L</td>
<td>0.3</td>
</tr>
<tr>
<td>RET V804M</td>
<td>0.4</td>
</tr>
<tr>
<td>RET M918T</td>
<td>0.4</td>
</tr>
<tr>
<td>CCDC6-RET</td>
<td>0.4</td>
</tr>
</tbody>
</table>

More Potent than MKI

Kinome selectivity for RET

1. Subbiah V et al. *Cancer Discovery* April 15 2018

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (CSTI) (www.cellsignal.com). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.
BLU-667 potently inhibits RET-driven tumor growth

KIF5B-RET NSCLC patient-derived xenograft

Potent Pathway inhibition

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

BID, two times per day; QD, once daily 1. Subbiah V et al. Cancer Discovery April 15 2018
**BLU-667 ARROW first-in-human study**

**Part 1: Dose escalation – completed**
- Opened March 2017
- Advanced RET-altered solid tumors
  - BOIN design
  - BLU-667 orally QD continuous
- MTD

**Part 2: Dose expansion – enrolling**
- NSCLC
  - Failed prior kinase inhibitor
- NSCLC
  - No prior kinase inhibitor
- Medullary Thyroid Cancer
- Other RET-altered solid tumors

**Key objectives**
- MTD, safety, pharmacokinetics, pharmacodynamics, anti-tumor activity

BOIN, Bayesian optimal interval; MTD, maximum tolerated dose
Demography and baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(N=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; median (range)</td>
<td>56 (19-83)</td>
</tr>
<tr>
<td>Sex, male; n (%)</td>
<td>30 (57)</td>
</tr>
<tr>
<td>ECOG PS; n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21 (40)</td>
</tr>
<tr>
<td>1</td>
<td>32 (60)</td>
</tr>
<tr>
<td>Metastatic disease; n (%)</td>
<td>50 (94)</td>
</tr>
<tr>
<td>Tumor type; n (%)</td>
<td></td>
</tr>
<tr>
<td><em>RET</em>-alteration</td>
<td>51 (96)</td>
</tr>
<tr>
<td>Medullary thyroid cancer</td>
<td>29 (55)</td>
</tr>
<tr>
<td>Non-small cell lung cancer</td>
<td>19 (36)</td>
</tr>
<tr>
<td>Papillary thyroid cancer</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Retroperitoneal Paraganglioma</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Non-<em>RET</em> altered solid tumor</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Prior systemic therapy; n (%)</td>
<td>41 (77)</td>
</tr>
<tr>
<td>Multikinase inhibitor; n (%)</td>
<td>27 (51)</td>
</tr>
<tr>
<td>Chemotherapy; n (%)</td>
<td>19 (36)</td>
</tr>
<tr>
<td>Immunotherapy; n (%)</td>
<td>18 (34)</td>
</tr>
<tr>
<td># of lines, median (range)</td>
<td>1 (0-8)</td>
</tr>
</tbody>
</table>

Data cut-off: April 6, 2018

ECOG PS, Eastern Cooperative Oncology Group performance score
Diverse RET genotypes enrolled

**RET Mutations**
- M918T: 72%
- Other RET: 10%
- Multiple: 7%
- V804M: 4%
- C634R: 7%

**RET Fusions**
- KIF5B: 63%
- CCDC6: 21%
- KIAA1468: 5%
- RET FISH+: 11%

**Non-small cell lung cancer**
- N=19

**Medullary thyroid cancer**
- N=29

**Paraganglioma**
- N=1
- RET R77H

**Papillary thyroid cancer**
- N=2
- CCDC6-RET: 100%

Data cut-off: April 6, 2018
# Dose escalation results

## Maximum Tolerated Dose – 400 mg QD

<table>
<thead>
<tr>
<th>Dose (mg QD)</th>
<th># Evaluable (N=49)</th>
<th>Dose limiting toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>60</td>
<td>6</td>
<td>None</td>
</tr>
<tr>
<td>100</td>
<td>5</td>
<td>Alanine transaminase increased (1)</td>
</tr>
<tr>
<td>200</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>300</td>
<td>11</td>
<td>Tumor lysis syndrome (1) Hypertension (1)</td>
</tr>
<tr>
<td><strong>400</strong></td>
<td><strong>10</strong></td>
<td>Asthenia (1) Hypertension (1)</td>
</tr>
<tr>
<td>600</td>
<td>4</td>
<td>Hyponatremia (1) Hypertension (1)</td>
</tr>
</tbody>
</table>

ALT, alanine aminotransferase

Data cut-off: April 6, 2018

41 of 53 patients remain on treatment (median 3.9 months [range: 0.3–11.5])

53

41

1 non-compliance

1 unrelated death

8 Progressive Disease

1 unrelated AE

1 related AE (↑ALT)
Dose-dependent exposure and RET pathway inhibition

Steady-state Pharmacokinetics

Tumor Pharmacodynamics

Percentage reduction in DUSP6 and SPRY4 vs Baseline

RET → MEK → ERK → DUSP6 / SPRY4

<table>
<thead>
<tr>
<th>BLU-667 mean plasma concentration (ng/mL)</th>
<th>Time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 mg QD</td>
<td>0 5 10 15 20 25</td>
</tr>
<tr>
<td>60 mg QD</td>
<td></td>
</tr>
<tr>
<td>100 mg QD</td>
<td></td>
</tr>
<tr>
<td>200 mg QD</td>
<td></td>
</tr>
<tr>
<td>300 mg QD</td>
<td></td>
</tr>
<tr>
<td>400 mg QD</td>
<td></td>
</tr>
<tr>
<td>600 mg QD</td>
<td></td>
</tr>
</tbody>
</table>
Dose-dependent decline in MTC tumor markers

Carcinoembryonic antigen (CEA)

Calcitonin

Data cut-off: April 6, 2018
Potent activity against highly invasive \textit{RET}-mutant MTC

27-year-old male; \textit{RET} L629-D361 Del; initiated at 60 mg; ongoing at 400 mg with confirmed PR
Potent activity against KIF5B-RET NSCLC – post chemotherapy

Baseline

FISH

Breakpoint

FUSION

Month 4

Potent activity against KIF5B-RET NSCLC – post chemotherapy

37-year-old female; ongoing at 400 mg with confirmed PR

Subbiah V et al. Cancer Discovery April 15 2018
Potent activity against KIF5B-RET NSCLC – post-vandetinib+everolimus

Baseline

First Assessment (Month 2)

74-year-old male; initiated at 300 mg; ongoing at 400 mg; PR at month 5 pending confirmation  Subbiah V et al. Cancer Discovery April 15 2018
Activity against KIF5B-RET NSCLC brain metastases

Baseline First assessment (Month 2)

69-year-old male; initiated at 400 mg; ongoing at month 4

Images courtesy of Drs. of Gainor, J and Lin, J of MGH
BLU-667 has broad anti-tumor activity against RET-altered cancers

Data cut-off: April 6, 2018

C, prior chemotherapy; CR, complete response; I, prior immunotherapy; M, prior MKI therapy; MKI, multikinase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease

Best Response | Evaluable Patients (N=40) n, (%)
---|---
CR* | 1 (3)
PR** | 17 (43)
SD | 20 (50)
PD | 2 (5)

* confirmed ** 10 confirmed, 7 pending confirmation

C, prior chemotherapy; CR, complete response; I, prior immunotherapy; M, prior MKI therapy; MKI, multikinase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease

Data cut-off: April 6, 2018
BLU-667 has durable activity and high response rate in RET-altered NSCLC

Prior Therapy

- M
- IC
- I
- MC
- C
- IC
- IC
- IC
- MC
- MIC
- MIC
- C
- MIC
- I
- C
- MIC

Treatment Duration (days)

Best Response | Evaluable Patients (N=14); n (%) |
---|---|
CR | 0 |
PR* | 7 (50) |
SD | 5 (36) |
PD | 2 (14) |

* 5 confirmed, 2 pending confirmation

Data cut-off: April 6, 2018

Treatment duration:
Median 3.9 months
Range 0.4–11.4 months
13/19 (68%) on treatment
BLU-667 has durable activity and high response rate in RET-altered MTC

Prior Therapy

Best Response | Evaluable Patients; (N=25) N (%)
--- | ---
CR* | 1 (4)
PR** | 9 (36)
SD | 15 (60)
PD | 0

*confirmed;**5 confirmed,4 pending confirmation

Treatment duration:
Median 4.7 months
Range 0.5–11.5 months
25/29 (86%) on treatment

Data cut-off: April 6, 2018
BLU-667 is well tolerated

Treatment-emergent Adverse Events ≥10% per CTCAE
(30-400 mg Safety Population, N=49)

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4/5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>10 (20)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ALT increased</td>
<td>10 (20)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>8 (16)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>4 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (10)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>6 (12)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>6 (12)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperphosphatemia</td>
<td>4 (8)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (10)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>5 (10)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>0</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>2 (4)</td>
<td>2 (4)</td>
<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (10)</td>
<td>2 (4)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>3 (6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Most adverse events were Grade 1
8 (16%) patients had Grade 3 treatment-related AE
No Grade 4/5 treatment-related AEs

AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CTCAE, common terminology criteria for adverse events

Data cut-off: April 6, 2018
Conclusions

• **BLU-667** delivers:
  – Potent RET pathway inhibition with favorable tolerability
  – Broad anti-tumor activity regardless of *RET* genotype, indication and prior therapy
  – High preliminary response rates and durable activity
    – ORR: RET-fusion NSCLC 50%
    – ORR: RET-mutant MTC 40%
    – ORR: *RET*-fusions and mutations (NSCLC, MTC and PTC) 45%
    – 41 of 51 *RET*-altered patients remain on treatment

• **ARROW** dose escalation data validate BLU-667 as a promising precision therapy for *RET*-altered cancers

• **ARROW** dose expansion is open and enrolling globally

• **BLU-667** manuscript published today in Cancer Discovery
  – Foundational preclinical work and clinical translation

Data cut-off: April 6, 2018
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  – Department of Medicine, Massachusetts General Hospital Cancer Center, Boston, United States
  – Chao Family Comprehensive Cancer Center University of California Irvine Medical Center, United States
  – Abramson Cancer Center, University Of Pennsylvania, United States
  – Vall d’Hebron Institute of Oncology Vall d’Hebron University Hospital, Barcelona, Spain