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

Vivek Subbiah\(^1\), Matthew Taylor\(^2\), Jessica Lin\(^3\), Mimi Hu\(^1\), Sai-Hong Ignatius Ou\(^4\), Marcia S. Brose\(^5\), Elena Garralda\(^6\), Corinne Clifford\(^7\), Michael Palmer\(^7\), Meera Tugnait,\(^7\) Erica Evans\(^7\), Hongliang Shi\(^7\), Beni Wolf\(^7\), and Justin Gainor\(^3\)

\(^1\)Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, United States;
\(^2\)The Knight Cancer Institute, Oregon Health & Science University, Portland, United States;
\(^3\)Department of Medicine, Massachusetts General Hospital, Boston, United States,
\(^4\)Chao Family Comprehensive Cancer Center, University of California Irvine Medical Center, United States;
\(^5\)Abramson Cancer Center, University Of Pennsylvania, Philadelphia, United States;
\(^6\)Vall d’Hebron Institute of Oncology, Vall d’Hebron University Hospital, Barcelona, Spain;
\(^7\)Blueprint Medicines Corporation, Cambridge, United States;

NCT03037385

©2018 Blueprint Medicines Corporation
Disclosures

I have the following financial relationships to disclose:

Grant/Research support from:

- Blueprint Medicines Corporation
- Novartis International AG
- Bayer AG
- GlaxoSmithKline plc
- NanoCarrier Co. Ltd
- Vegenics Pty Ltd
- Northwest Biotherapeutics
- Boston Biomedical Inc
- Berg
- Incyte Corporation
- Fujifilm Holdings Corporation
- PharmaMar
- D3
- Pfizer Inc
- MultiVir Inc
- Amgen Inc
- AbbVie Inc
- Loxo Oncology
- F. Hoffmann-La Roche AG / Genentech Inc
- National Comprehensive Cancer Network
- National Cancer Institute-Cancer Therapy Evaluation Program

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

Normal RET signaling

GDNF ligand

RET Receptor Tyrosine Kinase

\(\alpha1\)

TK1

TK2

\(\bullet\)

\(\checkmark\)

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

Organ development and tissue homeostasis

Normal RET signaling

- GDNF ligand
- RET Proto-oncogene
- GFRα1
- TK1
- TK2
- RAS/RAF/MEK/ERK
- ✓

Oncogenic RET signaling

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

**Tumorigenesis**
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

Other tumor types ≤1% RET-altered

- Esophageal cancer
- Breast cancer
- Melanoma
- Colorectal cancer
- Leukemia

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 inhibitors**

- **↑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 *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

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

**NSCLC**

- RET- fusion
- Chemotherapy
- Immunotherapy
- Multikinase inhibitors

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

**MTC**

- RET-mutation
- Multikinase inhibitors

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

**Refractory solid tumor**

- RET-fusion
- No standard of care

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

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (CSTI) ([www.cellsignal.com](http://www.cellsignal.com)). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.

1. Subbiah V et al. *Cancer Discovery* April 15 2018
BLU-667 potently inhibits RET-driven tumor growth

KIF5B-RET NSCLC patient-derived xenograft

Potent Pathway inhibition

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
<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>RET-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-RET 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>

ECOG PS, Eastern Cooperative Oncology Group performance score

Data cut-off: April 6, 2018
Diverse RET genotypes enrolled

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

RET Fusions
- KIF5B 63%
- CCDC6 21%
- KIAA 1468- 5%
- RET FISH+ 11%

Medullary thyroid cancer N=29
- Non-small cell lung cancer N=19

Paraganglioma N=1
- RET R77H

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

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

<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>
</tbody>
</table>
| 300          | 11                  | Tumor lysis syndrome (1)  
|              |                     | Hypertension (1)         |
| 400          | 10                  | Asthenia (1)  
|              |                     | Hypertension (1)         |
| 600          | 4                   | Hyponatremia (1)  
|              |                     | Hypertension (1)         |

Maximum Tolerated Dose – 400 mg QD

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

ALT, alanine aminotransferase

Data cut-off: April 6, 2018
Dose-dependent exposure and RET pathway inhibition

Steady-state Pharmacokinetics

Tumor Pharmacodynamics

- RET → MEK → ERK → DUSP6 / SPRY4

Percentage reduction in DUSP6 and SPRY4 vs Baseline

- BLU-667 mean plasma concentration (ng/mL)
- Time (h)
- Plasma IC\textsubscript{90}
- Brain IC\textsubscript{90}

30 mg QD  60 mg QD  100 mg QD  200 mg QD  300 mg QD  400 mg QD  600 mg QD
Dose-dependent decline in MTC tumor markers

Carcinoembryonic antigen (CEA)

Calcitonin

% reduction in CD21

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

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

Baseline

Month 4

FISH

Breakpoint

KIF5B
10p11.22

RET
10q11.21

FUSION

KIF5B Exons 1-15
Chr10:32315000

RET Exons 12-20
Chr10:43610000

Reduction in Tumor
cT DNA (% Baseline)

TP53 cDNA
KIF5B cDNA
Tumor

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

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Evaluable Patients (N=40) n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR*</td>
<td>1 (3)</td>
</tr>
<tr>
<td>PR**</td>
<td>17 (43)</td>
</tr>
<tr>
<td>SD</td>
<td>20 (50)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

* confirmed ** 10 confirmed, 7 pending confirmation
BLU-667 has durable activity and high response rate in RET-altered NSCLC

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Evaluable Patients (N=14); n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>0</td>
</tr>
<tr>
<td>PR*</td>
<td>7 (50)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (36)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (14)</td>
</tr>
</tbody>
</table>

* 5 confirmed, 2 pending confirmation

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

Prior Therapy

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

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

*confirmed;**5 confirmed, 4 pending confirmation

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></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
Acknowledgements

• We thank the participating patients, their families, all study co-investigators, and research co-ordinators at the following institutions:

  – Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, United States
  – The Knight Cancer Institute Oregon Health & Science University Portland, United States
  – 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