Clinical activity Of BLU-554, a potent, highly-selective FGFR4 inhibitor in advanced HCC with FGFR4 pathway activation

Yoon-Koo Kang*,1, Teresa Macarulla2, Thomas Yau3, Debashis Sarker4, Su Pin Choo5, Tim Meyer6, Jonathan Whisenant7, Max Sung8, Antoine Hollebecque9, Andrew Zhu10, Jung-Hwan Yoon11, Joong-Won Park12, Sandrine Faivre13, Hongliang Shi14, Terri Alvarez-Diaz14, Oleg Schmidt-Kittler14, Corinne Clifford14, Beni Wolf14, Richard Kim15

1Oncology, Asan Medical Center, Seoul, Republic of Korea, 2Medical Oncology, Vall d’Hebron University Hospital, Barcelona, Spain, 3Department of Medicine, Queen Mary Hospital, Hong Kong, Hong Kong, 4Early Phase Trials Unit, Guy’s Hospital, London, United Kingdom, 5Medical Oncology, National Cancer Centre, Singapore, Singapore, 6Oncology, UCL Cancer Institute, London, United Kingdom, 7Internal Medicine, Huntsman Cancer Institute, Salt Lake City, United States 8Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, United States, 9Oncology, Institut Gustave Roussy, Villejuif, France, 10Oncology, Massachusetts General Hospital, Boston, United States, 11Department of Internal Medicine, Seoul National University Hospital, 12Center for Liver Cancer, National Cancer Center, Goyang, Republic of Korea, 13Oncology, Beaujon University Hospital, Clichy, France, 14Clinical Development, Blueprint Medicines Corporation, Cambridge, United States, 15Gastrointestinal Oncology, Moffitt Cancer Center, Tampa, United States
Disclosures

• BLU-554 is an investigational agent currently in development by Blueprint Medicines Corporation (Blueprint Medicines)

• Dr Yoon-Koo Kang is an investigator for Blueprint Medicines’ ongoing Phase 1 studies in advanced HCC

• Dr Yoon-Koo Kang has the following disclosures:
  - Consultant: Blueprint Medicines, BMS, Ono, Astra Zenca, Roche, Merck, Novartis, Sanofi, Bayer, Daehwa, LSK Biopharma,
  - Equity interest: none
  - Research funding: Daehwa, LSK Biopharma, Novartis, Bayer
  - Expert testimony: none
  - Patents: none
**FGF19** identified as a potential HCC driver

- FGF19 is a mitogen that signals via FGFR4 and KLB
  - Normal liver and HCC express FGFR4 and KLB
- Aberrant FGF19 expression may drive HCC and confer poor prognosis

Pathway components

- **FGF19**
- **FGFR4**
- **KLB**

Pathway diagnostics

- **FGF19 IHC+**
  - ~30% HCC
- **FGF19 FISH+**
  - ~7% HCC

FGFR4, fibroblast growth factor receptor 4; FGF19, fibroblast growth factor 19; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; KLB, klotho-β.
BLU-554: a potent and highly selective FGFR4 inhibitor for HCC

### Inhibitory Mechanism and IC₅₀ Values

<table>
<thead>
<tr>
<th>Compound</th>
<th>Inhibitory Mechanism</th>
<th>TEL-FGFR4 IC₅₀ nM Cellular</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLU-554</td>
<td>Type 1 Irreversible</td>
<td>3.5</td>
</tr>
<tr>
<td>sorafenib</td>
<td>Type 2 Reversible</td>
<td>4,142</td>
</tr>
<tr>
<td>regorafenib</td>
<td>Type 2 Reversible</td>
<td>3,021</td>
</tr>
</tbody>
</table>

---

Kinome illustration reproduced courtesy of CSTI (www.cellsignal.com)
Sorafenib QD (once daily) dosing, BLU-554 BID (twice daily) dosing
BLU-554: first-in-human study

Key objectives

• Define MTD, safety profile, pharmacokinetics and pharmacodynamics
• Assess preliminary anti-tumor activity in relation to FGF19 IHC and FISH status

Part 1: Dose escalation – completed

Advanced HCC
• Child Pugh A
• ECOG PS 0-1
• No ascites
• ± prior sorafenib

• 3+3 dose escalation (140-900 mg PO QD)
• 600 mg established as MTD

Part 2: Dose expansion – enrolling

FGF19 IHC+ (n~50)
Retrospective FGF19 FISH

FGF19 IHC- (n~15)
FGF19 immunohistochemistry (IHC) identifies aberrant pathway activation

Central Laboratory IHC

Aberrant pathway activation in 27%

107/395 FGF19 IHC+ ≥ 1%

Number samples analyzed

FGF19 IHC- 277
FGF19 IHC+ 107
Not evaluable 11
## Patient demography and baseline characteristics

- Predominantly 2nd line/post-sorafenib patient population
- IHC+: more MVI* and higher AFP**

### Parameter, n (%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients, N = 77 n=25 escalation; n=52 expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years, median (range)</td>
<td>61 (18–85)</td>
</tr>
<tr>
<td>Gender – male</td>
<td>60 (78)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Non-viral</td>
<td>10 (13)</td>
</tr>
<tr>
<td>HBV</td>
<td>36 (47)</td>
</tr>
<tr>
<td>HCV</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>21 (27)</td>
</tr>
<tr>
<td>Metastatic Disease</td>
<td>61 (79)</td>
</tr>
<tr>
<td>FGF19 IHC</td>
<td></td>
</tr>
<tr>
<td>IHC ≥1% (IHC+)</td>
<td>44 (57)</td>
</tr>
<tr>
<td>IHC &lt;1% (IHC-)</td>
<td>28 (36)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (6)</td>
</tr>
</tbody>
</table>

### Prior Therapy

- Surgical resection: 58 (75)
- Radiotherapy: 25 (32)
- TACE / embolization: 40 (52)
- Immunotherapy: nivolumab: 18 (23)
- Kinase inhibitor: sorafenib: 63 (82)
- Systemic therapy: 70 (91)

### FGF19 FISH

- FISH+: 5 (6)
- FISH-: 58 (75)
- Unknown: 11 (14)
- Pending: 3 (4)

### FGF19 IHC+

- MacroVascular Invasion*: 18 (41)
- AFP ≥400 (ng/mL)**: 27 (61)

### FGF19 IHC-

- MacroVascular Invasion*: 5 (15)
- AFP ≥400 (ng/mL)**: 8 (24)

---

Data are preliminary as of data cut off: 18 August 2017.

AFP: alpha-fetoprotein; MVI: macrovascular invasion; TACE, transarterial chemoembolisation.
BLU-554 pharmacokinetics and pharmacodynamics

Steady state (C1 D15)

- Steady state exposure provides $C_{\text{trough}} > C_{\text{min}}$ associated with xenograft efficacy
- Long half life supports QD dosing
- Blood biomarkers demonstrate consistent pathway modulation

Plasma Concentration (ng/mL)

AUC = 73,500 ng*h/mL
$C_{\text{max}} = 8,100$ ng/mL
$T_{\text{max}} \sim 2h$, $t_{\frac{1}{2}} \sim 17$ h

Blood PD biomarkers

Cholesterol
Bile acids (C4)
FGF 19

Feedback loop

Data are preliminary as of data cut off: 18 August 2017
PK and PD represent 600mg expansion dose
AUC, area under the curve; C1, Cycle1; $C_{\text{max}}$, maximum blood plasma concentration; $C_{\text{min}}$, minimum blood plasma concentration; D15, Day15; PD, pharmacodynamics; PK, pharmacokinetic; QD, one a day; $T_{\text{max}}$, time to maximum blood plasma concentration
Radiographic response in post-sorafenib non-viral HCC

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>8</th>
<th>16</th>
<th>24</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>-26% SD</td>
<td>-44% PR</td>
<td>-45% PR</td>
<td>PD</td>
</tr>
</tbody>
</table>

Baseline

IHC+

FISH-

Week 16

-44% PR
Radiographic response in post-sorafenib HBV-related HCC

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>8</th>
<th>16</th>
<th>24</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>34%</td>
<td>49%</td>
<td>49%</td>
<td></td>
<td>PD</td>
</tr>
</tbody>
</table>

Baseline ctDNA Measure

<table>
<thead>
<tr>
<th>Allele fraction</th>
<th>Baseline</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>P53 Q192*</td>
<td>31.1%</td>
<td>Undetectable</td>
</tr>
<tr>
<td>FGF19 amp</td>
<td>8.3</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

cDNA, circulating tumor DNA; PD, progressive disease; PR, progressive response
IHC-positivity enriches for radiographic tumor reduction and response

- **ORR = 0% per RECIST 1.1**
- **PFS 2.1 months (1.8 – 5.6 95% CI)**

### Best Response

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR; CR</td>
<td>0; 0</td>
</tr>
<tr>
<td>SD</td>
<td>15 (52)</td>
</tr>
<tr>
<td>PD</td>
<td>14 (48)</td>
</tr>
</tbody>
</table>

### Maximum Reduction – sum of diameter change from baseline, %

- **ORR 6/38 = 16% (6-31% 95%CI) per RECIST 1.1**
- **PFS 3.7 months (2.8 – 7.3 95% CI)**
- **Activity against FISH- and FISH+**

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR; CR</td>
<td>5 (13)*; 1 (3)</td>
</tr>
<tr>
<td>SD</td>
<td>20 (53)</td>
</tr>
<tr>
<td>PD</td>
<td>12 (32)</td>
</tr>
</tbody>
</table>

*4 confirmed PR; 1 PR/1 CR, unconfirmed

Data are preliminary as of data cut off: 18 August 2017

CR, complete response; ORR, overall response rate; PFS, progression-free survival
FGF19 IHC+ tumor growth kinetics per prior kinase inhibitor treatment

Encouraging duration of treatment, particularly in kinase inhibitor naïve patients

Data are preliminary as of data cut off: 18 August 2017

Previous kinase inhibitor treatment  No prior kinase inhibitor treatment

<table>
<thead>
<tr>
<th>Study duration</th>
<th>FISH-/Unknown</th>
<th>FISH+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scr C1 C3 C5 C7 C9 C11 C13 C15</td>
<td>N = 32</td>
<td>3.7 (0.2-7.7) months on treatment 8 ongoing</td>
</tr>
<tr>
<td>N = 5</td>
<td>5.4 (2.4 – 12.3) months on treatment 2 ongoing &gt;11 months</td>
<td></td>
</tr>
</tbody>
</table>
## Adverse events*

Most AEs are Grade 1 or 2: manageable on-target toxicity

<table>
<thead>
<tr>
<th>Safety population, N=77</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any AE</td>
</tr>
<tr>
<td>Patients with at least 1 Related AE</td>
<td>75 (97)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>55 (71)</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (42)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28 (36)</td>
</tr>
<tr>
<td>AST</td>
<td>26 (34)</td>
</tr>
<tr>
<td>ALT</td>
<td>25 (32)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22 (29)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14 (18)</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>13 (17)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Anemia</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>10 (13)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>8 (10)</td>
</tr>
</tbody>
</table>

- 2 DLT at 900 mg (1 Gr 3 fatigue lasting > 7 days; 1 Gr 3 abdominal pain)
- BLU-554 discontinuations: PD n=42, AE n=11, investigator’s decision n=2, withdrew consent n=3

*Treatment-related adverse events reported in ≥10% patients; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity
Conclusions

• BLU-554 provides acceptable tolerability, pathway engagement and anti-tumor activity in heavily pre-treated FGF19 IHC+ patients
  • Aberrant pathway activation (FGF19 IHC+) demonstrated in ~30% of HCC patients
  • BLU-554 demonstrates clinical activity regardless of HCC etiology and prognostic factors
• These data validate FGFR4 as a therapeutic target and FGF19 IHC as selection marker for pathway activation in advanced HCC
• Planning is underway for further clinical development of BLU-554 in kinase inhibitor naïve, FGF19 IHC+ HCC alone and in combination with immunotherapy
Acknowledgements

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

- Moffitt Cancer Center, Tampa, United States
- Guy’s Hospital, London, United Kingdom,
- Vall d’Hebron University Hospital, Barcelona, Spain
- Queen Mary Hospital, Hong Kong, Hong Kong
- National Cancer Center, Singapore, Singapore
- UCL Cancer Institute, London, United Kingdom
- Institut Gustave Roussy, Villejuif, France
- Huntsman Cancer Institute, Salt Lake City, United States
- Asan Medical Center, Seoul, Republic of Korea
- Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, United States
- Seoul National University Hospital, Seoul, Republic of Korea
- Samsung Medical Center, Seoul, Republic of Korea
- Massachusetts General Hospital Cancer Center, Boston, United States
- Center for Liver Cancer, National Cancer Center, Goyang, Republic of Korea
- Beaujon University Hospital, Clichy, France
- Fondazione Istituto Nazionale Tumori (National Cancer Institute) IRCCS, Milan, Italy

We also thank Samantha Clark, BSc, of iMed Comms, an Ashfield company, who provided editorial writing support funded by Blueprint Medicines
References

Thank you