Phase Ib study of BI 836880 (VEGF/Ang2 nanobody®)
plus ezabenlimab (BI 754091; anti-PD-1 antibody)
in patients with solid tumors

Nicolas Girard,1* Martin Wermke,2 Fabrice Barlesi,3 Dong-Wan Kim,4 François Ghiringhelli,5 Jaafar Bennouna,6 Thierry Lesimple,7 Enriqueta Felip,8 David Berz,9 Jong-Seok Lee,4 Arnaud Jeanson,3 Céline Mascaux,10 Mark Voskoboynik,11,12 Piotr Serwatowski,13 Michael C. Burger,14 Harald Timotheus Landsteiner,15 Victoria Chen,16 Girish Jayadeva,17 Jürgen Alt,18 Björn Hackanson19

1Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France; 2NCT/UCC Early Clinical Trial Unit, Universitätsklinikum Carl Gustav Carus, Dresden, Germany; 3Aix-Marseille University, CEPCM CLIP2, Assistance Publique Hôpitaux de Marseille, Marseille, France; 4Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; 5Department of Medical Oncology, Center Georges Francois Leclerc, Dijon, France; 6Thoracic Medical Oncology Functional Unit - Pneumology Department, Saint Herblain, France; 7Clinical Research Department, CLIP2 and ARPEGO Network, Rennes, France; 8Medical Oncology Department, Vall d’Hebron University Hospital, Barcelona, Spain; 9Department of Internal Medicine, Beverly Hills Cancer Center, Los Angeles, CA, USA; 10Department of Pulmonology, University Hospital of Strasbourg, Strasbourg, France; 11Department of Medical Oncology, Alfred Hospital, Melbourne, Australia; 12Central Clinical School, Monash University, Melbourne, Australia; 13Dom Lekarski S.A., Szczecin, Poland; 14Dr. Senckenberg Institute for Neurooncology, Klinikum der Johann Wolfgang Goethe-Universität, Frankfurt, Germany; 15Division of Medicine/Clinical Operation, Boehringer Ingelheim RCV GmbH & Co. KG, Vienna, Austria; 16Biostatistics and Data Sciences, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA; 17TA Oncology Medicine, Boehringer Ingelheim International GmbH, Ingelheim, Germany; 18Department of Internal Medicine III, University Medical Center Mainz, Germany; 19Department of Hematology/Oncology, University Medical Center Augsburg, Augsburg, Germany

*Corresponding author email address: nicolas.girard2@curie.fr

This study was sponsored by Boehringer Ingelheim
Introduction

- Combining anti-VEGF/Ang2 with anti-PD-1 agents promotes an immunopermissive state, supportive of tumor cell destruction mediated by T cells\(^1\)\(^-\)\(^4\).
- BI 836880, a humanized bispecific nanobody\(^\circ\) that targets VEGF and Ang2, and ezabenlimab (BI 754091), an anti-PD-1 monoclonal antibody, have both shown safety and preliminary anti-tumor activity as monotherapies\(^5\),\(^6\).

Objective and Methods

- This ongoing Phase Ib study aims to assess the safety and anti-tumor activity of BI 836880 and ezabenlimab in patients with advanced or metastatic solid tumors

**Part 1: Dose escalation**
- 14 patients with PD-L1 positive mNSCLC (non-squamous)
- In Part 1, the RP2D was defined as BI 836880 720 mg + ezabenlimab 240 mg intravenously every 3 weeks

**Primary endpoint:**
- MTD or RP2D based on dose limiting toxicities

**Secondary endpoints:**
- Adverse events, pharmacokinetics

**Further endpoints include:**
- Best overall response

**Part 2: Cohort expansion**
- All patients to receive the RP2D: BI 836880 720 mg + ezabenlimab 240 mg intravenously every 3 weeks

**Cohort A (n=40)**
- mNSCLC after CPI monotherapy

**Cohort B (n=40)**
- mNSCLC after CT + CPI therapy

**Cohort C (n=30)**
- mSCLC after CT ± CPI therapy

**Cohort E (n=32*)**
- Immunotherapy-resistant metastatic melanoma

**Cohort F (n=30)**
- HCC after prior sorafenib or lenvatinib

**Cohort G (n=30)**
- Previously untreated unresectable HCC

**Cohort D (n=31*)**
- Recurrent GBM (1st and 2nd recurrences)

**Primary endpoint:**
- Shrinkage estimator of objective response, defined as best overall response (RECIST version 1.1)

**Secondary endpoints:**
- Adverse events, disease control, duration of response, progression-free survival, pharmacokinetics, tumor shrinkage

*Recruitment completed. CPI, checkpoint inhibitor; CT, chemotherapy; GBM, glioblastoma; HCC, hepatocellular carcinoma; m, metastatic; MTD, maximum tolerated dose; PD-L1, programmed death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended Phase II dose. 1. Girard N, et al. J Clin Oncol 2020;38(15_suppl):9566
Results

- As of March 1, 2021, 215 patients have been treated

Sex

- 30% Female
- 70% Male

Median age, years

- 62

ECOG PS*

- 52% Missing
- 42% 1
- 0

Prior CPI

- 51% No
- 49% Yes

Cohort

- Part 1 (n=14)
- Cohort A (n=35)
- Cohort B (n=32)
- Cohort C (n=19)
- Cohort D (n=31)
- Cohort E (n=32)
- Cohort F (n=29)
- Cohort G (n=23)

Cohort A, mNSCLC after CPI monotherapy; Cohort B, mNSCLC after CT + CPI therapy; Cohort C, mSCLC after CT ± CPI therapy; Cohort D, recurrent GBM (1st and 2nd recurrences); Cohort E, immunotherapy-resistant metastatic melanoma; Cohort F, HCC after prior sorafenib or lenvatinib; Cohort G, previously untreated unresectable HCC. CPI, checkpoint inhibitor; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma m, metastatic. *Total percentage exceeds 100% due to rounding.
Safety

- Grade 4 adverse events included hyperkalemia plus cardiac arrest, laryngospasm, gastrointestinal perforation (all non-drug-related) and drug-related anaphylactic reaction, cholestatic hepatitis, acute pancreatitis, and increased transaminases.

- Grade 5 adverse events included COVID-19 pneumonia, epilepsy, intracranial hemorrhage, cardio-respiratory arrest, hemoptysis, hepatic failure, general physical health deterioration, Glasgow coma scale abnormal plus shortness of breath (all non-drug-related) and drug-related tracheal hemorrhage.

<table>
<thead>
<tr>
<th>Patients with:</th>
<th>All grades n (%)</th>
<th>Grade 1 n (%)</th>
<th>Grade 2 n (%)</th>
<th>Grade 3 n (%)</th>
<th>Grade 4 n (%)</th>
<th>Grade 5 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event*</td>
<td>183 (85)</td>
<td>37 (17)</td>
<td>74 (34)</td>
<td>59 (27)</td>
<td>5 (2)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>48 (22)</td>
<td>27 (13)</td>
<td>15 (7)</td>
<td>6 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>41 (19)</td>
<td>7 (3)</td>
<td>18 (8)</td>
<td>16 (7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>30 (14)</td>
<td>20 (9)</td>
<td>9 (4)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>27 (13)</td>
<td>16 (7)</td>
<td>10 (5)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>25 (12)</td>
<td>15 (7)</td>
<td>9 (4)</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22 (10)</td>
<td>14 (7)</td>
<td>6 (3)</td>
<td>2 (1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related adverse event</td>
<td>118 (55)</td>
<td>42 (20)</td>
<td>43 (20)</td>
<td>28 (13)</td>
<td>4 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Immune-related adverse event</td>
<td>35 (16)</td>
<td>9 (4)</td>
<td>18 (8)</td>
<td>4 (2)</td>
<td>4 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>65 (30)</td>
<td>2 (1)</td>
<td>19 (9)</td>
<td>30 (14)</td>
<td>5 (2)</td>
<td>8 (4)</td>
</tr>
</tbody>
</table>

*Maximum Common Terminology Criteria for Adverse Events grade
Efficacy

- At data cut-off, 179 patients were evaluable for response and 106 patients were still on treatment.

### Best overall response:

- Complete response: n=1 (1%)
- Partial response: n=22 (12%)
- Stable disease: n=110 (61%)
- Progressive disease: n=46 (26%)

### Cohort Evaluation

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Evaluable, n</th>
<th>Complete response, n</th>
<th>Partial response, n</th>
<th>Stable disease, n</th>
<th>Progressive disease, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>14</td>
<td>0</td>
<td>2</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>A</td>
<td>24</td>
<td>0</td>
<td>4</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>B</td>
<td>30</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>C</td>
<td>17</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>D</td>
<td>28</td>
<td>0</td>
<td>4</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>E</td>
<td>31</td>
<td>0</td>
<td>3</td>
<td>18</td>
<td>10</td>
</tr>
<tr>
<td>F</td>
<td>25</td>
<td>1</td>
<td>3</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>G</td>
<td>10</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Cohort A, mNSCLC after CPI monotherapy; Cohort B, mNSCLC after CT + CPI therapy; Cohort C, mSCLC after CT ± CPI therapy; Cohort D, recurrent GBM (1st and 2nd recurrences); Cohort E, immunotherapy-resistant metastatic melanoma; Cohort F, HCC after prior sorafenib or lenvatinib; Cohort G, previously untreated unresectable HCC.
Key findings and conclusions

- BI 836880 plus ezabenlimab had a manageable safety profile
- Preliminary anti-tumor activity was observed in a range of tumor types

- This ongoing Phase Ib study is evaluating the safety and anti-tumor activity of BI 836880 and ezabenlimab in patients with advanced or metastatic solid tumors
- As of March 2021, 215 patients have been treated
- Overall, 183 (85%) patients have experienced an adverse event, most commonly asthenia (22%) and hypertension (19%)
- Of the 179 patients evaluable for response at data cut-off, 1 patient had a confirmed complete response, 22 patients had partial response, and 110 patients had stable disease
- At data cut-off, 106 patients remain on treatment