Phase I trial of the DLL3/CD3 IgG-like T-cell engager BI 764532 in patients with DLL3-positive tumours: focus on extrapulmonary neuroendocrine carcinomas

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DECLARATION OF INTERESTS

Valentina Gambardella

- Advisory Board: Boehringer Ingelheim
- Research Funding: Bayer, Boehringer Ingelheim, Roche
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First-in-human dose-escalation trial of BI 764532 in patients with SCLC or epNECs: NCT04429087

- BI 764532, a novel DLL3-targeting T-cell engager, redirects the patient’s own T-cells to lyse DLL3-expressing cancer cells

**Regimen A**
- Dose A1
- Dose A2
- Dose A3
- Dose A4
- Dose A5
- Switch to B1 based on regimen A data
- IV dose every 3 weeks (Q3W)

**Regimen B**
- Dose B1.1
- Dose B1.2
- Dose B1.3
- Dose A.n
- Switch to step-in dosing (B2) based on regimen A and B1 data
- IV dose once every week (QW)

**Regimen B1**
- Dose B2.1
- Dose B2.2
- Dose B2.3
- Dose B2.n

**Regimen B2**
- Dose B3.1
- Dose B3.2
- Dose B3.n

**Regimen B3**
- Dose B3.1
- Dose B3.2
- Dose B3.n

**Primary endpoints**
- MTD
- DLTs in the MTD evaluation period

**Secondary endpoints**
- Objective response (RECIST v1.1)
- PK parameters

BLRM, Bayesian Logistic-Regression Model with overdose control; DLL3, delta-like canonical Notch ligand 3; DLTs, dose-limiting toxicities; IV, intravenous; MTD, maximum tolerated dose; epNECs, extrapulmonary neuroendocrine carcinomas; PK, pharmacokinetic; RECIST, Response Evaluation Criteria In Solid Tumours version 1.1; SCLC, small-cell lung cancer
## Inclusion criteria and patient baseline characteristics

### Key inclusion criteria

- Advanced SCLC, LCNEC of the lung or epNEC
- DLL3-positive (archived tissue or in-study biopsy) according to central* review
- Failed/ineligible for available standard therapies (≥1 line of platinum-based chemotherapy)
- Adequate liver, bone marrow and renal function
- ECOG PS 0/1

### As of 14 August 2023

<table>
<thead>
<tr>
<th></th>
<th>N=132</th>
<th>Patients with epNEC (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>60 (32–81)</td>
<td>61 (33–81)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>79 (60)</td>
<td>35 (65)</td>
</tr>
<tr>
<td><strong>Prior lines of therapy, n (%)†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>38 (29)</td>
<td>19 (35)</td>
</tr>
<tr>
<td>2</td>
<td>54 (41)</td>
<td>16 (30)</td>
</tr>
<tr>
<td>≥3</td>
<td>39 (30)</td>
<td>18 (33)</td>
</tr>
<tr>
<td><strong>ECOG PS 0/1, n (%)†</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>37 (28) / 94 (71)</td>
<td>21 (39) / 32 (59)</td>
</tr>
<tr>
<td><strong>Prior PD-1/PD-L1, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>63 (48)</td>
<td>9 (17)</td>
</tr>
<tr>
<td><strong>Brain/liver metastases, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>49 (37) / 77 (58)</td>
<td>3 (6) / 41 (76)</td>
</tr>
</tbody>
</table>

*Ventana DLL3 (SP347) assay at the Roche CDx CAP/CLIA laboratory

†Not available for one patient
DLTs, TRAEs and AE in patients with epNEC (≥5 patients)

- CRS was the most common TRAE and was managed with supportive care, corticosteroids, and/or anti-IL-6R antibodies
- MTD not reached; dose escalation ongoing
- Overall, six patients had DLTs; two epNEC patients had DLTs (grade 3 CRS and grade 5 ICANS*)
- One grade 5 TRAE: ICANS in a patient with epNEC

<table>
<thead>
<tr>
<th>TRAEs, n (%)</th>
<th>Patients with epNEC (n=54)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>51 (94)</td>
</tr>
<tr>
<td>CRS</td>
<td>39 (72)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16 (30)</td>
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<tr>
<td>Dysgeusia</td>
<td>10 (19)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9 (17)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (11)</td>
</tr>
<tr>
<td>AST increased</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (9)</td>
</tr>
</tbody>
</table>

†Safety population: ≥1 dose of BI 764532 as of 14 Aug 2023
Efficacy in all patients and epNEC patients (all dose levels)

<table>
<thead>
<tr>
<th>n, (%)</th>
<th>All patients (n=126)*</th>
<th>epNEC patients (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>27 (21)</td>
<td>12 (24)</td>
</tr>
<tr>
<td>SD</td>
<td>30 (24)</td>
<td>10 (20)</td>
</tr>
<tr>
<td>PD</td>
<td>52 (41)</td>
<td>23 (45)</td>
</tr>
<tr>
<td>DCR</td>
<td>57 (45)</td>
<td>22 (43)</td>
</tr>
<tr>
<td>NE†</td>
<td>17 (14)</td>
<td>6 (12)</td>
</tr>
</tbody>
</table>

DCR, disease control rate; NE, not evaluable; PD, progressive disease; PR, partial response; RECIST v.1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; SOD, sum of diameters.

*Efficacy population: ≥1 post-baseline tumour assessment or permanently discontinued prior to tumour assessment as of 14 Aug 2023; responses evaluated per RECIST v1.1 criteria; †Discontinued prior to first post-baseline tumour assessment.

Responses occur at dose levels ≥90 µg/kg
Efficacy in patients with epNEC by organ system (≥90 µg/kg)

Responses occur across organ classes of epNEC

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Responses to date appear durable and are ongoing

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*Duration of objective response (DOR) is defined as the time from first documented complete response (CR) or partial response (PR) until the earliest of disease progression or death among patients with objective response according to RECIST v.1.1.
Summary and conclusions

- The safety profile of BI 764532 is acceptable and manageable at clinically efficacious dose levels in patients with epNEC
- CRS was reported in 72% of patients with epNEC; cases were mostly grade 1–2, occurred during initial drug administrations, and were manageable with standard supportive care
- Promising efficacy was observed in patients with epNEC: ORR of 29% at BI 764532 doses $\geq 90$ $\mu$g/kg
- Responses appeared to be durable
- Further dose optimisation is ongoing
Acknowledgments

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Back-up slides
BI 764532: a novel DLL3-targeting T-cell engager

- BI 764532 redirects the patient’s own T-cells to lyse DLL3-expressing cancer cells
- Potent preclinical activity against DLL3-positive cells and xenograft models

DLL3: Notch ligand selectively expressed on the cell surface of SCLC, and epNECs

Human IgG-like structure

BI 764532

CD3

DLL3

Cancer cell

Inactive T-cell

Activated T-cell

Cytolytic synapse

Cancer cell lysis

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