A Phase I, open-label, dose-escalation trial of BI 764532, a DLL3/CD3 bispecific antibody, in patients with small cell lung carcinoma or other neuroendocrine neoplasms expressing DLL3

Martin Wermke,1* Enriqueta Felip,2 Valentina Gambardella,3 Yasutoshi Kuboki,4 Daniel Morgensztern,5 Zohra Oum’ Hamed,6 Junxian Geng,7 Matus Studeny,8 Taofeek K. Owonikoko9

1Department of Thoracic Oncology, Carl-Gustav-Carus Dresden University Hospital, Dresden, Germany; 2Department of Medical Oncology, Vall d’Hebron University Hospital, Barcelona, Spain; 3Department of Medical Oncology, Biomedical Research Institute INCLIVA, University of Valencia, Valencia, Spain; 4Department of Experimental Therapeutics, National Cancer Center Hospital East, Kashiwa, Chiba, Japan; 5Washington University School of Medicine, St. Louis, MO, USA; 6Boehringer Ingelheim France S.A.S., Reims, France; 7Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT, USA; 8Boehringer Ingelheim International GmbH, Ingelheim, Germany; 9Winship Cancer Institute, Emory University, Atlanta, GA, USA

*Corresponding author email address: Martin.Wermke@uniklinikum-dresden.de

This study was sponsored by Boehringer Ingelheim

Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, Virtual Format, June 4–8, 2021
Introduction

- Standard of care for patients with metastatic SCLC and NEC is platinum-based chemotherapy ± immunotherapy
  
- The addition of anti-PD-1 antibodies has improved outcomes, but nearly all patients relapse, and prognosis is poor

- BI 764532 is a DLL3/CD3 T cell engaging bispecific antibody
  - DLL3 is expressed on the cell surface of many SCLC and NEC tumors
  - In preclinical studies, BI 764532 induced cytotoxicity of DLL3-positive cells

CD3, cluster of differentiation 3; DLL3, delta-like canonical Notch ligand 3; NEC, neuroendocrine carcinoma; PD-1, programmed cell death protein-1; SCLC, small cell lung carcinoma

Study objectives

• To determine the MTD and recommended dosing regimen for further development of BI 764532 based on DLTs for patients with DLL3-positive tumors
• To evaluate safety, tolerability, PK and preliminary efficacy

As of April 2021, patients are being recruited in early dose escalation cohorts in the US, Japan, Spain, and Germany

DLL3, delta-like canonical Notch ligand 3; DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; PK, pharmacokinetics
• First-in-human, open-label, dose-escalation trial (NCT04429087) of BI 764532 administered intravenously in patients with SCLC or NEC DLL3-positive tumors (confirmed according to central review)
• DLL3 status to be assessed with the Ventana DLL3 (SP347) assay at the Roche CDx CAP/CLIA laboratory
• Phase Ia trial to assess up to three dosing regimens

• Patients are treated until disease worsening or a maximum duration of 36 months
• Dose escalation is guided by a Bayesian Logistic Regression Model with overdose control fitted to binary toxicity outcomes
Study design (cont’d)

**Key inclusion criteria**
- Adult patients (≥18 years of age)
- Diagnosis of advanced SCLC, LNEC or NEC
- Patient has failed or is ineligible for available standard therapies (including ≥1 line of platinum-based chemotherapy)
- Tumor must be positive for DLL3 expression (archived tissue or in-study biopsy) according to central review
- ≥1 evaluable lesion (modified RECIST 1.1) outside of CNS
- Adequate liver, bone marrow & renal function
- ECOG PS 0/1

**Key exclusion criteria**
- Previous treatment with T-cell engagers or DLL3-targeted therapies
- Persistent toxicity from previous treatment that has not resolved to ≤CTCAE grade 1†
- Anticoagulant treatment that cannot be safely interrupted
- Diagnosis of immunodeficiency or receiving immunosuppressive therapy within 7 days of first dose of BI 764532
- Prior anti-cancer therapy within 3 weeks/5 half-life periods or extensive field radiotherapy within 2 weeks of first dose of BI 764532

**Study endpoints**

<table>
<thead>
<tr>
<th>Primary endpoints</th>
<th>Secondary endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTD based on number of DLTs</td>
<td>Objective response based on RECIST 1.1</td>
</tr>
<tr>
<td>Number of patients with DLTs in the MTD evaluation period</td>
<td>PK parameters (C\text{max} and AUC\text{τ}) after first and multiple doses in all regimens</td>
</tr>
</tbody>
</table>

*†Except for alopecia, CTCAE grade 2 neuropathy, asthenia/fatigue or grade 2 endocrinopathies controlled by replacement therapy*

AUC, area under the concentration-time curve of the analyte over a uniform dosing interval; \( C\text{max} \), maximum measured concentration; CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; LNEC, large cell neuroendocrine lung carcinoma; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1
Key points

Background

• DLL3 is widely expressed in SCLC and NEC tumors\(^1\)-\(^3\)
• BI 764532 induces cytotoxicity and killing of DLL3-positive tumor cells\(^4\)
• Preclinical data support testing BI 764532 on patients with DLL3-positive tumors\(^4\)

Objectives of the trial

• To determine the MTD and characterize safety for BI 764532 in patients with SCLC or NEC DLL3-positive tumors

Study design

• First-in-human, Phase I, open-label, multicenter trial (NCT04429087)
• Three dosing regimens of BI 764532 to be assessed

Current status

• Patients are being recruited and treated in early dose escalation cohorts in the US, Germany, Spain and Japan

DLL3, delta-like canonical Notch ligand 3; MTD, maximum tolerated dose; NEC, neuroendocrine carcinoma; SCLC, small cell lung carcinoma