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

#TPS8588

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. Owonikoko[9]

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

Introduction

- Standard of care for patients with metastatic SCLC and NEC is platinum-based chemotherapy ± immunotherapy[1]
- The addition of anti-PD-1 antibodies has improved outcomes, but nearly all patients relapse, and prognosis is poor[1]
- BI 764532 is a DLL3/CD3 T cell engaging bispecific antibody[2] (Figure 1)
  - DLL3 is expressed on the cell surface of many SCLC and NEC tumors[3–5]
  - In preclinical studies, BI 764532 induced cytotoxicity of DLL3-positive cells[2]

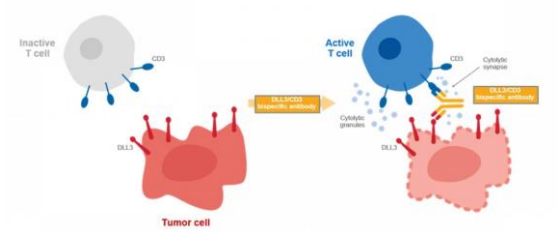

Figure 1. T-cell engager mechanism of action

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 design

- First-in-human, open-label, dose-escalation trial (NCT04429087) of BI 764532 administered IV 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 (Figure 2)
- 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

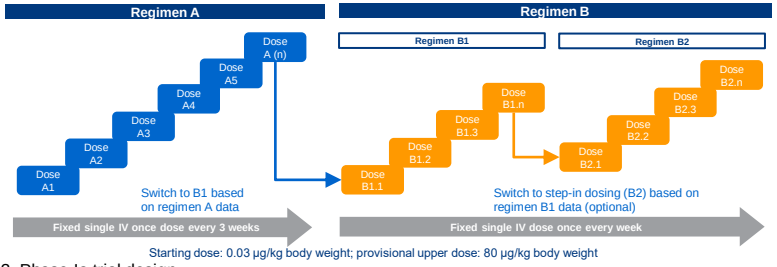

Figure 2. Phase Ia trial design

CAP/CLIA, College of American Pathologists & Clinical Laboratory Improvement Amendments; IV, intravenously

Key points

Rationale

- DLL3 is widely expressed in SCLC and NEC tumors[3–5]
- BI 764532 induces cytotoxicity and killing of DLL3-positive tumor cells[2]
- Preclinical data support testing BI 764532 on patients with DLL3-positive tumors[2]

Objectives

- 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)
- Up to three dosing regimens of BI 764532 to be assessed

Current status

- Patients are being recruited and treated in early dose escalation cohorts

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

Study status

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

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

Inclusion and exclusion criteria

Key inclusion criteria	Key exclusion criteria
Adult patients (≥18 years of age)	Previous treatment with T-cell engagers or DLL3-targeted therapies
Diagnosis of advanced SCLC, LNEC or NEC	Persistent toxicity from previous treatment that has not resolved to ≤CTCAE grade 1†
Patient has failed or is ineligible for available standard therapies (including ≥1 line of platinum-based chemotherapy)	Anticoagulant treatment that cannot be safely interrupted
Tumor must be positive for DLL3 expression (archived tissue or in-study biopsy) according to central review	Diagnosis of immunodeficiency or receiving immunosuppressive therapy within 7 days of first dose of BI 764532
≥1 evaluable lesion (modified RECIST 1.1) outside of CNS	Prior anti-cancer therapy within 3 weeks/5 half-life periods or extensive field radiotherapy within 2 weeks of first dose of BI 764532
Adequate liver, bone marrow & renal function	
ECOG PS 0/1	

†Except for alopecia, CTCAE grade 2 neuropathy, asthenia/fatigue or grade 2 endocrinopathies controlled by replacement therapy. CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; DLTs, dose-limiting toxicities; ECOG PS, Eastern Cooperative Oncology Group performance status; LNEC, large cell neuroendocrine lung carcinoma; MTD, maximum tolerated dose; PK, pharmacokinetics; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1

Study endpoints

Primary endpoints	Secondary endpoints
MTD based on number of DLTs	Objective response based on RECIST 1.1
Number of patients with DLTs in the MTD evaluation period	PK parameters (C_{max} and AUC_t) after first and multiple doses in all regimens

AUC_t, area under the concentration-time curve of the analyte over a uniform dosing interval$_T$; C_{max}, maximum measured concentration

References

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

This study was funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version. Medical writing support for the development of this poster, under the direction of the authors, was provided by Becky O'Connor, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by Boehringer Ingelheim