# 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

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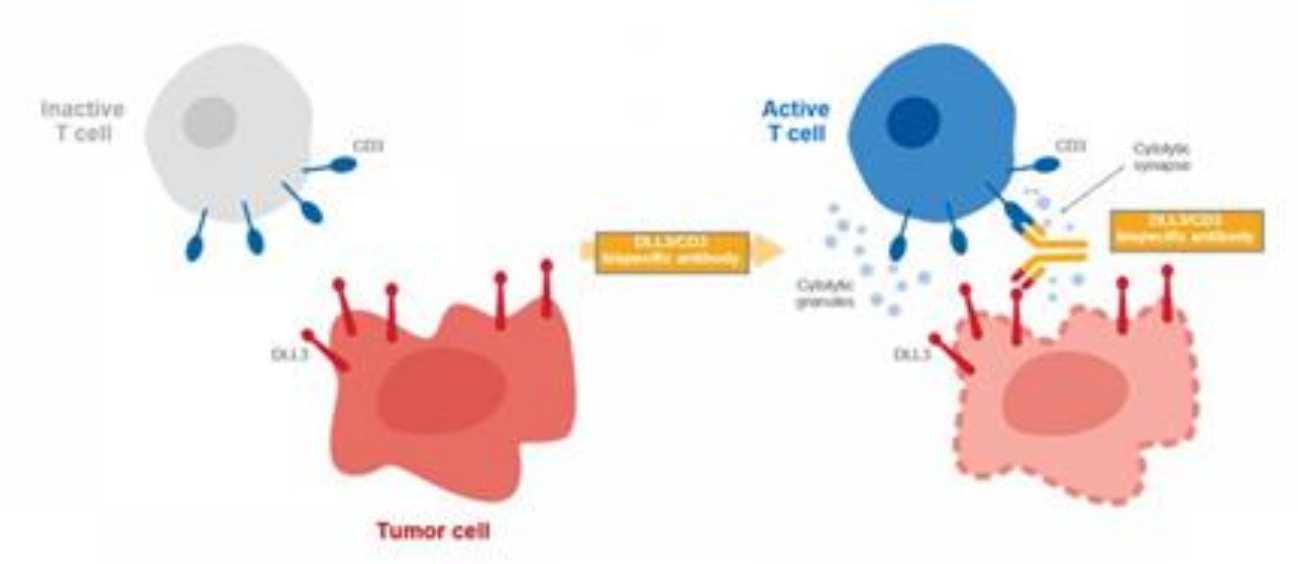
This study was sponsored by Boehringer Ingelheim

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[1]
- The addition of anti-PD-1 antibodies has improved outcomes, but nearly all patients relapse, and prognosis is poor[1]




T-cell engager mechanism of action

- BI 764532 is a DLL3/CD3 T cell engaging bispecific antibody[2]
  - 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]

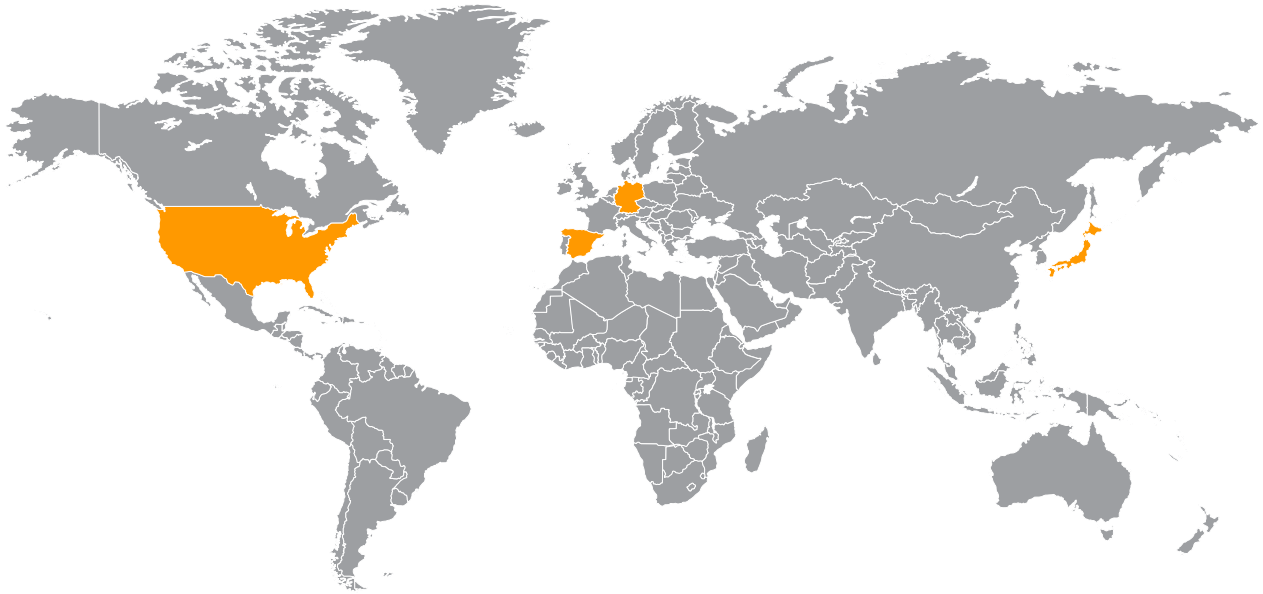
CD3, cluster of differentiation 3; DLL3, delta-like canonical Notch ligand 3; NEC, neuroendocrine carcinoma; PD-1, programmed cell death protein-1; SCLC, small cell lung carcinoma

1. Regzedmaa O, et al. Onco Targets Ther 2019;12:4605–20; 2. Hipp S, et al. Clin Cancer Res 2020;26(19):5258–68; 3. Saunders LR, et al. Sci Transl Med 2015;7:302ra136;
4. Rudin CM, et al. Lancet Oncol 2017;18:42–51; 5. Tanaka K, et al. Lung Cancer 2018;115:116–20

# 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

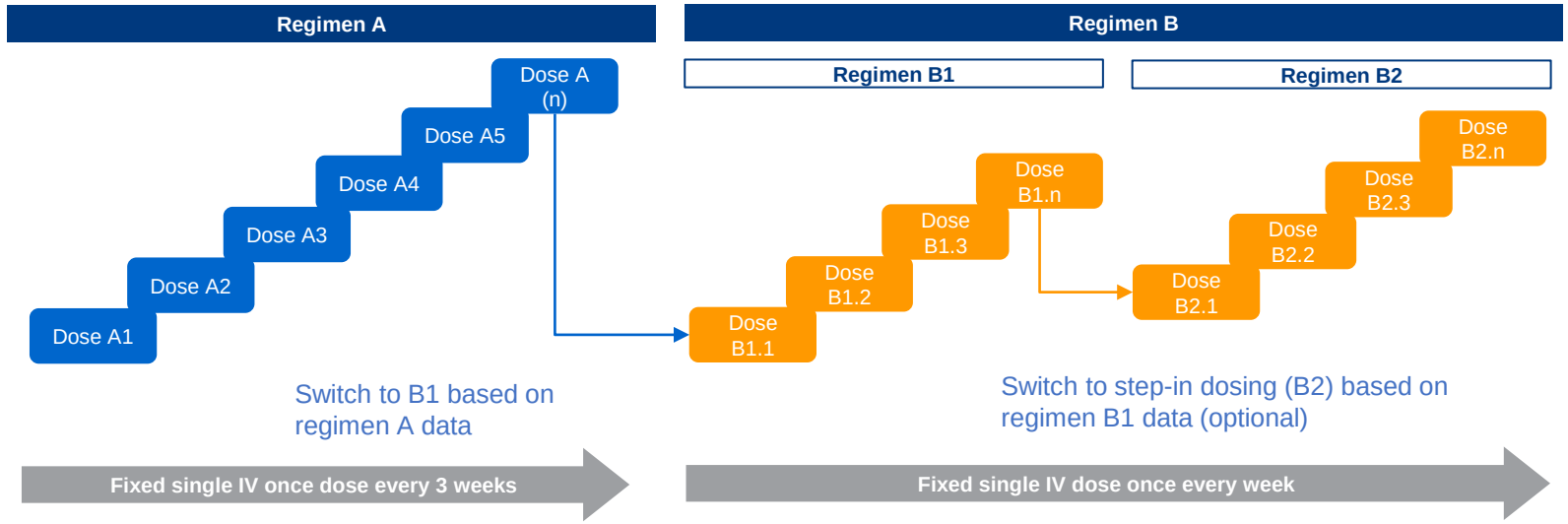
As of April 2021, patients are being recruited in early dose escalation cohorts in the US, Japan, Spain, and Germany



DLL3, delta-like canonical Notch ligand 3; DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; PK, pharmacokinetics

# Study design

- 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

CAP/CLIA, College of American Pathologists & Clinical Laboratory Improvement Amendments
DLL3, delta-like canonical Notch ligand 3; NEC, neuroendocrine carcinoma; SCLC, small cell lung carcinoma

# 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

| 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 $AUC_{\tau}$) after first and multiple doses in all regimens |

†Except for alopecia, CTCAE grade 2 neuropathy, asthenia/fatigue or grade 2 endocrinopathies controlled by replacement therapy
$AUC_{\tau}$, area under the concentration-time curve of the analyte over a uniform dosing interval$_{\tau}$; $C_{max}$, 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

1. Saunders LR, et al. Sci Transl Med 2015;7:302ra136; 2. Rudin CM, et al. Lancet Oncol 2017;18:42–51; 3. Tanaka K, et al. Lung Cancer 2018;115:116–20;
4. Hipp S, et al. Clin Cancer Res 2020;26(19):5258–68;