Clinical Trial Protocol

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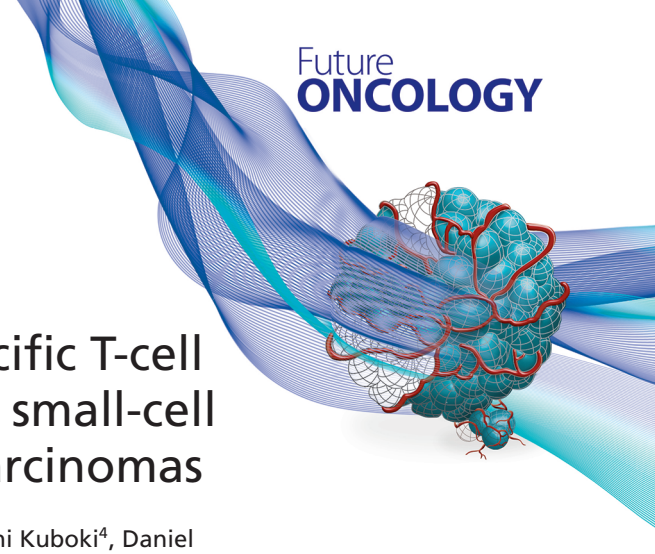

Phase I trial of the DLL3/CD3 bispecific T-cell engager BI 764532 in DLL3-positive small-cell lung cancer and neuroendocrine carcinomas

Martin Wermke*[,1], Enriqueta Felip[2], Valentina Gambardella[3], Yasutoshi Kuboki[4], Daniel Morgensztern[5], Zohra Oum' Hamed[6], Meiruo Liu[7], Matus Studeny[8] & Taofeek K Owonikoko[9]

[1]Technical University Dresden, Medical Faculty, NCT/UCC Early Clinical Trial Unit, Dresden, Germany

[2]Department of Medical Oncology, Vall d'Hebron University Hospital & Vall d'Hebron Institute of Oncology, Barcelona, Spain

[3]Department of Medical Oncology, Hospital Clínico Universitario, INCLIVA Biomedical Research Institute, 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 63110, USA

[6]Boehringer Ingelheim France S.A.S., Reims, France

[7]Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, CT 06877, USA

[8]Boehringer Ingelheim International GmbH, Ingelheim, Germany

[9]Division of Hematology/Oncology, UPMC Hillman Cancer Center, University of Pittsburgh, PA 15232, USA

*Author for correspondence: martin.wermke@uniklinikum-dresden.de

Poorly differentiated neuroendocrine carcinomas such as small-cell lung cancer (SCLC) have poor survival and high relapse rates. DLL3 is found on these carcinomas and has become a target of increasing interest in recent years. The bispecific DLL3/CD3 T-cell engager BI 764532 has been shown to induce complete tumor regression in a human T cell-engrafted mouse model. Here, we describe the study design of a first-in-human, phase I, multicenter, open-label, non-randomized, dose-escalation study in patients with SCLC or other DLL3-positive neuroendocrine carcinomas. The study will determine the maximum tolerated dose and evaluate safety, tolerability, pharmacokinetics and preliminary efficacy of BI 764532 monotherapy.

Plain language summary: DLL3 is a protein involved in development of the embryo during pregnancy. It has also been found on the surface of cells involved in the development of certain types of lung cancer and other tumors. The T-cell engager BI 764532 binds to DLL3 and cells of the immune system simultaneously, resulting in the death of tumor cells. Here we describe the rationale for, and design of, a clinical study of BI 764532 in patients with small-cell lung cancer and other tumors containing DLL3. The aim of the study is to find the highest acceptable dose of BI 764532 that can be tolerated by patients, and explore the safety and efficacy of BI 764532.

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Small-cell lung cancer (SCLC) is a poorly differentiated, aggressive neuroendocrine tumor with a 5-year survival rate of ~7% [1,2]. Other neuroendocrine carcinomas (NECs) have similarly poor survival rates [3]. Standard of care for patients with metastatic SCLC and other NECs is platinum-based chemotherapy with or without immunotherapy [4]. While the addition of anti-PD-1 antibodies has improved outcomes in SCLC, nearly all patients relapse, hence alternative therapies are needed [2].

DLL3 is a member of the Notch receptor ligand family, a group of proteins crucial for Notch signaling during embryonal development [5]. DLL3 is normally only widely expressed during embryonal development and predominantly localizes internally to the Golgi apparatus; however, DLL3 expression is associated with a neuroendocrine cancer phenotype and diffuse expression on the cell surface has been demonstrated in many cases of SCLC and other NECs [6–12]. DLL3 has become a target of increasing interest in recent years [13]. Various

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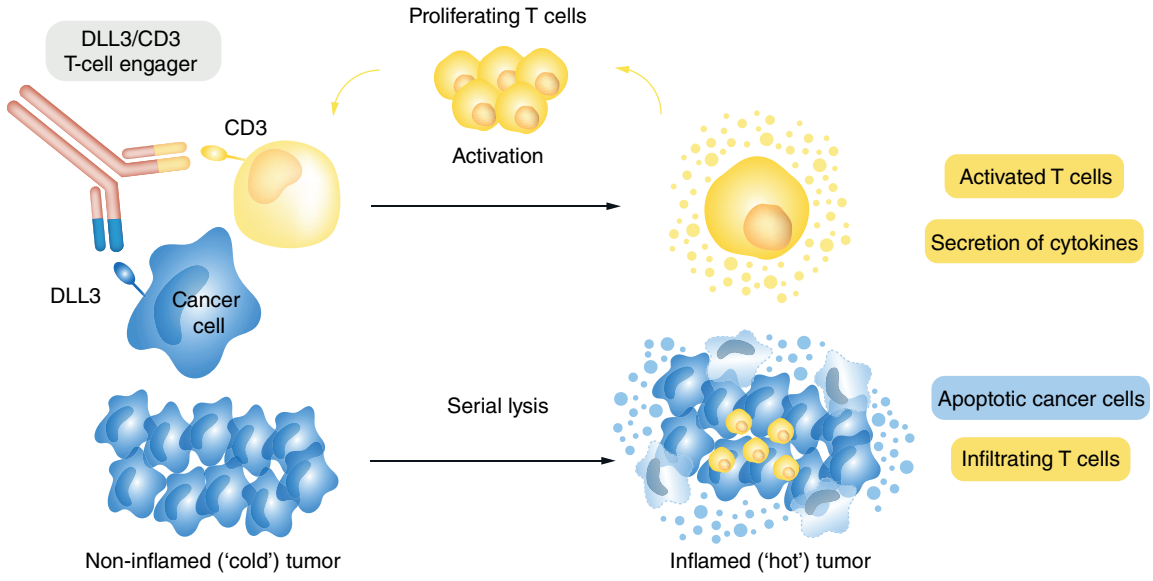

Figure 1. BI 764532 mechanism of action.

approaches for targeting DLL3 have been undertaken, including antibody–drug conjugates [14], DLL3/CD3 bispecific T-cell engagers [5,13,15–17] and DLL3-targeting CAR-T [13].

Background & rationale

The bispecific DLL3/CD3 IgG-like T-cell engager (TcE) BI 764532 acts to induce the formation of a major histocompatibility complex (MHC)-independent cytolytic synapse by concomitant binding to DLL3 on tumor cells and CD3 on T cells, leading to T cell-mediated antitumor cytolytic activity (Figure 1) [5]. BI 764532 has demonstrated activity in preclinical studies. In a human T-cell engrafted mouse model, it induced potent, DLL3-dependent lysis of tumor cells and T-cell infiltration of tumor tissue, resulting in complete tumor regression [5].

The ongoing study described in this paper is a first-in-human, phase I study of intravenous (i.v.) BI 764532 monotherapy in patients with SCLC, large cell NEC, NEC or small-cell carcinomas of any other origin (NCT04429087). The objectives of this study are to determine the maximum tolerated dose (MTD) for BI 764532 in patients with SCLC or other NECs, and to evaluate safety, tolerability, pharmacokinetics (PK) and preliminary efficacy.

Methods & analysis

Study design

This phase I study is a multicenter, open-label, non-randomized, dose-escalation study. In the phase Ia period, BI 764532 is administered using up to three dosing regimens: regimen A is a fixed dose once every 3 weeks, regimen B1 is a fixed dose once a week (on days 1, 8 and 15 of a 3-week cycle), and regimen B2, which is per protocol as optional, includes an initial step-in dose(s) followed by a fixed weekly dose. Regimens are assessed sequentially, starting with regimen A (Figure 2). Patients will be treated until disease worsening or for a maximum of 36 months.

These schedules of administration were selected according to pharmacokinetic modelling based on preclinical data. Regimen A is expected to avoid clinically significant drug accumulation beyond the first cycle. Accordingly, it was considered appropriate to explore the safety of a single dose BI 764532 using a Bayesian Logistic Regression Model (BLRM) with an initial MTD period of 3 weeks. The exploration of regimen B will only be initiated once the totality of all data from regimen A, including safety, pharmacokinetics, biomarker analysis, potential of drug accumulation and possible efficacy have been assessed. Regimen B2 is potentially considered once the safety and MTD of the 'flat' dosing are defined, particularly in case adverse events (AEs), e.g., cytokine release syndrome (CRS) preclude the efficacious exposure.

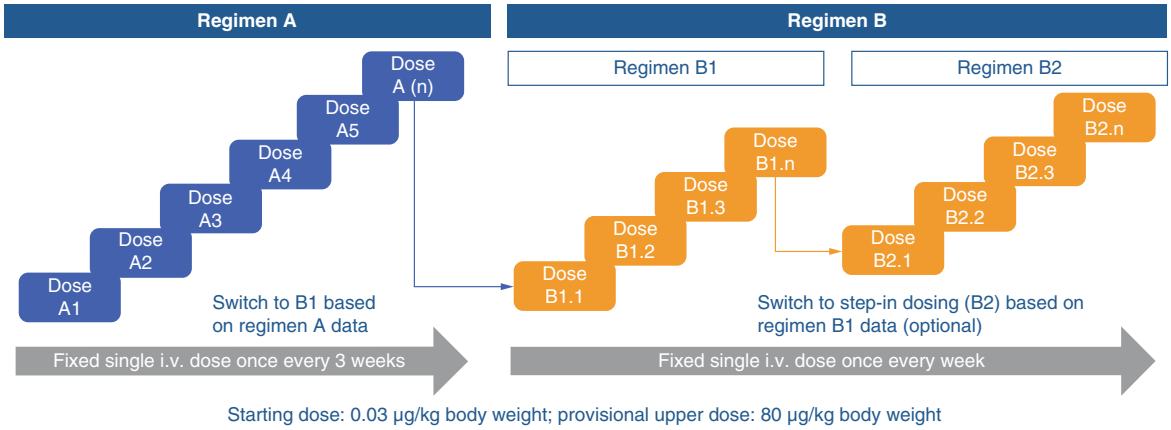

Figure 2. Phase Ia trial design.
i.v.: Intravenous.

Eligibility criteria

Inclusion criteria

Patients included in the study must be adults (≥18 years) with locally advanced or metastatic cancer of the following histologies: SCLC; large cell neuroendocrine lung carcinoma; NEC or small-cell carcinoma of any other origin. All included patients must have tumors positive for DLL3 expression according to central pathology review of archived tissue or an in-study biopsy. Enrolled patients are those who have failed or are not eligible for available standard therapies. Prior standard therapies should include ≥1 line of chemotherapy; patients with small-cell carcinomas should have received platinum-based therapy. Patients have an Eastern Cooperative Oncology Group performance status of 0 or 1, at least one evaluable lesion outside of the central nervous system (CNS), as defined by modified Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 criteria, adequate organ function, and have provided written informed consent.

For patients with brain metastases, the following additional inclusion criteria apply: radiotherapy or surgery for brain metastases completed ≥2 weeks prior to the first administration of BI 764532; non-physiologic doses of steroids discontinued ≥7 days prior; and anti-epileptic drugs discontinued ≥7 days prior or on stable doses of anti-epileptic drugs for malignant CNS disease.

Exclusion criteria

Exclusion criteria are: previous treatment with TcEs or DLL3-targeted therapies; persistent toxicity from previous treatment that has not resolved to less than Common Terminology Criteria for Adverse Events (CTCAE) grade 1, except for alopecia, CTCAE grade 2 neuropathy, asthenia/fatigue or grade 2 endocrinopathies controlled by replacement therapy; administration of anticoagulant treatment that cannot be safely interrupted; diagnosis of immunodeficiency or receiving immunosuppressive therapy within 7 days of first dose of BI 764532; prior anticancer therapy within 3 weeks/5 half-life periods or extensive field radiotherapy within 2 weeks of first dose of BI 764532; other active malignancy that could interfere with the prognosis and treatment of the study-related disease; major surgery within 28 days for the first dose of BI 764532; known leptomeningeal disease; active infection requiring medical therapy or other clinically significant intervention; laboratory evidence of hepatitis virus infection, or known HIV infection; continued intake of restricted medications (other investigational therapy or anticancer agent; immunosuppressive medications taken for non-study reasons; live attenuated vaccines during the trial or up to 30 days after the last dose of BI 764532; palliative radiotherapy during cycle 1) or any drug likely to interfere with the safe conduct of the trial; serious concomitant disease or medical condition affecting study compliance or which may impact study drug evaluation; and any laboratory abnormality that may increase the study-related risk and would make the patient inappropriate for study entry in the judgement of the investigator.

Planned sample size

No formal statistical power calculations were performed for the determination of the study sample size. Sample sizes were estimated based on simulation studies according to different dose-toxicity scenarios. According to these

studies, ~60 patients are expected for regimen A and ~50 patients are expected for regimen B. Hence, for the dose escalation, a total of 110 patients are estimated but might vary depending on the number of tested dose cohorts.

Study schedule

Patients will undergo two screening steps. In 'screen 01' DLL3 expression status will be assessed using archival material or fresh biopsies. 'Screen 02' is prerequisite for entering the treatment period. Screen 02 occurs within 3 weeks after the start of the treatment period.

Each cycle has duration of 3 weeks (21 days), regardless of regimen. The schedule for regimen A is as follows: cycles 1, 2, 3 and 4 require three visits on days 1, 8 and 15, cycles 5 and 6 require two visits (day 1 and day 8) and other cycles require one visit on day 1. In regimen B, all cycles require three visits on days 1, 8 and 15. Included in the schedule for all regimens is an end-of-treatment (EOT) visit within 7 days of the decision to discontinue treatment, and a follow-up visit to assess safety 30–35 days after the last dose.

Maximum treatment duration for all patients is 36 months. Patients will be considered as having completed the trial if they discontinue for the following reasons: progressive disease and has completed the safety follow-up visit; lost to follow-up; death; withdrawal of consent for further evaluation at the end of treatment visit; or any other reason. In the case of any other reason, the patient will be considered to have withdrawn.

Study assessments

Efficacy will be assessed by tumor response according to RECIST version 1.1. Safety assessments include physical examination, vital signs, safety monitoring (vital signs and oxygen saturation) during and after drug administration, laboratory parameters (hematology, coagulation, biochemistry, immunoglobulins, urinalysis, pregnancy test), electrocardiogram, and AEs, serious AEs and AEs of special interest (dose-limiting toxicities [DLTs], infusion reactions, hepatic injury), AE severity, and causal relationship of AEs to study drug.

Other assessments include drug concentrations and PK, and exploratory biomarker evaluation (which may include DLL3 percentage positivity; DLL3 expression levels; immune cell infiltration; immuno-oncology related markers; apoptosis, immune cell subsets; cytokine secretion and soluble DLL3 levels in blood; immuno-oncology related gene expression in tumor tissues; and tumor mutational burden).

Study treatment & patient allocation

Dose selection & escalation

In regimen A, the starting dose of BI 764532 is 0.03 μg/kg, based on a pharmacologically active dose, estimated from the 20% effect concentrations of the most sensitive *in vitro* pharmacology assay [data on file]. The dose of BI 764532 is then escalated according to the following provisional dose levels: 0.1, 0.3, 0.9, 2.5, 5, 10, 20, 40 and 80 μg/kg. Of note, the trial protocol allows for lower or higher doses to be investigated as long as they fulfil the escalation with overdose control (EWOC) principle. Application of the EWOC principle means that any dose tested should be unlikely (<25% posterior probability) to result in a DLT rate of ≥33%.

The starting dose for regimen B1 will be determined by the Safety Monitoring Committee (SMC), based on matching exposure with a safe dose established in regimen A. If ≥ grade 2 toxicity occurs in regimen B1 after the first administration of fixed doses and this toxicity is determined to be due to CRS or related symptoms, the SMC may decide to switch to regimen B2 using a step-in dose regimen. In the optional step-in regimen, the initial one or two administrations of regimen B2 will be composed of a fraction of the target dose (e.g., 20–50%), followed by full dosing at next administration and thereafter. The target step-in dose for regimen B2 will be determined after incorporation of all available safety data.

The SMC may recommend stopping the dose escalation phase after the criterion for MTD is fulfilled, and further patients may be included to confirm this MTD estimate. If no DLT is observed at a dose considered to have sufficient efficacy, the SMC may decide to include an additional number of patients at this dose level and to declare this dose as the recommended dose for expansion.

Premedication with steroids

In order to reduce the severity of potential CRS/infusion-related reactions (IRRs), patients undergoing BI 764532 dose escalation in regimen A receive premedication 30–60 minutes prior to the start of BI 764532 administration. Premedication consists of acetaminophen/paracetamol 1000 mg administered orally or i.v., or equivalent, and i.v. antihistamine, equivalent to i.v. diphenhydramine 50 mg.

In the event that CRS/IRRs of ≥ grade 2 occur after BI 764532 administration in more than one patient per dose level, the SMC can elect to add i.v. steroids equivalent to prednisolone 100 or 16 mg dexamethasone to the premedication regimen. The steroid-containing premedication regimen will be implemented in all subsequent patients regardless of BI 764532 dose, with steroid dose managed on an individual patient level according to the patient's tolerance of BI 764532. If steroids are not already implemented at the B1 starting dose, the SMC may introduce steroids later during the dose escalation of regimens B1 or B2. The SMC may decide to implement steroids first and step-in dosing second or *vice versa* depending on the overall observed data in regimen B.

Assigning patients to treatment groups

In regimen A, single-patient dose levels are planned for the early dose escalation steps (<1 μg/kg) in order to reduce the number of patients exposed to predicted sub-therapeutic doses. A single-patient dose group can be increased to three patient cohorts in the case of AEs of ≥ grade 2 not due to underlying malignancy or an extraneous cause, or if an objective response according to RECIST 1.1 occurs.

Back-fill cohorts, including three additional patients per dose level, are planned to assess target engagement and pharmacodynamic biomarkers using mandatory pre-treatment and on-treatment biopsies, and for collection of additional safety data. Back-fill cohorts are provisionally planned for dose levels of 5 μg/kg or more but may be introduced at a lower dose level if AEs of ≥ grade 2 occur at that dose and are clearly not due to underlying malignancy or an extraneous cause. Back-fill cohort recruitment will only start after the next higher dose escalation level is cleared for safety by the SMC and fulfils the EWOC criterion (dose is below MTD level).

Recruitment for regimen A is beginning first. Patients are entered into the study sequentially, with enrolment in the current dose level cohort prioritized over recruitment for back-fill cohorts.

Drug assignment & dose administration

Before being assigned to a dose tier, patients will undergo screening for DLL3 status and screening for entry into the treatment period. The dose tier is then confirmed by the clinical monitor, and the patient begins treatment at that dose following administration of mandatory premedication.

In the event of CRS/IRR, the dose of BI 764532 will be reduced according to the rules summarized in Table 1. If other AEs that qualify for DLTs (Table 2) occur, the patient may continue treatment at a reduced dose only after recovery from the DLT to grade ≤1 or baseline and when re-treatment criteria are met. The dose will be one dose level down from the previous dose administered to the patient, and a subsequent dose increase is not allowed. The occurrence of a second toxicity requiring dose reduction will result in the patient discontinuing treatment.

Patients allocated to dose levels of ≤20 μg/kg may be able to receive an increased dose of BI 764532 once the patient has completed the MTD evaluation period if no DLTs were experienced. These patients may receive the highest dose level explored in the trial and deemed safe by the SMC.

Data collection & storage

Study data are collected using case report forms. Investigators are expected to prepare and maintain adequate and accurate source documents and study records that include all observations and other pertinent data pertinent for each patient participating in the study. The trial site(s) will retain the source and essential documents (including investigator site file) according to the local requirements valid at the time of the end of the trial or 15 years (whatever is longer).

Study end points

The primary end points of the phase Ia period are: MTD in any studied regimen, defined as the highest dose with <25% risk of the true DLT rate being ≥33% during the MTD evaluation period, with separate MTDs determined in regimen A and regimen B; and the number of patients with DLTs in the MTD evaluation period.

The secondary end points of the phase Ia period are objective response based on RECIST 1.1 criteria in patients with measurable disease, and the PK parameters maximum measured concentration of BI 764532 (C_{max}) and the area under the concentration-time curve of the analyte over a uniform dosing interval τ (AUC_{τ}). Further end points include DLL3 expression; tumor pathology and grade; immunogenic response; pharmacodynamic biomarker modulation in tumor tissue and blood; the number of patients with DLT during the entire treatment period; progression-free survival and duration of response; changes in soluble DLL3 in plasma over time; changes in circulating tumor cell counts over time (in SCLC patients only); and additional PK parameters.

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Table 1. Recommendations for the management of BI 764532 infusion in case of infusion-related reactions/cytokine release syndrome.

NCI CTC v5 grade	Description of severity (according to CTCAE v5)	Management of current BI 764532 infusion	Minimal treatment intervention	BI 764532 dose and infusion management at next cycle
1	IRR: mild transient reaction; infusion interruption not indicated; intervention not indicated CRS: fever with or without constitutional symptoms	Consider temporary interruption or reduced infusion rate	• Acetaminophen or paracetamol as needed for fever • i.v. fluids as needed • Assess for infection with blood and urine cultures, and chest x-ray as needed • Consider corticosteroids or IL-6 antagonist for persistent (>3 days) or refractory fever	Continue BI 764532 at the same dose level if recovery to baseline 2 days before next dose administration
2	IRR: therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, i.v. fluids); prophylactic medications indicated for ≤24 h CRS: hypotension responding to fluids; hypoxia responding to <40% O_2	Interrupt infusion. Restart infusion at reduced rate once recovery to baseline within maximum stability time of BI 764532	• i.v. fluid bolus of 500–1000 ml normal saline; repeat as necessary to maintain systolic blood pressure >90 mmHg • Consider early administration of IL-6 antagonist together with i.v. fluids for high-risk patient (e.g., co-morbidities or older age) • If hypotension persists after two fluid boluses administer IL-6 antagonist, start vasopressor and transfer patient to ICU • Use supplemental oxygen as needed to maintain oxygen saturation above 90% • If hypoxia persists below 90% saturation administer IL-6 antagonist and transfer patient to ICU • Manage fever and assess for infections as in grade 1	• If improvement to grade ≤1 within 8 h, continue at the same dose level or consider administration at reduced infusion rate • If grade 2 persists for >8 h, continue at reduced dose (one level lower) • For subsequent treatment cycles consider premedication
3	IRR: prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion) recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae CRS: hypotension managed with one pressor; hypoxia requiring ≥40% O_2	Stop BI 764532 infusion. Do not re-start BI 764532 infusion	• Transfer patient to ICU if not already done, initiate hemodynamic monitoring • Start steroids, e.g., dexamethasone 8 mg i.v. every 6 h until recovery to grade 1 or increase to 20 mg i.v. every 6 h if refractory • Use IL-6 antagonist • Use fluid boluses and vasopressors as needed • Use supplemental oxygen with appropriate breathing device as needed to maintain oxygen saturation above 90% • Manage fever and assess for infections as in grade 1 CRS	• If improvement to grade ≤1 within 48 h: continue at the reduced dose (one dose level lower) after premedication with steroids; consider administration at reduced infusion rate • If improvement to grade ≤1 takes >48 h: permanently discontinue BI 764532
4	IRR: life-threatening consequences; urgent intervention indicated CRS: life-threatening consequences; urgent intervention indicated	Stop BI 764532 infusion. Do not re-start BI 764532 infusion	• ICU transfer, i.v. fluids, vasopressors and hemodynamic monitoring as indicated for grade 3 • Use IL-6 antagonist and steroids as for grade 3 • Start high dose methylprednisolone • Use mechanical ventilation as needed • Manage fever and assess for infections as in grade 1 CRS • Symptomatic management of organ toxicity as per local guidelines	Permanently discontinue BI 764532

CRS: Cytokine release syndrome; CTCAE: Common Terminology Criteria for Adverse Event; h: Hour; ICU: Intensive care unit; IRR: Infusion-related reaction; i.v.: Intravenous; v5: Version 5.

Statistical analysis

Determination of the MTD

For each dosing regimen, a separate BLRM employing the EWOC principle will be used during the escalation phase for the selection of the dose levels and the estimation of the MTD, where applicable [18,19]. The estimated probability of a DLT at each dose level from the model will be summarized using the following intervals: under toxicity, 0.00–0.16; targeted toxicity, 0.16–0.33; and over toxicity, 0.33–1.00. Applying the EWOC criterion, it should be unlikely (less than 25% probability) that the DLT rate at that dose will exceed 0.33.

The MTD may be considered reached if one of the following criteria is fulfilled: the posterior probability of the true DLT rate in the target toxicity interval of the MTD is above 0.5, or at least 15 patients have been treated in the dose escalation phase of the trial, of which at least six have been treated at the MTD.

Intra-patient dose escalation is allowed to dose levels cleared by the Safety Monitoring Committee.

Table 2. Overview of dose-limiting toxicities.

Category	Criteria
Non-hematologic	**CRS/IRR** • CRS/IRR ≥ CTC grade 4 • CRS/IRR ≥ CTC grade 3 if not resolved to grade 1 ≤ within 48 h (despite appropriate intervention) **Other non-hematologic AEs grade ≥3 except for** • Laboratory values unless they meet the criteria specified below • Fatigue/asthenia, if present at baseline, there must be an increase of ≥2 grades, lasting more than 7 days to qualify for DLT • Grade 3 nausea or grade 3 vomiting or grade 3 diarrhea lasting ≤48 h, and which resolved to ≤ grade 1 either spontaneously or with conventional medical intervention. • TLS grade 3 • TLS grade 4 if clinically manageable and resolving within 24 h **Non-hematologic clinically significant laboratory value of CTC grade 4** **Non-hematologic clinically significant laboratory value of CTC grade 3** **if:** • Hospitalization results from the lab value • The abnormality persists for >72 h despite appropriate interventions (e.g., replacement therapy for electrolyte abnormalities, when indicated). **Liver laboratory parameters:** • **For patients with normal liver function at baseline (ALT, AST, and bilirubin within normal limits at baseline):** ◦ An elevation of AST and/or ALT ≥threefold ULN combined with an elevation of total bilirubin ≥twofold ULN measured in the same blood draw sample with the exclusion of the causes due to underlying diseases, and/or ◦ Marked peak aminotransferase (ALT, and/or AST) elevations ≥tenfold ULN with the exclusion of the causes due to underlying diseases, and persistence for >72 h despite appropriate treatment • **For patients with abnormal liver function at baseline (AST and/or ALT>ULN)** ◦ An elevation of AST and/or ALT ≥fivefold ULN combined with an elevation of total bilirubin ≥twofold ULN measured in the same blood draw sample, with the exclusion of the causes due to underlying diseases, and/or ◦ Marked peak aminotransferase (ALT, and/or AST) elevations ≥tenfold ULN with the exclusion of the causes due to underlying diseases, and persistence for >72 h despite appropriate
Hematological	• Hematologic toxicity CTC grade 4 (e.g., neutropenia, thrombocytopenia, anemia) except for lymphopenia • Anemia of any grade requiring red cells transfusion • Thrombocytopenia of any grade requiring platelets transfusion • Neutropenia of any grade requiring treatment with growth factors • Grade 3 neutropenia with documented infection • Grade 3 neutropenia lasting >3 days • Febrile neutropenia • Grade 3 thrombocytopenia (<50,000/mm^3)
Other	• AE that leads to administration of <70% of the planned dose per cycle despite infusion interruption and infusion time prolongation • AE that requires permanent discontinuation of BI 764532 • Other toxicity considered significant enough to be qualified as DLT in the opinion of the investigators, SMC or sponsor

AE: Adverse event; CRS: Cytokine release syndrome; CTC: Common Terminology Criteria; DLT, Dose-limiting toxicity; IRR: Infusion-related reaction; SMC: Safety Monitoring Committee; TLS: Tumor lysis syndrome; ULN: Upper limit of normal.

Planned analyses

The analyses in this trial are descriptive and exploratory. No formal statistical tests will be performed, and no formal interim analysis of efficacy is planned. The population used in the analysis of MTD will be the treated set (patients treated with ≥1 dose of study drug) excluding patients who need to be replaced. For all other end points, all patients in the treated set will be included in the analysis. Secondary and further end points will be analyzed descriptively. PK parameters will be calculated using non-compartmental analysis and, and descriptive statistics presented.

AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs occurring between the start of treatment and 30 days after the last dose of study drug will be considered on-treatment and evaluated. Statistical analysis and reporting of AEs will focus on treatment-emergent AEs, defined as those occurring during the above evaluation period. AEs that start before first drug intake and deteriorate under treatment will also be considered treatment emergent. AEs are graded according to CTCAE version 5.0. Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA at database lock.

Laboratory data will be analyzed via comparison of laboratory data to their reference ranges, and treatment groups will be compared descriptively with regard to distribution parameters and the frequency and percentage of patients with abnormal values or clinically relevant abnormal values. Vital signs, physical examinations, or other safety-relevant data observed during the course of the trial (screening to EOT evaluation) will be assessed with regard to possible changes compared with findings before start of treatment.

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Handling of missing data

No imputation will be performed on missing efficacy data. Missing baseline laboratory values will be imputed by the respective values from the screening visit. No other imputations will be performed on missing data. Every effort will be made to obtain complete information on all AEs, particularly potential DLTs, and to include all concentration data in a PK analysis.

Ethical considerations

The trial is being carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, and in accordance with: the International Conference on Harmonization Guideline for Good Clinical Practice (GCP); relevant standard operating procedures of the sponsor; the EU directive 2001/20/EC/EU regulation 536/2014; the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, 27 March 1997); and other relevant regulations.

Conclusion

This paper describes the protocol of a first-in-human phase I, multicenter, open-label, non-randomized, dose-escalation study of BI 764532 i.v. monotherapy in patients with SCLC, LCNEC, NEC or small-cell carcinomas of any other origin. Of note, this study is characterized by the flexible nature of the trial design with regards to dosing, and the careful approach to patient safety with the predicted sub-therapeutic nature of the early dose levels.

To date, efforts to treat SCLC with DLL3-targeted antibodies have yielded mixed results. The anti-DLL3 antibody–drug conjugate (ADC), rovalpituzumab tesirine (Rova-T), demonstrated promising safety and efficacy in a phase I trial of patients with pretreated SCLC [20], but these findings were not confirmed in subsequent phase III trials [14,21]. Consequently, the development of Rova-T was terminated. While these findings could potentially question the validity of DLL3 as a drug target in SCLC, it seems more likely that the trials failed due to design features of the ADC itself and its mechanism of action [22]. Indeed, alternative antibody-based approaches for targeting DLL3 show considerable promise. An ongoing first-in-human trial of tarlatamab (AMG 757), which, like BI 764532, is a DLL3-targeted TcE, has demonstrated encouraging efficacy (overall response rate in 60 evaluable patients: 13%; disease control rate: 43%) and acceptable tolerability in patients with relapsed/refractory SCLC (NCT03319940) [23]. The most common treatment-related AE was CRS (42%), which presented mainly as fever (31%), tachycardia (17%), nausea (13%), fatigue (9%) and hypotension (9%). CRS was generally manageable and did not lead to any treatment discontinuations. Grade ≥3 AEs were reported in 25% of patients including a case of grade 5 pneumonitis. Ongoing trials are assessing tarlatamab in patients with relapsed/refractory SCLC (phase II; NCT05060016) [24] and patients with neuroendocrine prostate cancer (phase Ib; NCT04702737) [25]. Another DLL3-targeted TcE, HPN 328, has also recently demonstrated preliminary activity and tolerability in patients with SCLC and other NECs [26].

While these early data suggest that targeting DLL3 with a T-cell engaging agent may be a promising approach in the treatment of SCLC, it is noteworthy that the study, unlike the BI 764532 trial described in this paper, did not mandate DLL3 positivity and restricted enrollment to patients with SCLC. The results of the BI 764532 study should provide valuable insight into the safety and preliminary efficacy of targeting DLL3 in patients with DLL3-positive SCLC or NECs.

Executive summary

Background

- Small-cell lung cancer (SCLC) is a poorly differentiated, aggressive neuroendocrine neoplasm with a 5-year survival rate of ~7%.
- Other undifferentiated neuroendocrine carcinomas (NECs) have similarly poor survival rates.
- While the addition of anti-PD-1 antibodies has improved outcomes in SCLC, nearly all patients relapse, and there is a need for alternative therapies.
- DLL3 is a member of the Notch receptor ligand family, usually only widely expressed during embryonal development.
- DLL3 expression has been found on the cell surface of many SCLC and other NECs, and thus has become a target of increasing interest.
- Various approaches have been taken to targeting DLL3, including drug-immunoconjugates, DLL3/CD3 bispecific T-cell engagers and DLL3-targeting CAR-T.

BI 764532

- BI 764532 is a bispecific DLL3/CD3 IgG-like T-cell engager.
- It acts to induce the formation of a major histocompatibility complex-independent cytolytic synapse by concomitant binding to DLL3 on tumor cells and CD3 on T cells, leading to T cell-mediated antitumor cytolytic activity.
- In a human T cell-engrafted mouse model, BI 764532 induced potent, DLL3-dependent lysis of tumor cells and T-cell infiltration of tumor tissue, resulting in complete tumor regression.

First-in-human trial of BI 764532

- This is an ongoing phase I, multicenter, open-label, non-randomized, dose-escalation study of BI 764532 monotherapy in patients with SCLC and other DLL3-positive NECs.
- Eligible patients are adults with locally advanced or metastatic SCLC, large cell neuroendocrine lung carcinoma, NEC or small-cell carcinoma of any other origin, positive for DLL3 expression. Enrolled patients are those who have failed or are not eligible for available standard therapies, with an Eastern Cooperative Oncology Group performance status of 0 or 1 and $\geq$1 evaluable lesion outside of the central nervous system.
- In the phase Ia period, BI 764532 is administered using up to three dosing regimens: regimen A is a fixed dose once every 3 weeks, regimen B1 is a fixed dose once a week (on days 1, 8 and 15 of a 3-week cycle), and optional regimen B2 includes an initial step-in dose(s) followed by a fixed weekly dose. Regimens are assessed sequentially, starting with regimen A, which will have a starting dose of 0.03 μg/kg.
- Doses will then be escalated until the maximum tolerated dose (MTD) is reached. The starting dose for regimen B1 will be determined by the Safety Monitoring Committee, and the target step-in dose for regimen B2 will be determined after incorporation of all available safety data.
- The objectives of this study are to determine the MTD for BI 764532 in patients with SCLC or other DLL3-positive NECs, and to evaluate safety, tolerability, pharmacokinetics and preliminary efficacy of BI 764532.
- As of April 2021, patients are being recruited in early dose-escalation cohorts in the USA, Japan, Spain and Germany.
- The estimated sample size for dose escalation is approximately 110 patients; the final number of patients will depend on the number of dose cohorts tested.

Supplementary data

An infographic accompanies this paper. To view or download this infographic in your browser please click here: www.futuremedicine.com/doi/suppl/10.2217/fon-2022-0196

Author contributions

The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development and have approved the final version.

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Data sharing statement

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Researchers should use the https://vivli.org/ link to request access to study data and visit https://www.mystudywindow.com/msw/datasharing for further information.

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