Phase I dose-escalation study of BI 836826 (CD37 antibody) in patients with relapsed or refractory non-Hodgkin lymphoma of B cell origin

#286

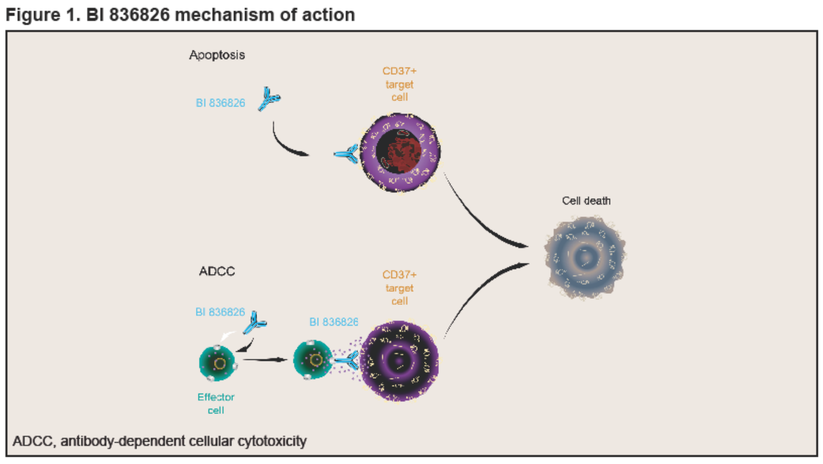
Frank Kroschinsky,[1] Antonio Pezzutto,[2] Mathias Witzens-Harig,[3] Reda Bouabdallah,[4] Paul La Rosée,[5] Carmen Straube,[6] Andreas Viardot,[7] Norbert Schmitz,[8] Gilles Salles,[9] Sven Dillenburger,[10] Charlotte A. Russell,[11] Celine Veau,[10] Ute von Wangenheim,[10] Oliver Ottmann[12]

[1]Medical Department I, University Hospital at the Technical University of Dresden, Dresden, Germany; [2]Medical Clinic M. S. Hematology Oncology and Tumor Immunology, Charité - University Medicine Berlin, Berlin, Germany; [3]Internal Medicine V: Hematology, Oncology and Rheumatology, University Hospital Heidelberg, Heidelberg, Germany; [4]Department of Hematology, Institut Paoli Calmettes, Marseille, France; [5]Klinik für Innere Medizin II, Abt. Hämatologie u. internistische Onkologie, Universitätsklinikum Jena, Jena, Germany; [6]Department of Haematology and Medical Oncology, University Hospital Göttingen, Göttingen, Germany; [7]Department of Internal Medicine III, University of Ulm, Ulm, Germany; [8]Department of Haematology and Oncology, Asklepios Klinik St. Georg, Hamburg, Germany; [9]Department of Hematology, University Hospital of South Lyon, Pierre Benite, France; [10]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, Germany; [11]Boehringer Ingelheim Denmark A/S, Copenhagen, Denmark; [12]Department of Internal Medicine II, Hematology/Oncology, University Hospital, JW Goethe University, Frankfurt, Germany

INTRODUCTION

- CD37 is a transmembrane protein of the tetraspanin superfamily that is predominantly expressed on mature B cells, but not on plasma cells, and to a lesser extent on other leucocyte subsets[1,2]
- CD37 functions as a signalling death receptor[3] and has a role in regulating B/T cell interactions[1,4]
- CD37 is widely expressed on mature B cell malignancies including non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukaemia.[2,5] Its expression pattern and role in apoptotic signalling makes CD37 an attractive target for NHL of B cell origin
- BI 836826 is a novel Fc-engineered IgG1 type II monoclonal antibody targeting CD37[6]
- BI 836826 has a dual mode of action by directly inducing apoptosis and mediating increased antibody-dependent cellular cytotoxicity (ADCC) due to Fc-engineering for enhanced binding to Fcγ-receptors (Figure 1)[6]
- In preclinical studies, BI 836826 treatment resulted in a greater ADCC and apoptosis of B-NHL cells than rituximab[6,7]
- This Phase I study evaluates the safety, maximum tolerated dose (MTD), pharmacokinetics and activity of BI 836826 in patients with relapsed/refractory NHL of B cell origin (NCT01403948; 1270.2)

Figure 1. BI 836826 mechanism of action



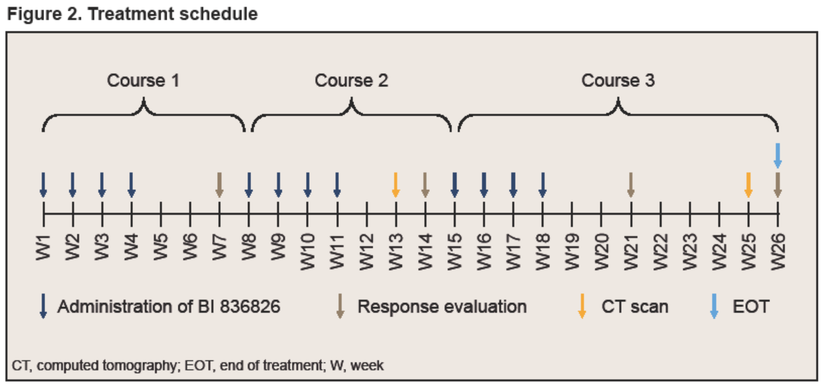
ADCC, antibody-dependent cellular cytotoxicity

METHODS

Study design

- The trial has a dose-escalation phase (modified 3+3 design) and an expansion phase at the MTD
- Eligible patients are treated with up to three courses of an intravenous (iv) infusion of BI 836826 once weekly for 4 weeks followed by an observation period of 27 days in Courses 1 and 2, or 55 days in Course 3 (Figure 2)
- The duration of the two first courses is 7 weeks and the duration of the third course is 12 weeks. Patients with response or stable disease with clinical benefit and good tolerability after two courses can receive a third course
- Premedication (acetaminophen/paracetamol 1,000 mg, or equivalent; antihistamine equivalent to diphenhydramine 50 mg iv; glucocorticoid, equivalent to prednisolone 100 mg iv) is mandatory 30–120 minutes prior to BI 836826 administration to prevent or reduce the severity of infusion-related reactions (IRRs)
  - Supportive care (e.g. granulocyte colony stimulating factor, antibiotics, antivirals) is permitted according to local guidelines

Figure 2. Treatment schedule



CT, computed tomography; EOT, end of treatment; W, week

- Single-patient cohorts were treated until the occurrence of a drug-related adverse event (AE) Grade ≥2 during the first 2 weeks of the first treatment course (the MTD evaluation period). All subsequent cohorts were expanded to three patients following a fixed dose-escalation design with dose de-escalation steps
- The MTD was defined on the basis of dose-limiting toxicities (DLTs) observed during the first 2 weeks of the first treatment course
  - A DLT is defined as any drug-related non-haematological AE ≥3, except IRRs

Endpoints

Primary endpoint

- MTD and number of DLTs

Secondary endpoints

- Tumour size reduction, best overall response, progression-free survival, failure-free survival

Main eligibility criteria

Selected inclusion criteria

- Aged ≥18 years with relapsed or refractory NHL of B cell origin (mature B cell lymphoma according to the World Health Organization) not considered candidates for intensive anti-lymphoma therapy
- Patients must have either aggressive NHL and received ≥1 (≥2 for patients enrolled in France) prior anti-CD20-containing immunochemotherapy or indolent NHL and received anti-CD20 therapy and ≥2 prior therapies
- Life expectancy of ≥3 months
- Eastern Cooperative Oncology Group performance status (ECOG PS) 0–2
- Written informed consent

Selected exclusion criteria

- Primary central nervous system (CNS) lymphoma or known CNS involvement
- Prior history of malignancy
- Inadequate organ function or significant concurrent medical disease or condition considered relevant for the evaluation of the safety of the study drug

Assessments

- Clinical response was assessed at the administration of the first and last of the four infusions in each course and 3 weeks after the last infusion
- CT scans were performed prior to treatment, after two courses of treatment and at the end of treatment, with tumour response assessed according to the standardised response criteria[8]
- Safety is assessed via AEs collected during the course of the clinical trial, via laboratory data and physical examinations, and graded according to Common Terminology Criteria for AEs (v4.0)
- The analyses in this trial are descriptive and exploratory. No formal statistical tests were performed

RESULTS

Patients

- A total of 37 patients were treated in the dose-escalation part (Table 1). The study is currently enrolling patients in an expansion cohort at MTD

Table 1. Patient demographics

Characteristic	N=37
Male/female, n (%)	26 (70.3)/11 (29.7)
Mean age, years (SD)	67.5 (11.4)
ECOG PS 0/1/2, n (%)	9 (24.3)/21 (56.8)/7 (18.9)
Ann Arbor stage, n (%) I/II/III/IV/missing	3 (8.1)/5 (13.5)/9 (24.3)/19 (51.4)/1 (2.7)
Lymphoma subtype, n (%) Follicular/diffuse B cell/mantle cell/other	19 (51.4)/14 (37.8)/3 (8.1)/1 (2.7)
Received prior anti-lymphoma therapy, n (%) 1/2/3/4/5/6/≥7 lines	37 (100) 1 (2.7)/4 (10.8)/7 (18.9)/6 (16.2)/8 (21.6)/6 (16.2)/5 (13.5)
Number of previous therapies, median (range)	5 (1–11)
Patients with prior stem cell transplant, n (%)	7 (18.9)
Patients refractory to last therapy, n (%)*	23 (62.2)

*Patients with best response to last therapy of stable disease or progressive disease and patients with progression <6 months within last therapy
ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation

Treatment exposure

- Of the 37 patients, 37 (100%) had initiated one treatment course, 13 (35.1%) had initiated two courses, and four (10.8%) had initiated three courses
- As of 14 October 2014, one patient (2.7%) remained on study and 36 patients (97.3%) had discontinued. Most patients discontinued due to progressive disease (63.9%)
- Six patients (16.2%) experienced ≥1 dose interruption; median duration of infusion including the interruption was 3.82 hours (range: 0.05–24.60)

Determination of the MTD

- Dose escalation proceeded through 1 mg (n=1), 3 mg (n=4), 9 mg (n=3), 25 mg (n=4), 50 mg (n=6) and100 mg (n=3) with no DLTs observed
- At 200 mg, one of three patients enrolled experienced DLTs. The 200 mg dose cohort was expanded to a total of seven patients, and although no further DLTs were reported, five of the seven patients experienced Grade 3/4 leukopenia and/or neutropenia lasting more than 1 week resulting in a delay in the administration of next infusion (Table 2). As a result, the 200 mg dose was considered to have exceeded the MTD
- Three of six patients treated with a reduced dose of 150 mg experienced a DLT during the MTD evaluation period. In addition, four of the six patients experienced Grade 3/4 leukopenia and/or neutropenia >7 days suggesting that this dose also exceeded the MTD
- No further DLT events were seen across all treatment courses for patients treated in the dose-escalation phase of the trial

Table 2. DLTs and haematological abnormalities during the MTD evaluation period

Dose level (mg)	Treated patients	Evaluable patients	DLTs (n)	Severe haematological abnormalities based on laboratory data (n)
200	7*	6	Grade 3 oral herpes, stomatitis and febrile neutropenia (1)	Grade 4 neutropenia and/or leukopenia not recovered after 1 week resulting in a dose delay (5)
150	6	6	Grade 4 hypophosphataemia (2) Grade 3 hypokalaemia and hypocalcaemia (1)	Grade 4 neutropenia and/or leukopenia not recovered after 1 week resulting in a dose delay (4)
100‡	6§	6	None	None

*One patient withdrew consent during MTD evaluation period and was replaced; ‡Determined to be the MTD; §Three patients in initial cohort plus three additional patients to determine the MTD
DLTs, dose-limiting toxicities

Safety

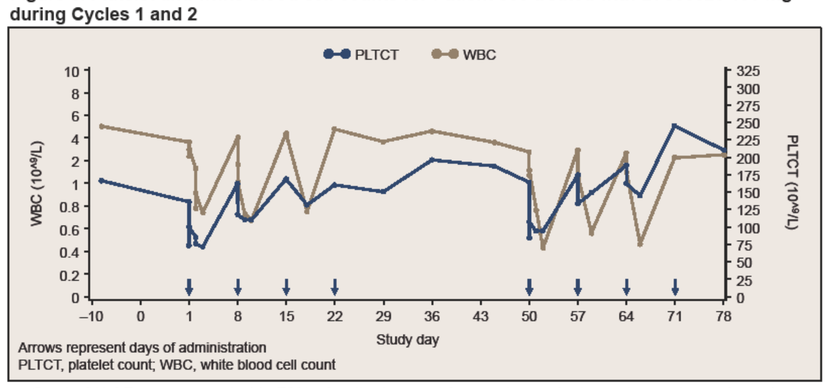
- All patients had at least one AE (Table 3), most commonly leukopenia, neutropenia, thrombocytopenia and IRRs
  - Most IRRs were Grade 1/2; one patient had a Grade 4 IRR leading to a protocol amendment with a change in the infusion schedule. The most common symptoms associated with IRRs were chills and pyrexia
  - The infusion rate was changed to a slowly increasing rate beginning at 10 mL/h and increasing every 30 minutes by 10 mL/h to a maximum of 80 mL/h if tolerable
  - Following the change in infusion schedule, two patients had reversible Grade 3 IRRs; all IRRs after the infusion schedule was changed have been manageable

Table 3. Adverse events occurring in ≥10% overall

	N=37				
Adverse events, n (%)	All grade	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	22 (59.5)	1 (2.7)	–	2 (5.4)	19 (51.4)
Neutropenia	21 (56.8)	–	–	4 (10.8)	17 (45.9)
Thrombocytopenia	18 (48.6)	7 (18.9)	4 (10.8)	6 (16.2)	1 (2.7)
Infusion-related reaction	15 (40.5)	4 (10.8)	8 (21.6)	2 (5.4)	1 (2.7)
Chills	13 (35.1)	7 (18.9)	6 (16.2)	–	–
Anaemia	13 (35.1)	1 (2.7)	5 (13.5)	7 (18.9)	–
Hypokalaemia	12 (32.4)	9 (24.3)	2 (5.4)	1 (2.7)	–
Oedema peripheral	10 (27.0)	9 (24.3)	1 (2.7)	–	–
C-reactive protein increased	10 (27.0)	3 (8.1)	2 (5.4)	3 (8.1)	2 (5.4)
Lymphopenia	10 (27.0)	–	–	–	10 (27.0)
Nausea	8 (21.6)	6 (16.2)	1 (2.7)	1 (2.7)	–
Pyrexia	8 (21.6)	5 (13.5)	1 (2.7)	2 (5.4)	–
Fatigue	8 (21.6)	4 (10.8)	3 (8.1)	1 (2.7)	–
Dyspnoea	8 (21.6)	3 (8.1)	2 (5.4)	3 (8.1)	
General physical health deterioration	8 (21.6)	–	3 (8.1)	3 (8.1)	2 (5.4)
CD4 lymphocytes decreased	8 (21.6)	–	–	1 (2.7)	7 (18.9)
Cough	7 (18.9)	6 (16.2)	1 (2.7)	–	–
Constipation	6 (16.2)	5 (13.5)	1 (2.7)	–	–
Tachycardia	6 (16.2)	3 (8.1)	3 (8.1)	–	–
Decreased appetite	6 (16.2)	3 (8.1)	3 (8.1)	–	–
Urinary tract infection	6 (16.2)	1 (2.7)	2 (5.4)	3 (8.1)	–
Hypophosphataemia	6 (16.2)	–	2 (5.4)	1 (2.7)	3 (8.1)
Vomiting	5 (13.5)	5 (13.5)	–	–	–
Hypertension	5 (13.5)	1 (2.7)	3 (8.1)	1 (2.7)	–
Vertigo	4 (10.8)	4 (10.8)	–	–	–
Night sweats	4 (10.8)	3 (8.1)	1 (2.7)	–	–
Diarrhoea	4 (10.8)	3 (8.1)	1 (2.7)	–	–
Blood creatinine increased	4 (10.8)	3 (8.1)	1 (2.7)	–	–
Back pain	4 (10.8)	2 (5.4)	2 (5.4)	–	–
Mucosal inflammation	4 (10.8)	2 (5.4)	2 (5.4)	–	–
Pleural effusion	4 (10.8)	1 (2.7)	2 (5.4)	1 (2.7)	–
Bronchitis	4 (10.8)	1 (2.7)	2 (5.4)	1 (2.7)	–

- During the course of the trial, seven patients experienced a total of nine episodes of Grade 4 neutropenia lasting more than 1 week resulting in a delay in the administration of next infusion (based on laboratory data). Prolonged neutropenia was seen in all dose cohorts except BI 836826 1 mg, 3 mg and 50 mg. At the MTD (100 mg), one of six patients had one episode of Grade 4 neutropenia lasting more than 1 week resulting in a delay in the administration of next infusion (duration: 11 days); this episode did not require a dose reduction or discontinuation of the study drug. Two patients in the 200 mg cohort had concomitant Grade 3 infections
  - The platelet and white blood cell counts for a representative patient treated with BI 836826 100 mg are shown in Figure 3

Figure 3. Platelet and white blood cell counts for Patient 505 treated with BI 836826 100 mg during Cycles 1 and 2



Arrows represent days of administration
PLTCT, platelet count; WBC, white blood cell count

- Grade 3/4 AEs were reported in 78% of patients; most frequent were leukopenia, neutropenia and lymphopenia
- There were seven deaths; all were the result of progressive disease and none were considered treatment-related

Pharmacokinetics

- Plasma exposure increased with increasing doses (Figure 4)
- Clearance of BI 836826 decreased and apparent half-life increased with increasing dose (Table 4)

Figure 4. Plasma concentration–time profiles from six individual patients following the first infusion of BI 836826 150 mg

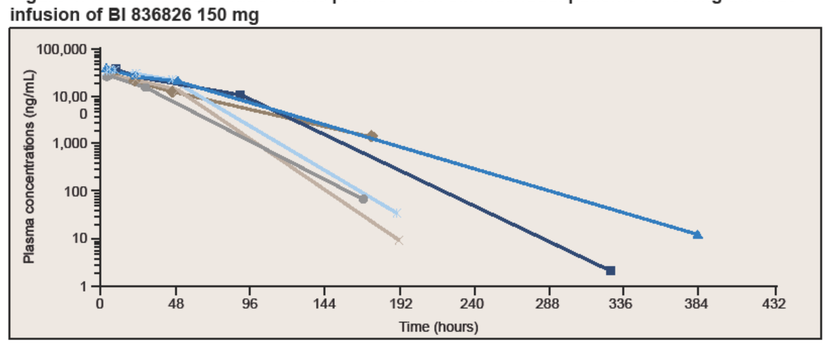


Table 4. Preliminary pharmacokinetic parameters of BI 836826

Parameter, gmean (gCV)	1 mg (n=1)	3 mg (n=4)	9 mg (n=3)	25 mg (n=4)	50 mg (n=5)	100 mg (n=3)	150 mg (n=6)	200 mg (n=7)
C_{max} (µg/mL)	0.0546	0.266 (134)	1.35 (48.2)	4.41 (34.1)	8.25 (54.7)	13.8 (37.4)	31.3 (11.9)	42.0 (16.0)
CL (mL/min)	77.6	29.6 (214)	9.50 (107)	4.71 (84.7)	4.87 (200)	7.54 (75.2)	1.62 (27.5)	1.34 (76.4)
$t_{1/2}$ (h)	1.31	2.07 (60.0)	4.81 (58.6)	10.5 (137)	10.4 (134)	5.28 (26.9)	22.0 (41.4)	35.7 (116)
V_{ss} (L)	11.9	6.39 (89.3)	4.98 (35.8)	5.08 (13.3)	5.12 (42.0)	5.54 (53.7)	3.82 (19.2)	4.91 (28.7)

CL, clearance; C_{max}, maximum concentration; gCV, geometric coefficient of variance; $t_{½}$, apparent terminal half-life of the analyte; V_{ss}, volume of distribution in steady state

Efficacy

- According to latest data, two patients with follicular lymphoma treated with BI 836826 100 mg had a 33% (Patient 505) and 44% (Patient 409) tumour reduction, as measured by the sum of the product of the longest perpendicular dimensions, respectively
  - Patient 409 has no documented progressive disease. The patient received subsequent treatment with bevacizumab 179 days after last administration of BI 836826
  - Patient 505 had progressive disease documented 98 days after last administration of BI 836826; subsequent therapy has not yet been determined
- In addition, one patient with mantle cell lymphoma (MCL; Patient 701) with leukaemic manifestation had a clearance of leukaemic MCL cells and haematopoietic recovery with a duration of 171 days

CONCLUSIONS

- The MTD for BI 836826 was defined as 100 mg, which is being used in the ongoing expansion phase
  - Efficacy and haematological side effects will be further studied in the expansion phase of the study
- Patients treated with BI 836826 100 mg who experienced neutropenia and leukopenia recovered before the next scheduled weekly infusion and the events were considered manageable. Mechanism of CD37-related neutropenia is under investigation; initial preclinical data point to the involvement of a non-myelotoxic, chemokine-mediated redistribution effect[9]
- The most frequent AEs observed were haematological and IRRs
- IRRs were manageable after amending the infusion schedule and mainly Grade 1/2

REFERENCES

1. van Spriel AB, et al. J Immunol 2004;172:2953–61
2. Deckert J, et al. Blood 2013;122:3500–10
3. Lapalombella R, et al. Cancer Cell 2012;21:694–708
4. Knobeloch KP, et al. Mol Cell Biol 2000;20:5363–9
5. Beckwith KA, et al. Front Physiol 2015;6:91
6. Heider KH, et al. Blood 2011;118:4159–68
7. Wu H-S, et al. Oncol Res Treat 2014;37: (abstract P243)
8. Cheson BD, et al. J Clin Oncol 1999;17:1244–1253
9. Deckert J, et al. Blood 2014;124: (abstract 3119)

ACKNOWLEDGEMENTS AND DISCLOSURES

The authors would like to acknowledge the support of all trial investigators and clinical trial support staff and of all patients and their families participating in this trial

The authors were fully responsible for all content and editorial decisions, and were involved at all stages of poster development and have approved the final version. This study was funded by Boehringer Ingelheim. Victoria A. Robb of GeoMed, an Ashfield company, part of UDG Healthcare plc, provided medical writing assistance during the preparation of this poster, supported financially by Boehringer Ingelheim

AV: Janssen, Gilead, Roche, Amgen for consultancy or advisory role; Janssen, Roche, Pfizer for honoraria; Roche, Amgen travel grants. CR: Boehringer Ingelheim, Genmab A/S for employment; Genmab A/S stock ownership. FK: Roche, Pfizer, Amgen for honoraria; Boehringer Ingelheim, Amgen for sponsored travel and other expenses; Roche for consultancy or advisory role. GS: Participation in advisory boards for Celgene, Gilead, Roche, Mundipharma, Janssen; Amgen, Celgene, Gilead, Roche, Mundipharma, Janssen for honoraria; Roche for research funding. NS: Roche for consultancy or advisory role; Celgene stock ownership; Roche, Takeda, CTI Life Sciences, Riemser for honoraria; Boehringer Ingelheim, Roche for research funding. OO: Boehringer Ingelheim for consultancy or advisory role and honoraria. UW, SD, CV: employees of Boehringer Ingelheim Pharma GmbH & Co. KG. AP, PL, RB, CS have no disclosures

Presented at the 13th International Conference on Malignant Lymphoma, Lugano, Switzerland, 17–20 June 2015