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Phase IA/II, multicentre, open-label study of the CD40 antagonistic monoclonal antibody lucatatumumab in adult patients with advanced non-Hodgkin or Hodgkin lymphoma

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Conflicts of interest

Dr Fanale reports receiving research funding and honoraria from Novartis. Dr Assouline reports research funding from and consulting for Novartis. Dr Kuruvilla reports research support and honoraria from Novartis. Dr Corradini reports receiving honoraria from Celgene, Novartis, Sanofi, Takeda, and Gentium. Dr Engert reports receiving research funding and honoraria from Millennium and Takeda; Drs Carreon and Ewald are employees of Novartis and Dr Baeck is an employee of and holds equity in Novartis. Dr Younes reports receiving research support and honoraria from Novartis. Dr Freedman reports serving as consultant to GlaxoSmithKline, Axio, and Pfizer and receiving speaking fee for CME talks for 'Knowledge to Practice'. Drs Solal-Céligny, Heo, Verhoef, Abramson, Offner, and Dyer report no conflicts to disclose.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table SI. Summary of [¹⁸F] fluorodeoxyglucose (FDG)-positron emission tomography response definitions.

Table SII. Best metabolic clinical response ([¹⁸F] fluorodeoxyglucose-positron emission tomography) by lymphoma subtype.

Table SIII. Pharmacokinetic parameters by treatment group (cycle 1 only).

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Summary

Despite advancements in the treatment of non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), patients continue to relapse and thus a need for new targeted therapies remains. The CD40 receptor is highly expressed on neoplastic B cells and activation leads to enhanced proliferation and survival. Lucatumumab (HCD122) is a fully human antagonistic CD40 monoclonal antibody. A phase IA/II study was designed to determine the maximum tolerated dose (MTD) and activity of lucatumumab in patients with relapsed/refractory lymphoma.

Determination of the MTD was the primary objective of the phase IA dose escalation portion and clinical response was the primary objective of the phase II dose expansion portion. Patients received escalating doses of lucatumumab administered intravenously once weekly for 4 weeks of an 8-week cycle. MTD was determined at 4 mg/kg of lucatumumab. A total of 111 patients with NHL ($n = 74$) and HL ($n = 37$) were enrolled. Responses were observed across various lymphoma subtypes. The overall response rate by computed tomography among patients with follicular lymphoma (FL) and marginal zone lymphoma of mucosa-associated lymphatic tissue (MZL/MALT) was 33.3% and 42.9%, respectively. Lucatumumab demonstrates modest activity in relapsed/refractory patients with advanced lymphoma, suggesting that targeting of CD40 warrants further investigation.

Keywords

non-Hodgkin lymphoma; Hodgkin lymphoma; monoclonal antibodies

Antibody-based therapies have had a significant impact on the outcomes of patients with non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). However, there remains a need for new treatments in patients who have refractory or relapsed disease (Fisher *et al*, 2005; Dotan *et al*, 2010). CD40 is an appealing target for therapeutic development in NHL and HL, as it is a type-1 transmembrane protein of the tumour necrosis factor receptor superfamily, which is expressed at >90% on the cell surface of many malignancies of B-cell lineage (Uckun *et al*, 1990; Carbone *et al*, 1995a,b; Gruss & Dower, 1995; Luqman *et al*, 2008).

Because it is present from the pro-B phase through to the plasma cell phase, CD40 has a greater range of expression than CD20. Also, CD40 is present on other cell types including dendritic cells, monocytes, and macrophages (Biancone *et al*, 1999; van Kooten & Banchereau, 2000). The activation of CD40 *in vitro* by its ligand, CD40L (CD40LG), or by an agonist monoclonal antibody (mAb), results in enhanced proliferation and survival of neoplastic B cells. Therefore, one rationale for targeting CD40 is to block ligand-induced proliferation, in addition to both complement-mediated or antibody-dependent cellular cytotoxicity (ADCC) induced by mAb therapy (Luqman *et al*, 2008). Importantly, CD40 signalling may mediate resistance not only to standard chemotherapeutic regimens but also to targeted agents. When CD40 is activated in B-chronic lymphocytic leukaemia (B-CLL)

cells, downstream effects occur including phosphorylation of ERK 1/2 (MAPK3/1) and IKK, as well as upregulation of Mcl-1 (MCL1) and Bcl-xl (BCL2L1), which collectively are involved in development of the malignant phenotype (Luqman *et al*, 2008). Preclinical studies have shown that CD40 signalling from T cells modulates activity of the BCL6 transcriptional repressor. In malignant B cells, CD40 signalling quickly interferes with the ability of BCL6 to recruit the silencing mediator of retinoid and thyroid receptor corepressor complex, and thus leads to derepression of BCL6 target genes (Polo *et al*, 2008). Also, in classic HL, the CD40L-positive T cells in the microenvironment of the Hodgkin Reed-Sternberg (HRS) cells are thought to contribute to the HRS growth and survival through CD40L-driven upregulation of interferon regulatory factor 4 (Aldinucci *et al*, 2012). Together, these data support the investigation of agents targeting CD40 as a single agent or in combination with chemotherapy in patients with haematological malignancies.

The biological significance of CD40 has led to the development of CD40-directed therapies that range in activity from agonists to antagonists (Schoenberger *et al*, 1998; Advani *et al*, 2009; Lewis *et al*, 2011). Lucatumumab is a fully human antagonistic anti-CD40 mAb. Despite the 5-9-fold higher level of expression of CD20 compared with CD40 in B-CLL cells, in preclinical models the average maximal lysis of B cells was 18% higher with lucatumumab compared with the anti-CD20 mAb rituximab (Luqman *et al*, 2008). Lucatumumab has been evaluated in phase 1 trials in relapsed B-CLL and multiple myeloma (MM). Twenty-six patients with relapsed B-CLL were enrolled in a phase 1 study in which lucatumumab was administered weekly for 4 weeks for one cycle (Byrd *et al*, 2012). Maximum tolerated dose (MTD) was 3 mg/kg. Stable disease (SD) was observed in 17 patients and 1 patient had a nodular partial response (PR) that lasted over 7 months (Byrd *et al*, 2012). In another phase 1 study, 28 patients with relapsed MM received lucatumumab once weekly for 4 weeks for up to 2 cycles (Bensinger *et al*, 2012). MTD was 4.5 mg/kg and efficacy analyses demonstrated 1 PR and SD among 6 patients (Bensinger *et al*, 2012). In both studies, the most commonly observed adverse events (AEs) were asymptomatic elevation of amylase and/or lipase.

Based on preclinical data in malignant B-cells combined with tolerability observed in other haematologic malignancies, this phase I/II trial reported herein was conducted in patients with relapsed/refractory NHL or HL. The primary objective of the dose escalation phase was to determine the MTD and safety of weekly lucatumumab in patients with various forms of lymphoma. In the dose expansion phase, the primary objective was response rate. Secondary objectives included safety, tolerability, and pharmacokinetic analyses (Trial registration: [ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT00670592).

Materials and methods

Study design

This phase IA/II study consisted of a dose escalation phase and a dose expansion phase. The primary objective of the phase IA dose escalation portion was to determine the MTD or the recommended phase 2 dose of lucatumumab. In the dose expansion phase, the primary objective was assessment of clinical response. An overall response [complete response (CR) + partial response (PR)] rate of 25% would be considered promising while a response rate of

10% would be considered unworthy of further study. A hierarchic Bayesian model-based methodology for conducting a phase II clinical trial in a disease with multiple subtypes was used (Thall *et al*, 2003). Secondary objectives included safety and tolerability, pharmacokinetics (PK) and antitumour activity (including tumour response and duration of response).

This trial was reviewed by the independent ethics committee or institutional review board for each centre and was conducted according to the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from each patient prior to trial enrollment.

Patient eligibility and treatment

Adult patients with advanced HL or B-cell NHL subtypes [including follicular lymphoma (FL), marginal zone lymphoma (MZL) of mucosa-associated lymphatic tissue (MALT), diffuse large B-cell lymphoma (DLBCL), or mantle cell lymphoma (MCL)], according to the World Health Organization (WHO) classification (Swerdlow *et al*, 2008), having progressed after at least 2 previous therapies, were enrolled. Patients must have received prior rituximab, if indicated as a standard of care. Autologous stem cell transplant was considered as one therapy, and patients who did not receive prior autologous stem cell transplant were required to receive two prior systemic therapies. Patients who received prior allogeneic stem cell transplant, prior CD40 antibody treatment, or had WHO performance status > 2, or evidence of central nervous system, meningeal or epidural disease, including brain metastasis, were not included in the study.

Lucatumumab was administered by intravenous infusion on days 1, 8, 15, and 22 of an 8-week cycle with a starting dose of 3.0 mg/kg. At week 8, patients had the option of retreatment with lucatumumab if disease assessment demonstrated SD or better and patients had not experienced any significant prolonged toxicities. Whereas patients in the retreatment phase received the same dose, patients treated in the dose escalation phase could receive the highest tolerated dose identified at the time they consented for retreatment. After the MTD was identified, patients who continued on lucatumumab received the MTD for subsequent retreatment cycles. Patients who completed five retreatment cycles were eligible for the continuation segment of the study, during which treatment was continued but the study assessments and frequency of visits were reduced.

Assessment of response

Non-Hodgkin lymphoma and HL tumour response was determined according to the Revised Response Criteria for Malignant Lymphoma proposed by the International Harmonization Project (Cheson *et al*, 2007). Disease status assessments were performed using computed tomography scans at baseline, weeks 8 and 16, once every 3 months thereafter, and at end of study. Metabolic response was determined through quantification of [¹⁸F] fluorodeoxyglucose (FDG) uptake using positron emission tomography (PET). FDG-PET was performed at selected study sites. Patients with a positive baseline FDG-PET scan received follow-up assessments within 7 d prior to the following time points: day 50 (week 8) and follow-up visits starting from day 106, day 162, and then once every 12 ± 2 weeks until disease progression. An end-of-study scan was performed if it was not done within the

previous 4 weeks. The percent change in the sum of the maximum standard uptake value (% $sSUV_{max}$) of the tumour from baseline was calculated for response assessment. Response definitions for FDG-PET are summarized in Table SI.

Determination of DLTs and MTD

A dose-limiting toxicity (DLT) was defined as an AE (generally grade 3 for >7 d or grade 4) or abnormal laboratory value (generally 2–3 × upper limit of normal) assessed as unrelated to disease progression, intercurrent illness, or concomitant medications, and occurring during either the treatment course or 28 d following the last dose. Assessment criteria for DLTs were based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 3 (CTCAE v3.0) (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf). Patients who experienced DLT at any dose level received no further infusions of lucatumumab and were monitored.

Cohorts of three to six patients were evaluated at each dose level in the escalation phase. A minimum of six evaluable patients had to be treated at a given dose before MTD could be declared. Only those patients who completed 4 infusions of lucatumumab and an additional 4 weeks (28 d) of safety monitoring or who left the study prior to week 8 (study day 50) due to a DLT were considered evaluable for the purpose of determining the MTD.

Safety assessments

Safety assessments were based on CTCAE v3.0. Special safety assessments included monitoring of infusion reactions; laboratory haematology; laboratory chemistry for hepatic, renal, pancreatic, and metabolic function; serum quantification of immunoglobulin (IgA, IgG, and IgM); electrocardiogram; cardiac enzymes; and cardiac imaging (multigated acquisition scan or echocardiogram).

Decreases in B-cell and total lymphocyte counts are pharmacodynamic effects of lucatumumab and were not considered AEs for this study; however, sequelae of lymphopenia, such as infections, were considered AEs.

PK analysis

Blood samples were collected at specified time points to determine the PK and immunogenicity of lucatumumab.

Analysis of PK included parameters such as drug concentration at the end of infusion (C_{max}), area under the plasma concentration-time curve (AUC), serum clearance and serum half-life. These were calculated after single and multiple dosing using noncompartmental methods. Immunogenicity was assessed by the evaluation of antilucatumumab antibodies on day 1 preinfusion, day 50 (± 5 d), and at the end of study in all patients who were included in the PK analysis.

Statistical analysis

An adaptive Bayesian logistic regression model guided by the escalation with overdose control principle, adopted from Babb *et al* (1998), was used for the determination of the

MTD or recommended phase 2 dose. All information available from 2 ongoing trials in CLL and MM about the dose-toxicity (dose-DLT) curve of lucatumumab was encapsulated in an informative previous distribution of the model parameters, which was then updated after each cohort of patients with the DLT data from the present trial. The dose-toxicity (DLT) relationship in the dose escalation part of the study was described by a 2-parameter Bayesian logistic regression model. A hierarchic Bayesian logistic regression model was used to assess the treatment effect on the log-odds of response within each disease subtype and overall for the disease (on an average across subtypes).

All completed patients were included in the PK data analysis. $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} were used in informal dose proportionality analysis using the power model (Gough *et al*, 1995). PK parameters and dose levels were analysed on the log scale. A linear model was applied with $\ln(\text{dose})$ as a fixed factor. The 90% confidence interval (CI) of the slope was computed from this model. In a formal dose-proportionality analysis, the obtained 90% CI was compared with the prespecified critical region (bL, bU) (Smith *et al*, 2000).

Results

Patients and enrollment

A total of 111 patients with NHL ($n = 74$) and HL ($n = 37$) were enrolled across the three dose cohorts (Table I). The most common NHL subtypes enrolled included DLBCL ($n = 34$) and FL ($n = 21$) (Table I). Overall, the patient population was heavily pretreated, with a median of four prior therapy regimens (range, 1–14), which included one patient with MZL/MALT who received only one prior regimen due to a protocol violation (Table I). In addition, nearly half (48%) of all patients treated had received prior autologous stem cell transplant. Patients were treated at escalating doses of lucatumumab with a starting dose of 3 mg/kg according to the study design outlined in Patients and Methods. DLTs were observed at doses of 3, 4, and 6 mg/kg. These DLTs included grade 3 lipase elevation for >7 d ($n = 4$), and grade 3 alanine transferase elevation for >7 d ($n = 2$). Based on the observed DLTs, the MTD was determined to be 4 mg/kg, and patient enrollment in the phase 2 portion of the trial continued at this dose.

Safety

AEs according to the CTCAE v3.0 are outlined in Table II. Overall, most AEs observed were mild to moderate. The most common AEs of any grade included chills (38.7%) and pyrexia (34.2%), and occurred within 4 h after infusion. Lipase elevation of grade 3/4 was observed in 25.2% of patients, but was not symptomatic. Serious AEs were observed in 31 (27.9%) of patients, and the most common serious AEs included dyspnea ($n = 7$), pyrexia ($n = 6$) and chills ($n = 3$).

Efficacy

Clinical activity of lucatumumab was observed in patients with HL and several NHL subtypes (Table III). The overall response rate (ORR, PR) by computed tomography among patients with FL was 33.3% (7/21). Among patients with FL, 1 CR and 6 PRs were observed, with 11 patients demonstrating a best response of SD. As shown in Fig 1, most

patients with FL ($n = 15$) had a reduction in tumour size. Among patients with FL who demonstrated responses, durable responses were observed (Fig 2). The range of duration of response was 7.9 to 31 weeks. Responses were also observed in patients with other subtypes including HL [ORR, 5/37 (13.5%)], DLBCL [ORR, 4/34 (11.8%)], and MZL/MALT [ORR, 3/7 (42.9%)]. Of note, a patient with DLBCL demonstrated a CR lasting 62.9 weeks (Fig 2).

Metabolic responses, as demonstrated by FDG-PET, were also observed among patients with HL and NHL subtypes (Table SII). In patients with NHL, metabolic responses were observed among all subtypes, DLBCL [partial metabolic response (PMR), 23.5%], FL (PMR, 61.9%), MCL (PMR, 16.7%), and MALT (PMR, 28.6%). PMRs were also observed among patients with HL (PMR, 35.1%).

Pharmacokinetics

Cycle 1 PK analyses for patients with available data are summarized in Table SIII. A dose-dependent trend in peak plasma concentration was observed. $C_{\max}$ after the first infusion at the MTD was 86.3 µg/ml. Consistent with other mAb therapies, lucatumumab was associated with a relatively long half-life of 109.5 h at the MTD. Accumulation of lucatumumab was observed as the bioavailability, peak plasma concentrations and half-life all increased following the fourth infusion compared with the first infusion (Table SII).

Discussion

Monoclonal antibody therapy targeting CD20 has markedly changed the treatment paradigm for B-cell lymphomas. In particular, integration of rituximab into the therapy of both indolent and aggressive B-cell lymphomas has improved response rates, duration of remissions, and overall survival in a broad range of histological subtypes (Dotan *et al*, 2010). However, as with other therapies for malignancies, resistance arises to rituximab and rituximab-containing regimens. Thus, the development of agents with a novel mechanism of action, including mAbs that target other cell-surface antigens, is a promising approach to the treatment of relapsing and resistant B-cell malignancies. Lucatumumab, which targets CD40, was well tolerated and demonstrated a broad range of activity against B-cell lymphomas in this clinical trial. The major toxicities included infusion reactions, which were manageable, and asymptomatic elevations of aspartate aminotransferase, amylase and lipase. Responses were observed in 13% to 42% of patients among the various lymphoma subtypes, with the highest percentage in patients with relapsed FL and MZL/MALT.

Other CD40-directed therapies have been evaluated in clinical trials. CP-870,893 is a CD40 fully human agonist mAb that is believed to act by augmenting T-cell-dependent antitumour immunity (Schoenberger *et al*, 1998). A phase I study showed a 14% ORR with all responders having melanoma and a 19% ORR in combination with gemcitabine for patients with advanced pancreatic cancer (Vonderheide *et al*, 2007; Beatty *et al*, 2011). Further trials are being conducted in patients with solid tumours, including a phase I combination with tremelimumab, the antibody to cytotoxic T lymphocyte-associated antigen 4 (NCT01103635).

Dacetuzumab (SGN-40) is a partial agonist antibody to CD40 that demonstrated preclinical additive to synergistic effects in combination with rituximab in NHL cell line and mouse models (Lewis *et al*, 2011). A dose-escalation phase I trial of dacetuzumab in patients with relapsed/refractory B-cell NHL reported an ORR of 12%. Grade 3 AEs included anaemia, pleural effusion, and thrombocytopenia (Advani *et al*, 2009). Although a higher level of CD40 expression was seen among patients with DLBCL, the level of CD40 expression did not correlate with efficacy; however, a 15-gene signature including coexistence of *TP53* mutations and *BCL6* expression predicted tumour response in 67% of patients with DLBCL (Burlington *et al*, 2011). A follow-up phase Ib protocol evaluated dacetuzumab, rituximab, and gemcitabine in patients with relapsed DLBCL or FL ($N = 31$). Common AEs observed included nausea, thrombocytopenia, and fatigue. ORR was 47% with a CR rate of 20% in the first 28 patients assessed (Forero-Torres *et al*, 2013). A phase 2b double-blind randomized trial in patients with relapsed/refractory DLBCL compared the efficacy and safety of R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) plus dacetuzumab versus R-ICE plus placebo. The CR rate was not increased by the addition of dacetuzumab, and enrollment was suspended. There was a trend toward improved failure-free and overall survival in the patients who received dacetuzumab. For patients who underwent autologous stem cell transplant, the overall survival improvement was statistically significant, with a 14% reduction in death due to disease progression in patients who received dacetuzumab versus placebo (Fayad *et al*, 2011). However, the rationale for these observations has not been determined.

The biology of CD40 is complex; thus, targeting of CD40 through various modalities, including different anti-CD40 mAbs, could lead to differences in efficacy or AEs. CD40 has broad expression in normal B-cell ontogeny, from the progenitor B-cell stage through to plasma cells. CD40 is also present on cells involved in mediating immune responses, including dendritic cells, monocytes, and macrophages (Biancone *et al*, 1999; van Kooten & Banchereau, 2000). The ligation of CD40 by its natural ligand CD40L or by agonist mAbs triggers B-cell proliferation and survival. As lucatumumab exerts only an antagonistic activity on signalling via CD40, in addition to inducing ADCC, it is well suited for potential therapy against CD40-expressing lymphomas. These differentiating mechanisms between lucatumumab and other monoclonal anti-CD40 antibodies can explain differences observed in the efficacy of these agents. Of course, these phase II data are preliminary and would require further study.

Lucatumumab has been studied previously in patients with both CLL and MM. In patients with CLL, lucatumumab was given weekly for 4 weeks and the MTD was established at 3 mg/kg. Four patients at dose levels of 4.5 or 6 mg/kg demonstrated grade 3–4 asymptomatic elevation of amylase and lipase. SD was demonstrated in 17 patients and 1 PR was observed (Byrd *et al*, 2012). In MM, similar toxicity was seen with limited antitumour activity (Bensinger *et al*, 2012). In comparison, in this study similar patient tolerability but higher response rates were observed. Whether differences in response rates between the patients with MM or CLL compared with the responses in patients with lymphoma are attributable to the relative importance of CD40-CD40L signalling in the different diseases, or whether the additional cycles of treatment evaluated here contributed to the increased responses, remains to be determined.

The current challenge for the treatment of lymphomas is improving on rituximab-based therapy for patients who develop resistance. As preclinical data demonstrated that lucatumumab induced ADCC to a greater extent than rituximab in malignant B cells isolated from patients, CD40 represents a rational target for patients with relapsed/refractory disease (Luqman *et al*, 2008). In this study, lucatumumab demonstrated activity in patients with multiply treated aggressive and indolent B-cell NHL and HL. Given the potential mechanisms of action, lucatumumab may be able to induce responses where other mAbs targeting this receptor have demonstrated limited activity, because mechanisms other than ADCC may, in part, be responsible for its antitumour activity. With its modest activity in multiple disease subtypes and with multiple targeted agents in clinical development, the optimal treatment niche and disease setting for this agent must be determined. Further studies of agents targeting CD40 in combination with other therapies, including mAbs or chemotherapy, will need to be guided by a strong preclinical rationale and enhanced assessment of agents targeting CD40-responsive biomarkers. In addition, a more thorough understanding of the importance of CD40 in promoting survival in specific lymphoma subtypes, as well more preclinical work looking at synergy with other anti-lymphoma agents will help guide the development of this agent.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1.

Percent change in tumour size as demonstrated by the difference in the sum of the product of the greatest diameters (SPD) of the six largest dominant masses measured by computed tomography for patients with follicular lymphoma ($n = 21$). For the patient denoted with an asterisk (*), the increase in tumour size was 173%. The axis was truncated at 100% for presentation.

Fig 2.

Duration of response across lymphoma subtypes. The duration of response (weeks) is noted for a patients who achieved an anatomic response for each lymphoma subtype including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), Hodgkin lymphoma (HL) and mucosa-associated lymphatic tissue lymphoma (MALT). No responses were observed in patients with mantle cell lymphoma. Complete repsonse (CR) is noted in black and partial response (PR) is noted in grey. The '+' symbol indicates that the patient had not progressed as of the last recorded visit.

Table I

Patient demographics.

	4 mg/kg (MTD) <i>n</i> = 91	All <i>N</i> = 111
Median age, years (range)	57 (19–84)	57 (19–84)
Male/female, <i>n</i> (%)	66 (72.5)/25 (27.5)	77 (69.4)/34 (30.6)
WHO performance status, <i>n</i> (%)		
0	37 (40.7)	47 (42.3)
1	45 (49.5)	52 (46.8)
2	9 (9.9)	12 (10.8)
Lymphoma classification, <i>n</i> (%)		
FL	16 (17.6)	21 (18.9)
DLBCL	26 (28.6)	34 (30.6)
MALT	7 (7.7)	7 (6.3)
MCL	8 (8.8)	12 (10.8)
HL	34 (37.4)	37 (33.3)
Ann Arbor stage at baseline, <i>n</i> (%)		
Stage I	4 (4.4)	5 (4.5)
Stage II	15 (16.5)	17 (15.3)
Stage III	26 (28.6)	30 (27)
Stage IV	46 (50.5)	59 (53.2)
Prior therapy regimens (<i>n</i>), median (range)	4 (1–10)	4 (1–14)

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphatic tissue lymphoma; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; WHO, World Health Organization.

Table II

Adverse events, due to any cause occurring in 10% of patients ($N = 111$).

Adverse event	Any grade <i>n</i> (%)	Grade 3/4 <i>n</i> (%)
All adverse events	111 (100)	72 (64.9)
Chills	43 (38.7)	1 (0.9)
Pyrexia	38 (34.2)	2 (1.8)
Lipase increased	30 (27)	28 (25.2)
Fatigue	28 (25.2)	2 (1.8)
Nausea	26 (23.4)	1 (0.9)
Dyspnea	25 (22.5)	7 (6.3)
Cough	20 (18)	2 (1.8)
Headache	20 (18)	1 (0.9)
Back pain	16 (14.4)	1 (0.9)
Hypotension	16 (14.4)	1 (0.9)
Constipation	15 (13.5)	0 (0)
Vomiting	14 (12.6)	1 (0.9)
Asthenia	13 (11.7)	3 (2.7)
Diarrhoea	13 (11.7)	0 (0)
Oedema, peripheral	13 (11.7)	2 (1.8)

Table III

Best anatomic clinical response (computed tomography) by lymphoma subtype.

Subtype	4 mg/kg (MTD)	All
FL	<i>n</i> = 16	<i>n</i> = 21
ORR, <i>n</i> (%)	6 (37.5)	7 (33.3)
CR, <i>n</i> (%)	1 (6.3)	1 (4.8)
PR, <i>n</i> (%)	5 (31.3)	6 (28.6)
SD, <i>n</i> (%)	7 (43.8)	11 (52.4)
PD, <i>n</i> (%)	3 (18.8)	3 (14.3)
NE, <i>n</i> (%)	–	–
DLBCL	<i>n</i> = 26	<i>n</i> = 34
ORR, <i>n</i> (%)	2 (7.7)	4 (11.8)
CR, <i>n</i> (%)	1 (3.8)	2 (5.9)
PR, <i>n</i> (%)	1 (3.8)	2 (5.9)
SD, <i>n</i> (%)	8 (30.8)	11 (32.4)
PD, <i>n</i> (%)	12 (46.2)	15 (44.1)
NE, <i>n</i> (%)	4 (15.4)	4 (11.8)
MALT	<i>n</i> = 7	<i>n</i> = 7
ORR, <i>n</i> (%)	3 (42.9)	3 (42.9)
CR, <i>n</i> (%)	1 (14.3)	1 (14.3)
PR, <i>n</i> (%)	2 (28.6)	2 (28.6)
SD, <i>n</i> (%)	1 (14.3)	1 (14.3)
PD, <i>n</i> (%)	2 (28.6)	2 (28.6)
NE, <i>n</i> (%)	1 (14.3)	1 (14.3)
MCL	<i>n</i> = 8	<i>n</i> = 12
ORR, <i>n</i> (%)	–	–
CR, <i>n</i> (%)	–	–
PR, <i>n</i> (%)	–	–
SD, <i>n</i> (%)	3 (37.5)	5 (41.7)
PD, <i>n</i> (%)	4 (50.0)	5 (41.7)
NE, <i>n</i> (%)	1 (25.0)	2 (16.7)
HL	<i>n</i> = 34	<i>n</i> = 37
ORR, <i>n</i> (%)	4 (11.8)	5 (13.5)
CR, <i>n</i> (%)	–	–
PR, <i>n</i> (%)	4 (11.8)	5 (13.5)
SD, <i>n</i> (%)	11 (32.4)	12 (32.4)
PD, <i>n</i> (%)	13 (38.2)	14 (37.8)
NE, <i>n</i> (%)	6 (17.6)	6 (16.2)

CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphatic tissue lymphoma; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.