Sponsor

Novartis

Generic Drug Name

Not applicable

Therapeutic Area of Trial

Follicular lymphoma, diffuse large B-cell lymphoma, mantle cell lymphoma, marginal zone lymphoma/mucosa-associated lymphoid tissue and Hodgkin lymphoma

Approved Indication

Investigational drug

Protocol Number

HCD122A2103

Title

A Phase IA/II, multi-center, open-label study of HCD122 administered intravenously once weekly for four weeks in adult patients with advanced non-Hodgkin's or Hodgkin's lymphoma who have progressed after at least two prior therapies

Study Phase

Phase IA/II

Study Start/End Dates

28-Mar-2008 to 06-Feb-2013

Study Design/Methodology

This was a Phase IA/II, multi-center, open-label study of HCD122 administered intravenously once weekly for 4 weeks in adult patients with advanced non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (HL) who have progressed after at least 2 prior therapies. The study consisted of a Phase I dose escalation phase and a Phase II dose expansion phase. In the dose escalation phase patients received HCD122 at the 3.0, 4.0 or 6.0 mg/kg dose levels, administered via iv infusions once weekly for 4 weeks and maximum tolerated dose was determined to be 4.0 mg/kg using a Bayesian logistic regression model. In the dose expansion phase the tumor response of different lymphoma subtypes was assessed at 4.0 mg/kg using a hierarchical Bayesian model.

The primary analysis of this study was conducted when all patients completed a 4-week HCD122 treatment (once weekly) or discontinued from the study. The results were reported in the primary analysis clinical study report (CSR) for Study HCD122A2103.

Note: Two patients continued on treatment after the cut-off date for the interim CSR. Additional data for these 2 patients was reported in a second, final CSR (data was not presented in tabular format for the final report).

Centers

27 centers in 10 countries: Australia (2), Belgium (3), Canada (2), France (6), Germany (2), Hong Kong (1), Italy (3), S. Korea (1), UK (2), USA (5)

Publication

Fanale M, Assouline S, Kuruvilla J, et al (2013) Phase IA/II, multicentre, open-label study of the CD40 antagonistic monoclonal antibody Lucatumumab in adult patients with advanced non-Hodgkin or Hodgkin lymphoma. Br J Haematol; doi: 10.1111/bjh.12630 (Epub ahead of print).

Test Product, Doses, and Mode of Administration

HCD122 was administered via intravenous infusion once weekly for 4 weeks at doses of 3.0, 4.0, and 6.0 mg/kg. The batch numbers used in the study are: 07-0658US, 07-0678US, 07-0679US, 08-0511US, 09-0695US, and 12-0952CH.

Statistical Methods

In the expansion phase, efficacy analysis was based on a hierarchical Bayesian model upon the full analysis set (FAS), which included all patients who received at least 1 complete or partial dose of HCD122. In the escalation phase, the analysis of dose-limiting toxicity data was based on a Bayesian logistic regression model upon the dose-determining set, which consisted of all patients from the safety set of the dose escalation phase who completed 4 weeks (28 days) of safety monitoring after the fourth infusion of HCD122, or discontinued earlier due to DLT. All other safety tabulations were based on the safety set, which included all patients who received at least 1 complete or partial dose of HCD122, and had at least 1 post-baseline safety assessment. A formal interim analysis was not planned or performed.

The following populations were considered in data analysis:

The FAS consists of all patients who receive at least one (partial or full) dose of HCD122.

The safety set consists of all patients who received at least one (partial or full) dose of HCD122, and had at least one valid post-baseline safety assessment.

The per-protocol set consists of all patients in the FAS who did not have any major protocol deviation, were evaluated for efficacy at least once post-baseline and completed four infusions of HCD122 unless discontinuing for early disease progression or adverse events.

The dose-determining set consists of all patients from the safety set (at least in the dose escalation phase) who completed 4 weeks (28 days) of safety monitoring following the fourth infusion of HCD122, or discontinued earlier due to dose-limiting toxicity.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

Patients were included in the study if they met all of the following criteria:

- Patients had confirmed diagnosis of HL or NHL (follicular, marginal zone / mucosa-associated lymphoid tissue, diffuse large B-cell, or mantle cell) per Revised European American Lymphoma / World Health Organization classification,
- Patients progressed after at least 2 prior therapies (autologous stem cell transplantation was considered as 1 therapy),
- Patients were ≥ 18 years,
- Patients had life expectancy >3 months,
- Patient had adequate laboratory results,
- Patients had World Health Organization Performance Status grade 0, 1, or 2,
- Patients had at least one site of measurable disease,
- Patients discontinued any previous monoclonal antibody or radioimmunotherapy, and recovered fully from the side effects of that treatment prior to beginning study treatment,
- Patients were willing and able to sign the informed consent form and comply with the study protocol.

Exclusion criteria:

Patients were excluded from the study if they meet any of the following criteria:

- Patients who were treated with any anti-CD40 antibody,
- Patients who received prior allogeneic stem cell transplant,
- Patients who had a prior anaphylactic or other severe infusion reaction such that the patient was unable to tolerate human immunoglobulin or monoclonal antibody administration,
- Patients who had history or clinical evidence of central nervous system, meningeal, or epidural disease including brain metastasis,
- Women of child-bearing potential who were pregnant or breast feeding.

Other protocol-defined inclusion/exclusion criteria did apply.

Participant Flow

Disposition of patients in dose escalation phase by treatment group (FAS)

Disposition Reason	3.0 mg/kg N=15 n (%)	4.0 mg/kg N=12 n (%)	6.0 mg/kg N=5 n (%)	All Dose N=32 n (%)
Initial treatment (Week 1 to Week 8)				
Completed initial treatment	9 (60.0)	8 (66.7)	2 (40.0)	19 (59.4)
Discontinued initial treatment	6 (40.0)	4 (33.3)	3 (60.0)	13 (40.6)
Primary reason for discontinuation from initial treatment				
Adverse event(s)	0 (0.0)	2 (16.7)	0 (0.0)	2 (6.3)
Abnormal laboratory value(s)	2 (13.3)	0 (0.0)	2 (40.0)	4 (12.5)
Death	1 (6.7)	1 (8.3)	0 (0.0)	2 (6.3)
Disease progression	3 (20.0)	1 (8.3)	1 (20.0)	5 (15.6)
Retreatment				
Patients received retreatment	3	4	2	9
Number of retreatments completed				
1	1 (6.7)	4 (33.3)	0 (0.0)	5 (15.6)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	1 (6.7)	0 (0.0)	0 (0.0)	1 (3.1)
>3	1 (6.7)	0 (0.0)	0 (0.0)	1 (3.1)
Primary reason for study discontinuation from retreatment				
Lost to follow-up	0 (0.0)	0 (0.0)	1 (50.0)	1 (11.1)
Disease progression	1 (33.3)	1 (25.0)	1 (50.0)	3 (33.3)

Disposition of patients in the dose expansion phase by disease subtype (FAS)

Disposition Reason	HL N=27 n (%)	DLBCL N=24 n (%)	FL N=14 n (%)	MZL/MALT N=7 n (%)	MCL N=7 n (%)	All Dose N=79 n (%)
Initial treatment (Week 1 to Week 8)						
Completed initial treatment	19 (70.4)	10 (41.7)	7 (50.0)	4 (57.1)	1 (14.3)	41 (51.9)
Discontinued initial treatment	8 (29.6)	14 (58.3)	7 (50.0)	3 (42.9)	6 (85.7)	38 (48.1)
Primary reason for discontinuation from initial treatment						
Adverse event(s)	2 (7.4)	3 (12.5)	0 (0.0)	0 (0.0)	1 (14.3)	6 (7.6)
Abnormal laboratory value(s)	2 (7.4)	3 (12.5)	3 (21.4)	1 (14.3)	3 (42.9)	12 (15.2)
Patient withdrew consent	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	1 (1.3)
Disease progression	4 (14.8)	8 (33.3)	3 (21.4)	2 (28.6)	2 (28.6)	19 (24.1)
Retreatment						
Patients received retreatment	12	6	5	2	0	25
Number of retreatments completed						
1	3 (11.1)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (5.1)
2	1 (3.7)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	2 (2.5)
3	1 (3.7)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	2 (2.5)
>3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Primary reason for study discontinuation from retreatment						
Adverse event(s)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)
Abnormal laboratory value(s)	1 (8.3)	1 (16.7)	1 (20.0)	2 (100)	0 (0.0)	5 (20.0)
New cancer therapy	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)
Disease progression	9 (75.0)	2 (33.3)	3 (60.0)	0 (0.0)	0 (0.0)	14 (56.0)

Treatment cycle completion is defined as participation in the cycle through week 8 and completion of the week 8 study visit

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin's lymphoma; MCL: mantle cell lymphoma; MZL/MALT: marginal zone lymphoma /mucosa-associated lymphoid tissue.

Note: The 2 patients on-going after the data base lock for the interim CSR discontinued due to administrative problems.

Baseline Characteristics

Demographic summary in the dose escalation phase by treatment group (FAS)

Demographic variables	3.0 mg/kg N=15	4.0 mg/kg N=12	6.0 mg/kg N=5	All doses N=32
Age(Years)				
n	15	12	5	32
Mean	57.3	44.8	59.0	52.8
SD	15.97	17.60	16.75	17.38
Median	58.0	41.5	65.0	53.5
Minimum	27.0	19.0	35.0	19.0
Maximum	80.0	77.0	76.0	80.0
Age category				
18- 64 years	9 (60.0%)	10 (83.3%)	2 (40.0%)	21 (65.6%)
65-84 years	6 (40.0%)	2 (16.7%)	3 (60.0%)	11 (34.4%)
Gender				
Female	6 (40.0%)	2 (16.7%)	3 (60.0%)	11 (34.4%)
Male	9 (60.0%)	10 (83.3%)	2 (40.0%)	21 (65.6%)
Race				
Black	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Caucasian	15 (100%)	11 (91.7%)	4 (80.0%)	30 (93.8%)
Other	0 (0.0%)	0 (0.0%)	1 (20.0%)	1 (3.1%)
Weight (kg)				
n	15	12	5	32
Mean	72.1	84.5	70.3	76.4
SD	14.91	18.08	8.65	16.32
Median	79.0	88.0	71.2	79.3
Minimum	44.2	54.9	57.8	44.2
Maximum	88.3	115.9	80.0	115.9
Height (cm)				
n	15	12	5	32
Mean	172.3	177.3	165.6	173.1
SD	9.43	12.74	10.26	11.28
Median	172.0	180.0	168.0	175.5
Minimum	155.0	148.0	149.0	148.0
Maximum	191.0	196.0	176.0	196.0

Demographic summary in the dose expansion phase by disease subtype (FAS)

Demographic variables	HL N=27	DLBCL N=24	FL N=14	MZL/MALT N=7	MCL N=7	All doses N=79
Age(Years)						
n	27	24	14	7	7	79
Mean	40.2	61.2	64.5	66.4	66.9	55.6
SD	13.25	12.05	10.90	11.21	7.20	16.21
Median	39.0	63.0	63.5	66.0	70.0	60.0
Minimum	22.0	26.0	49.0	48.0	54.0	22.0
Maximum	75.0	79.0	83.0	84.0	74.0	84.0
Age category						
18- 64	25 (92.6%)	15 (62.5%)	7 (50.0%)	3 (42.9%)	2 (28.6%)	52 (65.8%)
65-84	2 (7.4%)	9 (37.5%)	7 (50.0%)	4 (57.1%)	5 (71.4%)	27 (34.2%)
Gender						
Female	9 (33.3%)	6 (25.0%)	5 (35.7%)	2 (28.6%)	1 (14.3%)	23 (29.1%)
Male	18 (66.7%)	18 (75.0%)	9 (64.3%)	5 (71.4%)	6 (85.7%)	56 (70.9%)
Race						
Black	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Caucasian	25 (92.6%)	18 (75.0%)	13 (92.9%)	5 (71.4%)	6 (85.7%)	67 (84.8%)
Oriental	1 (3.7%)	5 (20.8%)	0 (0.0%)	2 (28.6%)	1 (14.3%)	9 (11.4%)
Other	1 (3.7%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.5%)
Weight (kg)						
n	27	24	14	7	7	79
Mean	73.7	74.6	78.1	82.2	74.5	75.6
SD	15.71	19.02	15.40	30.25	11.76	17.78
Median	68.7	70.6	76.1	76.8	72.0	71.9
Minimum	51.5	35.2	57.9	53.0	58.0	35.2
Maximum	115.5	119.0	123.4	127.9	95.2	127.9
Height (cm)						
n	27	24	14	7	7	79
Mean	171.3	170.0	170.8	173.0	172.0	171.0
SD	6.74	11.19	9.60	8.91	11.28	9.17
Median	169.0	173.5	172.5	172.0	167.0	171.0
Minimum	158.0	142.0	156.0	162.0	157.0	142.0
Maximum	185.0	186.0	183.0	191.0	186.0	191.0

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin's lymphoma; MCL: mantle cell lymphoma; MZL/MALT: marginal zone lymphoma /mucosa-associated lymphoid tissue.

Baseline disease characteristics in the dose escalation phase by treatment group (FAS)

	3.0 mg/kg N=15 n (%)	4.0 mg/kg N=12 n (%)	6.0 mg/kg N=5 n (%)	All Doses N=32 n (%)
Lymphoma classification at baseline				
Follicular lymphoma	4 (26.7)	2 (16.7)	1 (20.0)	7 (21.9)
Grade 1: 0-5 centroblasts/hpf	0 (0.0)	1 (8.3)	1 (20.0)	2 (6.3)
Grade 2: 6-15 centroblasts/hpf	1 (6.7)	0 (0.0)	0 (0.0)	1 (3.1)
Grade 3b: >15 centroblasts form solid sheets with no residual centrocytes	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.1)
Mantle-cell lymphoma	4 (26.7)	1 (8.3)	0 (0.0)	5 (15.6)
Diffuse large B-cell lymphoma	4 (26.7)	2 (16.7)	4 (80.0)	10 (31.3)
Not otherwise specified: Germline center B-cell (GCB) type	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.1)
Not otherwise specified: Unknown molecular subgroup	3 (20.0)	0 (.00)	2 (40.0)	5 (15.6)
T-cell/histiocyte rich large B-cell lymphoma	0 (0.0)	1 (8.3)	1 (20.0)	2 (6.3)
Primary mediastinal (thymic) large B-cell lymphoma	1 (6.7)	0 (0.0)	0 (0.0)	1 (3.1)
Hodgkin's lymphoma	3 (20.0)	7 (58.3)	0 (0.0)	10 (31.3)
Hodgkin's lymphoma-Classical nodular sclerosis	3 (20.0)	7 (58.3)	0 (0.0)	10 (31.3)
Ann Arbor stage at baseline				
Stage I	1 (6.7)	0 (0.0)	0 (0.0)	1 (3.1)
Stage II	2 (13.3)	3 (25.0)	0 (0.0)	5 (15.6)
Stage III	2 (3.3)	2 (16.7)	2 (40.0)	6 (8.8)
Stage IV	10 (66.7)	7 (58.3)	3 (60.0)	20 (62.5)
Time from original diagnosis (Years)				
N	15	12	5	32
Median	4.53	4.98	9.24	4.98
Min-Max	1.24-10.42	0.99-25.00	0.85-11.95	0.85-25.00
Time from last relapse (Years)				
N	15	12	5	32
Median	0.20	0.39	0.53	0.31
Min-Max	0.03-2.05	0.03-2.73	0.06-1.10	0.03-2.73
Number of prior therapies				
N	15	12	5	32
Median	4.00	6.50	3.00	4.50

	3.0 mg/kg N=15 n (%)	4.0 mg/kg N=12 n (%)	6.0 mg/kg N=5 n (%)	All Doses N=32 n (%)
Min-Max	3.00-14.00	3.00-10.00	2.00-6.00	2.00-14.00
Patients that received Stem Cell Transplants				
Yes	8 (53.3)	7 (58.3)	3 (60.0)	18 (56.3)
No	7 (46.7)	5 (41.7)	2 (40.0)	14 (43.8)
Bulk >10 cm				
Yes	5 (33.3)	2 (16.7)	1 (20.0)	8 (25.0)
No	10 (66.7)	10 (83.3)	4 (80.0)	24 (75.0)
FcYRIII polymorphism				
V/V	1 (6.7)	0 (0.0)	0 (0.0)	1 (3.1)
F/F	4 (26.7)	5 (41.7)	3 (60.0)	12 (37.5)
V/F	9 (60.0)	5 (41.7)	1 (20.0)	15 (46.9)
Other	1 (6.7)	2 (16.7)	0 (0.0)	3 (9.4)
WHO performance status				
No restrictions	6 (40.0)	6 (50.0)	4 (80.0)	16 (50.0)
Only light work	6 (40.0)	3 (25.0)	1 (20.0)	10 (31.3)
Only self-care	3 (20.0)	3 (25.0)	0 (0.0)	6 (18.8)
Hemoglobin at baseline (g/dL)				
N	15	12	5	32
Median	108.00	112.50	128.00	118.00
Min-Max	88.00-145.00	75.00-137.00	121.00-135.00	75.00-145.00
LDH at baseline (units)				
N	15	12	5	32
Median	295.00	312.50	419.00	312.50
Min-Max	134.00-1732.00	109.00-832.00	168.00-486.00	109.00-1732.00
β2-microglobulin (µg/mL)				
N	15	12	5	32
Median	2.20	3.05	1.90	2.20
Min-Max	1.30-6.10	1.70-8.50	1.10-2.90	1.10-8.50

Baseline disease characteristics in the dose expansion phase by disease subtype (FAS)

	HL N=27 n (%)	DLBCL N=24 n (%)	FL N=14 n (%)	MZL/ MALT N=7 n (%)	MCL N=7 n (%)	All Doses N=79 n (%)
Lymphoma classification at baseline, n%						
Marginal zone B-cell lymphoma / MALT	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)	0 (0.0)	7 (8.9)
Follicular lymphoma	0 (0.0)	0 (0.0)	14 (100.0)	0 (0.0)	0 (0.0)	14 (17.7)
Grade 1: 0-5 centroblasts/hpf	0 (0.0)	0 (0.0)	2 (14.3)	0 (0.0)	0 (0.0)	2 (2.5)
Grade 2: 6-15 centroblasts/hpf	0 (0.0)	0 (0.0)	3 (21.4)	0 (0.0)	0 (0.0)	3 (3.8)
Grade 3: >15 centroblasts/hpf	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	1 (1.3)
Grade 3a: >15 centroblasts, but centrocytes still present	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	0 (0.0)	1 (1.3)
Mantle-cell lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (100.0)	7 (8.9)
Diffuse large B-cell lymphoma	0 (0.0)	24 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	24 (30.4)
Not otherwise specified: Germline center B-cell (GCB) type	0 (0.0)	4 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (5.1)
Not otherwise specified: Activated B-cell (ABC) type	0 (0.0)	3 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.8)
Not otherwise specified: Unknown molecular subgroup	0 (0.0)	12 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (15.2)
Primary mediastinal (thymic) large B-cell lymphoma	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Hodgkin's lymphoma	27 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	27 (34.2)
Hodgkin's lymphoma-Nodular lymphocyte - predominant	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Hodgkin's lymphoma-Classical nodular sclerosis	24 (88.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	24 (30.4)
Hodgkin's lymphoma-Classical mixed cellularity	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)
Ann Arbor stage at baseline						
Stage I	0 (0.0)	1 (4.2)	1 (7.1)	2 (28.6)	0 (0.0)	4 (5.1)
Stage II	6 (22.2)	3 (12.5)	3 (21.4)	0 (0.0)	0 (0.0)	12 (15.2)

Stage III	9 (33.3)	9 (37.5)	5 (35.7)	1 (14.3)	0 (0.0)	24 (30.4)
Stage IV	12 (44.4)	11 (45.8)	5 (35.7)	4 (57.1)	7 (100.0)	39 (49.4)
Time from original diagnosis (Years)						
N	27	24	14	7	7	79
Median	3.27	2.74	6.65	6.72	6.74	3.87
Min-Max	1.38-20.87	0.87-18.13	2.77-14.27	2.42-12.80	2.92-11.02	0.87-20.87
Time from last relapse (Years)						
N	26	23	14	7	7	77
Median	0.09	0.08	0.11	0.13	0.21	0.09
Min-Max	0.04-0.86	0.03-0.59	0.06-0.76	0.05-0.36	0.01-0.76	0.01-0.86
Number of prior therapies						
N	27	24	14	7	7	79
Median	4.00	4.00	5.00	3.00	4.00	4.00
Min-Max	2.00-8.00	2.00-10.00	2.00-10.00	1.00-8.00	3.00-5.00	1.00-10.00
Patient that received Stem Cell Transplants						
Yes	19 (70.4)	4 (16.7)	5 (35.7)	1 (14.3)	1 (14.3)	30 (38.0)
No	8 (29.6)	20 (83.3)	9 (64.3)	6 (85.7)	6 (85.7)	49 (62.0)
Bulk >10 cm						
Yes	2 (7.4)	6 (25.0)	2 (14.3)	1 (14.3)	3 (42.9)	14 (17.7)
No	25 (92.6)	18 (75.0)	12 (85.7)	6 (85.7)	4 (57.1)	65 (82.3)
FcYRIII polymorphism						
V/V	5 (18.5)	0 (0.0)	3 (21.4)	0 (0.0)	2 (28.6)	10 (12.7)
F/F	11 (40.7)	12 (50.0)	3 (21.4)	3 (42.9)	2 (28.6)	31 (39.2)
V/F	1 (3.7)	3 (12.5)	4 (28.6)	1 (14.3)	0 (0.0)	9 (11.4)
Other	2 (7.4)	6 (25.0)	2 (14.3)	1 (14.3)	1 (14.3)	12 (15.2)
WHO performance status						
No restrictions	9 (33.3)	11 (45.8)	5 (35.7)	3 (42.9)	3 (42.9)	31 (39.2)
Only light work	17 (63.0)	11 (45.8)	7 (50.0)	4 (57.1)	3 (42.9)	42 (53.2)
Only self-care	1 (3.7)	2 (8.3)	2 (14.3)	0 (0.0)	1 (14.3)	6 (7.6)
Hemoglobin at baseline (g/dL)						
N	27	24	14	7	7	79
Median	99.00	115.50	117.00	129.00	115.00	115.00
Min-Max	77.00-150.00	89.00-157.00	77.00-143.00	92.00-149.00	105.00-142.00	77.00-157.00
LDH at baseline (units)						
N	27	23	14	7	7	78
Median	242.00	264.00	252.00	193.00	494.00	252.00
Min-Max	141.00-850.00	166.00-1551.00	125.00-928.00	156.00-601.00	189.00-625.00	125.00-1551.00

β2-microglobulin (µg/mL)						
N	26	21	13	7	4	71
Median	2.15	2.20	2.80	3.00	2.75	2.40
Min-Max	1.20-8.00	1.10-10.00	1.50-6.70	2.10-5.60	2.30-5.60	1.10-10.00

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin's lymphoma; MCL: mantle cell lymphoma; MZL/MALT: marginal zone lymphoma /mucosa-associated lymphoid tissue.

Note: The demographic and other baseline characteristics for the 2 ongoing patients were described in the final report as follows:

- One patient was a 70-year old Caucasian male who entered the study with diffuse large B-cell lymphoma (Ann Arbor Stage IV, date of initial diagnosis: 07-Apr- 2007). Excluding the study drug, the patient had no antineoplastic therapy (including medication and radiotherapy) after the data cut-off date of 24-Aug-2011.
- One patient was a 79-year old Black female who entered the study with follicular lymphoma (Ann Arbor Stage III, date of initial diagnosis: 09-Sep-2004). Excluding the study drug, the patient had no antineoplastic therapy (including medication and radiotherapy) after the data cut-off date of 24-Aug-2011.

Outcome measures

Primary Outcome Results

Best clinical response in the dose escalation by treatment group (FAS)

	3.0 mg/kg N=15 n (%)	**4.0 mg/kg N=12 n (%)**	**6.0 mg/kg N=5 n (%)**	**All Doses N=32 n (%)**
Number of patients with no valid post-baseline evaluation	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.1)
Number of patients with valid post-baseline evaluation	15 (100)	11 (91.7)	5 (100)	31 (96.9)
Complete Response	1 (6.7)	0 (0.0)	0 (0.0)	1 (3.1)
Partial Response	2 (13.3)	1 (8.3)	1 (20.0)	4 (12.5)
Stable Disease	7 (46.7)	6 (50.0)	3 (60.0)	16 (50.0)
Progressive Disease	4 (26.7)	3 (25.0)	1 (20.0)	8 (25.0)
Unknown	1 (6.7)	1 (8.3)	0 (0.0)	2 (6.3)

Best clinical response in the dose expansion phase by disease subtype (FAS)

	HL N=27 n (%)	DLBCL N=24 n (%)	FL N=14 n (%)	MZL/MALT N=7 n (%)	MCL N=7 n (%)	All N=79 n (%)
Number of patients with no valid post-baseline evaluation	2 (7.4)	3 (12.5)	0 (0.0)	0 (0.0)	1 (14.3)	6 (7.6)
Number of patients with valid post-baseline evaluation	25 (92.6)	21 (87.5)	14 (100)	7 (100)	6 (85.7)	73 (92.4)
Complete Response (CR)	0 (0.0)	1 (4.2)	1 (7.1)	1 (14.3)	0 (0.0)	3 (3.8)
Partial Response (PR)	4 (14.8)	1 (4.2)	4 (28.6)	2 (28.6)	0 (0.0)	11 (13.9)
Stable Disease (SD)	7 (25.9)	7 (29.2)	6 (42.9)	1 (14.3)	3 (42.9)	24 (30.4)
Progressive Disease	12 (44.4)	11 (45.8)	3 (21.4)	2 (28.6)	3 (42.9)	31 (39.2)
Unknown	2 (7.4)	1 (4.2)	0 (0.0)	1 (14.3)	0 (0.0)	4 (5.1)

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin's lymphoma; MCL: mantle cell lymphoma; MZL/MALT: marginal zone lymphoma /mucosa-associated lymphoid tissue.

Summary of post distribution of response rate in the dose expansion phase by disease subtype (FAS)

	N	Response*	Observed Response Rate	Posterior Mean	Posterior SD	Posterior Prob (Observed RR>0.2)
FL	14	5	0.357	0.345	0.121	0.886
MZL/MALT	7	3	0.429	0.396	0.166	0.871
DLBCL	21	2	0.095	0.097	0.062	0.067
MCL	6	0	0.000	0.049	0.072	0.046
HL	25	4	0.160	0.159	0.068	0.254
Overall	73	14	0.192	0.186	0.179	0.330

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin's lymphoma; MCL: mantle cell lymphoma; MZL/MALT: marginal zone lymphoma /mucosa-associated lymphoid tissue.

Efficacy data for the 2 ongoing patients were as follows:

- One patient had 15 evaluations of the lymphoma tumor. An overall complete response of the lesion was observed at each evaluation. The last study dose was administered on 27-Nov-2012.
- One patient had 12 evaluations of the lymphoma tumor. At first evaluation a stable disease was reported. At Evaluation 2 to 8 the patient had a partial response. At Evaluation 9 to 11, the patient had a complete response and at the last evaluation (Evaluation 12) had progressive disease. The last study dose was administered on 28-Nov-2012.

Secondary Outcome Results

Summary of metabolic response from FDG-PET data in the dose escalation phase by treatment group (FAS)

	Overall Metabolic Response	3.0 mg/kg N=15 n (%)	4.0 mg/kg N=12 n (%)	6.0 mg/kg N=5 n (%)	All doses N=32 n (%)
D50					
	CMR	1 (6.7)	0(0.0)	0 (0.0)	1 (3.1)
	PMR	3 (20.0)	5 (41.7)	1 (20.0)	9 (28.1)
	SMD	5 (33.3)	5 (41.7)	2 (40.0)	12 (37.5)
Retreatment 1 D50					
	PMR	2 (13.3)	4 (33.3)	0 (0.0)	6 (18.8)
	SMD	1 (6.7)	0 (0.0)	1 (20.0)	2 (6.3)
	PMD	0 (0.0)	0 (0.0)	1 (20.0)	1 (3.1)

*Missing/Not done data only pertains to imaging data (screen failure, technical failure and missed visit)

Summary of metabolic response from FDG-PET data in the dose expansion phase by disease subtype (FAS)

	Overall Metabolic Response	HL N=27 n (%)	DLBCL N=24 n (%)	FL N=14 n (%)	MZL/MALT N=7 n (%)	MCL N=7 n (%)	All N=79 n (%)
D50							
	CMR	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
	PMR	6 (22.2)	6 (25.0)	5 (35.7)	2 (28.6)	0 (0.0)	19 (24.1)
	SMD	8 (29.6)	2 (8.3)	2 (14.3)	1 (14.3)	1 (14.3)	14 (17.7)
	PMD	1 (3.7)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)
Retreatment 1 D50							
	PMR	1 (3.7)	2 (8.3)	1 (7.1)	0 (0.0)	0 (0.0)	4 (5.1)
	SMD	4 (14.8)	1 (4.2)	1 (7.1)	0 (0.0)	0 (0.0)	6 (7.6)
	PMD	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin's lymphoma; MCL: mantle cell lymphoma; MZL/MALT: marginal zone lymphoma /mucosa-associated lymphoid tissue.

Summary of pharmacokinetic parameters of HCD122 by treatment group

		3.0 mg/kg N=9	4.0 mg/kg N=8	6.0 mg/kg N=1
Half-life, t1/2(hr)				
1st infusion	n	8	8	1
	mean	106.879	111.946	96.871
	std	48.48	36.556	
	median	89.632	97.244	96.871
	min	56.968	79.503	96.871
	max	190.986	185.694	96.871
4th infusion	n	9	8	1
	mean	220.594	327.066	407.801
	std	120.753	155.714	
	median	247.926	300.382	407.801
	min	60.351	100.616	407.801
	max	424.814	651.739	407.801
Retreatment 1 1st infusion	n	3	4	1
	mean	87.078	125.143	227.777
	std	33.793	28.005	
	median	68.54	130.814	227.777
	min	66.611	87.325	227.777
	max	126.083	151.617	227.777
Retreatment 1 4th infusion	n	3	4	1
	mean	229.77	341.279	1535.515
	std	138.186	115.076	
	median	293.571	331.798	1535.515
	min	71.211	210.502	1535.515
	max	324.528	491.019	1535.515
Cmax (µg/mL)				
1st infusion	n	8	8	1
	mean	56.624	87.409	131.86
	std	20.474	22.167	
	median	52.595	78.105	131.86
	min	37.85	58.35	131.86
	max	102.24	122.85	131.86
4th infusion	n	9	8	1
	mean	86.643	151.673	196.91
	std	19.025	57.697	
	median	83.94	148.44	196.91
	min	62.5	73.41	196.91
	max	118.87	232.65	196.91
Retreatment 1	n	3	4	1

		3.0 mg/kg N=9	4.0 mg/kg N=8	6.0 mg/kg N=1
1st infusion				
	mean	51.78	108.073	91.39
	std	9.769	20.975	
	median	57.42	102.99	91.39
	min	40.5	90.76	91.39
	max	57.42	135.55	91.39
Retreatment 1	n	3	4	1
4th infusion				
	mean	94.653	191.89	140.3
	std	9.026	64.313	
	median	95.04	169.27	140.3
	min	85.44	143.34	140.3
	max	103.48	285.68	140.3
AUC 0-168hr				
1st infusion	n	8	8	1
	mean	3730.266	6855.066	9921.14
	std	1422.956	2157.428	
	median	3352.417	6219.543	9921.14
	min	2512.919	4208.717	9921.14
	max	6955.733	10785.727	9921.14
4th infusion	n	9	8	1
	mean	8095.122	15590.814	27432.731
	std	2946.99	5874.102	
	median	6807.038	14554.544	27432.731
	min	4682.164	8827.41	27432.731
	max	12972.285	25063.209	27432.731
Retreatment 1	n	3	4	1
1st infusion				
	mean	3398.707	9387.295	8530.918
	std	109.531	1697.293	
	median	3428.14	8841.043	8530.918
	min	3277.466	8003.8	8530.918
	max	3490.514	11863.295	8530.918
Retreatment 1	n	3	4	1
4th infusion				
	mean	9575.278	19905.095	18803.998
	std	1302.76	5776.04	
	median	9622.36	18299.435	18803.998
	min	8249.616	15100.721	18803.998
	max	10853.859	27920.789	18803.998

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class and treatment group in the dose escalation phase (Safety set)

Primary system organ class	3.0 mg/kg N=15 n (%)	4.0 mg/kg N=12 n (%)	6.0 mg/kg N=5 n (%)	All doses N=32 n (%)
Total	15 (100. 0)	12 (100.0)	5 (100.0)	32 (100.0)
General disorders and administration site conditions	12 (80.0)	8 (66.7)	3 (60.0)	23 (71.9)
Gastrointestinal disorders	10 (66.7)	8 (66.7)	3 (60.0)	21 (65.6)
Investigations	7 (46.7)	6 (50.0)	4 (80.0)	17 (53.1)
Infections and infestations	8 (53.3)	5 (41.7)	2 (40.0)	15 (46.9)
Respiratory, thoracic and mediastinal disorders	9 (60.0)	5 (41.7)	1 (20.0)	15 (46.9)
Blood and lymphatic system disorders	6 (40.0)	5 (41.7)	2 (40.0)	13 (40.6)
Nervous system disorders	7 (46.7)	5 (41.7)	1 (20.0)	13 (40.6)
Metabolism and nutrition disorders	3 (20.0)	7 (58.3)	1 (20.0)	11 (34.4)
Skin and subcutaneous tissue disorders	7 (46.7)	3 (25.0)	1 (20.0)	11 (34.4)
Musculoskeletal and connective tissue disorders	3 (20.0)	6 (50.0)	1 (20.0)	10 (31.3)
Vascular disorders	3 (20.0)	3 (25.0)	3 (60.0)	9 (28.1)
Injury, poisoning and procedural complications	3 (20.0)	2 (16.7)	1 (20.0)	6 (18.8)
Psychiatric disorders	1 (6.7)	4 (33.3)	1 (20.0)	6 (18.8)
Cardiac disorders	3 (20.0)	1 (8.3)	1 (20.0)	5 (15.6)
Renal and urinary disorders	3 (20.0)	2 (16.7)	0 (0.0)	5 (15.6)
Eye disorders	1 (6.7)	1 (8.3)	1 (20.0)	3 (9.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps	2 (13.3)	0 (0.0)	0 (0.0)	2 (6.3)
Ear and labyrinth disorders	1 (6.7)	0 (0.0)	0 (0.0)	1 (3.1)
Endocrine disorders	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.1)
Reproductive system and breast disorders	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.1)

Arranged in descending order of frequency in “All Doses”.

Adverse events, regardless of study drug relationship, by primary system organ class and disease subtype in the dose expansion phase (Safety set)

Primary system organ class	HL N=27 n (%)	DLBCL N=24 n (%)	FL N=14 n (%)	MZL/MALT N=7 n (%)	MCL N=7 n (%)	All doses N=79 n (%)
Total	25 (92.6)	24 (100.0)	14 (100.0)	7 (100.0)	7 (100.0)	77 (97.5)
General disorders and administration site conditions	18 (66.7)	18 (75.0)	11 (78.6)	3 (42.9)	6 (85.7)	56 (70.9)
Respiratory, thoracic and mediastinal disorders	11 (40.7)	10 (41.7)	8 (57.1)	3 (42.9)	4 (57.1)	36 (45.6)
Gastrointestinal disorders	12 (44.4)	9 (37.5)	9 (64.3)	1 (14.3)	4 (57.1)	35 (44.3)
Investigations	10 (37.0)	6 (25.0)	7 (50.0)	4 (57.1)	4 (57.1)	31 (39.2)
Musculoskeletal and connective tissue disorders	10 (37.0)	9 (37.5)	7 (50.0)	0 (0.0)	1 (14.3)	27 (34.2)
Skin and subcutaneous tissue disorders	9 (33.3)	7 (29.2)	5 (35.7)	2 (28.6)	1 (14.3)	24 (30.4)
Infections and infestations	7 (25.9)	7 (29.2)	5 (35.7)	2 (28.6)	2 (28.6)	23 (29.1)
Nervous system disorders	7 (25.9)	7 (29.2)	7 (50.0)	1 (14.3)	1 (14.3)	23 (29.1)
Vascular disorders	6 (22.2)	6 (25.0)	4 (28.6)	1 (14.3)	2 (28.6)	19 (24.1)
Blood and lymphatic system disorders	2 (7.4)	9 (37.5)	1 (7.1)	1 (14.3)	1 (14.3)	14 (17.7)
Metabolism and nutrition disorders	1 (3.7)	6 (25.0)	3 (21.4)	3 (42.9)	1 (14.3)	14 (17.7)
Eye disorders	1 (3.7)	3 (12.5)	3 (21.4)	2 (28.6)	0 (0.0)	9 (11.4)
Cardiac disorders	4 (14.8)	2 (8.3)	2 (14.3)	0 (0.0)	0 (0.0)	8 (10.1)
Psychiatric disorders	3 (11.1)	2 (8.3)	2 (14.3)	0 (0.0)	0 (0.0)	7 (8.9)
Renal and urinary disorders	1 (3.7)	3 (12.5)	0 (0.0)	0 (0.0)	1 (14.3)	5 (6.3)
Injury, poisoning and procedural complications	2 (7.4)	1 (4.2)	1 (7.1)	0 (0.0)	0 (0.0)	4 (5.1)
Ear and labyrinth disorders	0 (0.0)	1 (4.2)	1 (7.1)	0 (0.0)	0 (0.0)	2 (2.5)
Immune system disorders	1 (3.7)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)
Hepatobiliary disorders	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)

Arranged in descending order of frequency in “All Doses”.

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin’s lymphoma; MCL: mantle cell lymphoma; MZL/MALT: marginal zone lymphoma /mucosa-associated lymphoid tissue.

Most frequent adverse events (greater than or equal to 10%*), regardless of study drug relationship, by preferred term and treatment group in the dose escalation phase (Safety set)

	Treatment Group			All patients N=32	
Preferred term **	**3.0 mg/kg N=15 n (%)**	**4.0 mg/kg N=12 n (%)**	**6.0 mg/kg N=5 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Total	15 (100)	12 (100)	5 (100)	32 (100)	24 (75.0)
Pyrexia	6 (40.0)	5 (41.7)	1 (20.0)	12 (37.5)	0 (0.0)
Lipase increased	4 (26.7)	4 (33.3)	2 (40.0)	10 (31.3)	10 (31.3)
Chills	5 (33.3)	4 (33.3)	0 (0.0)	9 (28.1)	0 (0.0)
Nausea	3 (20.0)	4 (33.3)	2 (40.0)	9 (28.1)	0 (0.0)
Fatigue	4 (26.7)	3 (25.0)	1 (20.0)	8 (25.0)	1 (3.1)
Asthenia	4 (26.7)	3 (25.0)	0 (0.0)	7 (21.9)	2 (6.3)
Constipation	5 (33.3)	2 (16.7)	0 (0.0)	7 (21.9)	0 (0.0)
Cough	4 (26.7)	2 (16.7)	1 (20.0)	7 (21.9)	1 (3.1)
Dyspnea	3 (20.0)	3 (25.0)	1 (20.0)	7 (21.9)	2 (6.3)
Headache	5 (33.3)	2 (16.7)	0 (0.0)	7 (21.9)	0 (0.0)
Hypotension	3 (20.0)	3 (25.0)	1 (20.0)	7 (21.9)	0 (0.0)
Diarrhea	3 (20.0)	2 (16.7)	1 (20.0)	6 (18.8)	0 (0.0)
Edema peripheral	4 (26.7)	1 (8.3)	1 (20.0)	6 (18.8)	2 (6.3)
Abdominal pain	3 (20.0)	2 (16.7)	0 (0.0)	5 (15.6)	0 (0.0)
Anemia	4 (26.7)	1 (8.3)	0 (0.0)	5 (15.6)	2 (6.3)
Decreased appetite	1 (6.7)	3 (25.0)	1 (20.0)	5 (15.6)	0 (0.0)
Vomiting	2 (13.3)	2 (16.7)	1 (20.0)	5 (15.6)	0 (0.0)
Back pain	1 (6.7)	2 (16.7)	1 (20.0)	4 (12.5)	1 (3.1)
Insomnia	0 (0.0)	3 (25.0)	1 (20.0)	4 (12.5)	0 (0.0)
Upper respiratory tract infection	2 (13.3)	1 (8.3)	1 (20.0)	4 (12.5)	0 (0.0)

* Only list AEs that are ≥ 10% of all patients in all grades

**Arranged by frequency in all patients

Most frequent adverse events (greater than or equal to 10%*), regardless of study drug relationship, by preferred term and disease subtype in the dose expansion phase (Safety set)

	Treatment Group					All patients N=79	
Preferred term **	**HL N=27 n (%)**	**DLBCL N=24 n (%)**	**FL N=14 n (%)**	**MZL/MALT N=7 n (%)**	**MCL N=7 n (%)**	**All Grades n (%)**	**Grade 3/4 n (%)**
Total	27 (100)	24 (100)	14 (100)	7 (100)	7 (100)	79 (100)	48 (60.8)
Chills	12 (44.4)	11 (45.8)	9 (64.3)	1 (14.3)	1 (14.3)	34 (43.0)	1 (1.3)
Pyrexia	11 (40.7)	8 (33.3)	5 (35.7)	2 (28.6)	0 (0.0)	26 (32.9)	2 (2.5)
Fatigue	5 (18.5)	7 (29.2)	4 (28.6)	2 (28.6)	2 (28.6)	20 (25.3)	1 (1.3)
Lipase increased	5 (18.5)	4 (16.7)	5 (35.7)	4 (57.1)	2 (28.6)	20 (25.3)	18 (22.8)
Dyspnea	5 (18.5)	4 (16.7)	4 (28.6)	1 (14.3)	4 (57.1)	18 (22.8)	5 (6.3)
Nausea	6 (22.2)	4 (16.7)	5 (35.7)	1 (14.3)	1 (14.3)	17 (21.5)	1 (1.3)
Cough	5 (18.5)	4 (16.7)	4 (28.6)	0 (0.0)	0 (0.0)	13 (16.5)	1 (1.3)
Headache	4 (14.8)	5 (20.8)	3 (21.4)	1 (14.3)	0 (0.0)	13 (16.5)	1 (1.3)
Back pain	5 (18.5)	4 (16.7)	2 (14.3)	0 (0.0)	1 (14.3)	12 (15.2)	0 (0.0)
Hypotension	2 (7.4)	4 (16.7)	1 (7.1)	1 (14.3)	1 (14.3)	9 (11.4)	1 (1.3)
Neutropenia	0 (0.0)	7 (29.2)	1 (7.1)	0 (0.0)	1 (14.3)	9 (11.4)	8 (10.1)
Vomiting	5 (18.5)	2 (8.3)	2 (14.3)	0 (0.0)	0 (0.0)	9 (11.4)	1 (1.3)
Blood amylase increased	1 (3.7)	2 (8.3)	2 (14.3)	2 (28.6)	1 (14.3)	8 (10.1)	4 (5.1)
Constipation	0 (0.0)	3 (12.5)	3 (21.4)	0 (0.0)	2 (28.6)	8 (10.1)	0 (0.0)

* Only list AEs that are ≥ 10% of all patients in all grades

**Arranged by frequency in all patients

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin's lymphoma; MCL: mantle cell lymphoma; MZL/MALT: marginal zone lymphoma /mucosa-associated lymphoid tissue.

Deaths, other serious or clinically significant adverse events or related discontinuations by disease subtype in the dose escalation phase (Safety set)

	3.0 mg/kg N=15 n (%)	**4.0 mg/kg N=12 n (%)**	**6.0 mg/kg N=5 n (%)**	**All doses N=32 n (%)**
Death	1 (6.7)	1 (8.3)	0 (0.0)	2 (6.3)
SAE(s)	5 (33.3)	5 (41.7)	0 (0.0)	10 (31.3)
DLT(s)	3 (20.0)	1 (8.3)	2 (40.0)	6 (18.8)
Clinically significant AE(s)				
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tumor lysis syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypophosphataemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoxia	2 (13.3)	1 (8.3)	0 (0.0)	3 (9.4)
Lymphopenia	0 (0.0)	0 (0.0)	1 (20.0)	1 (3.1)
Neutropenia	0 (0.0)	1 (8.3)	0(0.0)	1 (3.1)
Thrombocytopenia	1 (6.7)	2 (16.7)	0(0.0)	3 (9.4)
Amylase	2 (13.3)	1 (8.3)	0(0.0)	3 (9.4)
Lipase	4 (26.7)	4 (33.3)	2 (40.0)	10 (31.3)
ALT(SGOT)	1 (6.7)	0(0.0)	2 (40.0)	3 (9.4)
AST(SGPT)	1 (6.7)	0(0.0)	1 (20.0)	2 (6.3)
Discontinued due to SAE(s)	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.1)
Discontinued due to clin. sign. AE(s)	2 (13.3)	1 (8.3)	2 (40.0)	5 (15.6)

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotranserase;
clin. sign.: clinically significant; DLT: dose-limiting toxicity; SAE: serious adverse event; SGOT: serum glutamic oxaloacetic transaminase; SGPT: glutamic pyruvic transaminase.

Deaths, other serious or clinically significant adverse events or related discontinuations by disease subtype in the dose expansion phase (Safety set)

	HL N=27 n (%)	DLBCL N=24 n (%)	FL N=14 n (%)	MZL/MALT N=7 n (%)	MCL N=7 n (%)	All Doses N=79 n (%)
Death	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
SAE(s)	6 (22.2)	9 (37.5)	3 (21.4)	0 (0.0)	3 (42.9)	21 (26.6)
Clinically significant AE(s)						
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tumor lysis syndrome	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Hypophosphataemia	1 (3.7)	1 (4.2)	1 (7.1)	0 (0.0)	1 (14.3)	4 (5.1)
Hypoxia	0 (0.0)	0(0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphopenia	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Neutropenia	0 (0.0)	7 (29.2)	1 (7.1)	0 (0.0)	1 (14.3)	9 (11.4)
Thrombocytopenia	1 (3.7)	1 (4.2)	0 (0.0)	1 (14.3)	2 (28.6)	5 (6.3)
Amylase	1 (3.7)	2 (8.3)	2 (14.3)	2 (28.6)	1 (14.3)	8 (10.1)
Lipase	5 (18.5)	4 (16.7)	5 (35.7)	4 (57.1)	2 (28.6)	20 (25.3)
ALT(SGOT)	1 (3.7)	0 (0.0)	1 (7.1)	0 (0.0)	1 (14.3)	3 (3.8)
AST(SGPT)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	2 (2.5)
Discontinued due to SAE(s)	0 (0.0)	3 (12.5)	1 (7.1)	0 (0.0)	0 (0.0)	4 (5.1)
Discontinued due to clin. sign. AE(s)	4 (14.8)	7 (29.2)	4 (28.6)	3 (42.9)	3 (42.9)	21 (26.6)

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotranserase;
clin. sign.: clinically significant; DLBCL: diffuse large B-cell lymphoma; DLT: dose-limiting toxicity;
FL: follicular lymphoma; HL: Hodgkin's lymphoma; MCL: mantle cell lymphoma; MZL/MALT: marginal zone lymphoma /mucosa-associated lymphoid tissue; SAE: serious adverse event; SGOT: serum glutamic oxaloacetic transaminase; SGPT: glutamic pyruvic transaminase.

Deaths up to 28 days following study termination by preferred term and treatment group in the dose escalation phase (FAS)

Preferred term	3.0 mg/kg N=15 n (%)	4.0 mg/kg N=12 n (%)	All doses N=32 n (%)
Total deaths	1 (6.7)	1 (8.3)	2 (6.3)
Cardio-respiratory arrest	0 (0.0)	1 (8.3)	1 (3.1)
Pulmonary edema	1 (6.7)	0 (0.0)	1 (3.1)

Deaths up to 28 days following study termination by preferred term and treatment group in the dose expansion phase (FAS)

Preferred term	HL N=27 n (%)	DLBCL N=24 n (%)	All doses N=79 n (%)
Total deaths	1 (3.7)	4 (16.7)	5 (6.3)
H1N1 influenza	1 (3.7)	0 (0.0)	1 (1.3)
Study indication	0 (0.0)	4 (16.7)	4 (5.1)

DLBCL: diffuse large B-cell lymphoma; HL: Hodgkin's lymphoma.

Serious adverse events, by preferred term and treatment group in the dose escalation phase (Safety set)

Preferred term	3.0 mg/kg N=15 n (%)	4.0 mg/kg N=12 n (%)	6.0 mg/kg N=5 n (%)	All Doses N=32 n (%)
- Total	5 (33.3%)	5 (41.7%)	0 (0.0%)	10 (31.3%)
Dyspnea	1 (6.7%)	2 (16.7%)	0 (0.0%)	3 (9.4%)
Staphylococcal sepsis	1 (6.7%)	1 (8.3%)	0 (0.0%)	2 (6.3%)
Anemia	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Arterial thrombosis limb	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Cardio-respiratory arrest	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Convulsion	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Cough	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Diffuse axonal injury	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Dysphagia	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Ejection fraction decreased	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Febrile bone marrow aplasia	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Febrile neutropenia	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Hypovolaemia	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Hypoxia	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Esophageal rupture	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Pneumonia staphylococcal	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Pulmonary edema	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (3.1%)
Respiratory syncytial virus infection	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Syncope	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Transaminases increased	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Troponin T increased	0 (0.0%)	1 (8.3%)	0 (0.0%)	1 (3.1%)
Tumor pain	1 (6.7%)	0 (0.0%)	0 (0.0%)	1 (3.1%)

Incidence of SAEs, regardless of study drug relationship, by preferred term and disease subtype in the dose expansion phase (Safety set)

Preferred term	HL N=27 n (%)	DLBCL N=24 n (%)	FL N=14 n (%)	MZL/MALT N=7 n (%)	MCL N=7 n (%)	All Doses N=79 n (%)
- Total	6 (22.2%)	9 (37.5%)	3 (21.4%)	0 (0.0%)	3 (42.9%)	21 (26.6%)
Pyrexia	2 (7.4%)	4 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	6 (7.6%)
Dyspnea	0 (0.0%)	2 (8.3%)	1 (7.1%)	0 (0.0%)	1 (14.3%)	4 (5.1%)
Chills	2 (7.4%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (3.8%)
Hydronephrosis	1 (3.7%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.5%)
Pneumonia	0 (0.0%)	2 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.5%)
Renal failure acute	0 (0.0%)	2 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.5%)
Abdominal distension	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (1.3%)
Aphasia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (1.3%)
Arrhythmia supraventricular	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Bronchospasm	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Cardiac failure congestive	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Disease progression	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Dysphagia	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Electrocardiogram QT prolonged	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Febrile neutropenia	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Food intolerance	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
H1N1 influenza	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Hypertension	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Hypotension	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Infusion related reaction	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Lipase increased	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Lung infection	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Lung infiltration	0 (0.0%)	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Nodal arrhythmia	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Pleural effusion	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Renal failure	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Stomatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	1 (1.3%)
Tumor lysis syndrome	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
Vomiting	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin's lymphoma; MCL: mantle cell lymphoma; MZL/MALT: marginal zone lymphoma /mucosa-associated lymphoid tissue.

Treatment discontinuations, due to adverse events, by preferred term and treatment group in the dose escalation phase (Safety set,

	3.0 mg/kg N=15	4.0 mg/kg N=12	6.0 mg/kg N=5	All Doses N=32
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total discontinuations due to AE(s)	2 (13.3)	3 (25.0)	2 (40.0)	7 (21.9)
Lipase increased	1 (6.7)	1 (8.3)	1 (20.0)	3 (9.4)
Alanine aminotransferase increased	1 (6.7)	0 (0.0)	1(20.0)	2 (6.3)
Aspartate aminotransferase increased	1 (6.7)	0 (0.0)	0 (0.0)	1 (3.1)
Cardio-respiratory arrest	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.1)
Chills	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.1)
Pyrexia	0 (0.0)	1 (8.3)	0 (0.0)	1 (3.1)

Discontinuation may be due to more than one event

Treatment discontinuations, due to adverse events, by preferred term and disease subtype in the dose expansion phase (Safety set)

	HL N=27	DLBCL N=24	FL N=14	MZL/MALT N=7	MCL N=7	All Doses N=79
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Total discontinuations due to AE(s)	5 (18.5)	10 (41.7)	5 (35.7)	3 (42.9)	4 (57.1)	27 (34.2)
Lipase increased	3 (11.1)	2 (8.3)	4 (28.6)	3 (42.9)	0 (0.0)	12 (15.2)
Blood amylase increased	0 (0.0)	1 (4.2)	1 (7.1)	1(14.3)	1(14.3)	4 (5.1)
Neutropenia	0 (0.0)	3 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.8)
Chills	1 (3.7)	1(4.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)
Platelet count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (28.6)	2 (2.5)
Renal failure acute	0 (.0.0)	2 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)
Alanine aminotransferase increased	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Blood alkaline phosphatase increased	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Dyspnea	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (14.3)	1 (1.3)
Hypotension	0 (0.0)	0 (.00)	1 (7.1)	0 (.0.0)	0 (0.0)	1 (1.3)
Pleural effusion	0 (0.0)	1 (4.2)	0 (0.0)	0 (.0.0)	0 (0.0)	1 (1.3)
Pyrexia	1 (3.7)	0 (0.0)	0 (0.0)	0 (.0.0)	0 (0.0)	1 (1.3)
Renal failure	0 (0.0)	1 (4.2)	0 (0.0)	0 (.0.0)	0 (0.0)	1 (1.3)
Tumor lysis syndrome	0 (0.0)	1 (4.2)	0 (0.0)	0 (.0.0)	0 (0.0)	1 (1.3)

Discontinuation may be due to more than 1 event

DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin's lymphoma; MCL: mantle cell lymphoma; MZL/MALT: marginal zone lymphoma /mucosa-associated lymphoid tissue.

Note: no deaths, SAEs and significant AEs were reported for the 2 ongoing patients.

Other Relevant Findings

No other relevant findings were reported.

Date of Clinical Trial Report

15 October 2013

Date Inclusion on Novartis Clinical Trial Results Database

21 January 2014

Date of Latest Update