Use of anti-CD19 maytansinoid immunoconjugate antibody for the treatment of B-cell malignancies symptoms

The present invention relates to the use of anti-CD19 maytansinoid immunoconjugate for the treatment of B-cell malignancies symptom.

Cell surface molecules expressed by B cells and their malignant counterparts represent important targets for immunotherapy.

CD19 is the earliest differentiation antigen of the B lymphocyte lineage, expressed on most B cells, but not detected on plasma cells, stem cells, or on normal myeloid lineage.

Therefore, CD19 is expressed on tumor cells from all B cell derived neoplasms (Bcell non-Hodgkin's lymphoma, acute lymphoblastic leukemia, chronic lymphocytic leukemia) except myeloma.

B-cell Non-Hodgkin's lymphoma (B-NHL) is the fifth most common malignancy in the United States and continues to increase in incidence, especially in elderly patients. While patients with hematological malignancies have benefited over the past decade from therapeutic optimization using conventional drug therapy, a majority of patients still succumb to their disease and drug therapies remain highly toxic. Hence, future efforts towards developing new therapies to improve survival and quality of life of lymphoma patients must include strategies that specifically targets cancer cells and show improved safety and efficacy.

HuB4-DM4 is an antibody–drug conjugate composed of a humanized IgG1 monoclonal antibody, huB4, which specifically targets the CD19 antigen, conjugated through a disulfide link to the maytansinoid derivative DM4, a potent tubulin inhibitor. The structure of the HuB4-DM4 conjugate SAR3419 is disclosed on figure 1 and the sequence of the heavy and light chains of the antibody are listed in the enclosed sequence listing, said light chain having the sequence represented in SEQ ID NO. 7, and said heavy chain having the sequence represented in SEQ ID NO. 8.

After binding to the CD19 antigen, the HuB4-DM4 conjugate undergoes internalization and intracellular release of DM4.

In the first-in-man study TED6828 the HuB4-DM4 conjugate SAR3419 administered IV once every 3 weeks for 6 cycles (N=39) in patients with refractory/relapsed CD19+ NHL, 7 dose levels (10 mg/m² to 270 mg/m²) was tested. The Maximum Tolerated Dose (MTD) was 160 mg/m² every 3 weeks. The dose limiting toxicity was reversible corneal

toxicity. The most frequent drug related toxicity was ocular (all grades) observed in 43.5% of patients, 15.4% being of grade 3/4. The toxicities consisting mainly of blurred vision associated with microcystic deposits on the corneal epithelium (corneal toxicities) were reversible in all cases.

The preliminary results of this trial have been published in the abstracts of the ASH 2009 (Younes et al, ASH ANNUAL Meeting Abstracts, 2009, 114(22):585).

It has now been found that it is possible to reduce the toxicity, and in particular the ocular toxicity, resulting from the treatment with the HuB4-DM4 conjugate by administering the HuB4-DM4 conjugate with another dosage regimen.

It has furthermore been shown that the conjugate SAR3419 allows treating patients having B-cell Non-Hodgkin's lymphoma, in particular Diffuse Large B-cell lymphoma (DLBCL).

The invention relates to methods, compositions and articles as disclosed herein.

In one aspect the invention provides for a method of treating CD19+ B-cell malignancies symptom in a patient in need thereof, said method comprising administering to said patient therapeutically effective amounts of anti-CD19 maytansinoid immunoconjugate.

In a particular embodiment said method comprises administering to said patient therapeutically effective amounts of anti-CD19 maytansinoid immunoconjugate with a dose regimen reducing the ocular toxicity resulting from the treatment.

In an embodiment this toxicity results from the treatment with the HuB4-DM4 conjugate.

In another particular embodiment of this method the occurrence of eye related adverse events (all grades) is below 40 %.

In another particular embodiment of this method the occurrence of eye related adverse events grade 3 or 4 is below 13 %.

This method is safe and effective.

Although the present invention relates primarily to the treatment of CD19+ B-cell malignancies symptom in a patient in need thereof, B-cell malignancies symptom whatever the level of expression of CD19 in the cells can be also treated.

Thus in another aspect the invention provides for a method of treating B-cell malignancies symptom in a patient in need thereof, said method comprising

administering to said patient therapeutically effective amounts of anti-CD19 maytansinoid immunoconjugate.

These methods of treating can comprise the steps of administering to the patient an initial dose of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate and administering to the patient a plurality of subsequent doses of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate, wherein the subsequent doses are separated in time from each other by about one week.

In a particular embodiment of this method the administration of the initial dose is followed by the administration of at least 6 doses separated in time from each other by one week. In another embodiment the initial dose is followed by the administration of at least 7 or 8 doses separated in time from each other by about one week.

In another particular embodiment of this method the administration of the initial dose is followed by the administration of between 6 and 14 doses separated in time from each other by about one week. In another embodiment the administration of the initial dose is followed by the administration of between 7 and 13 doses or 8 to 12 doses.

Thus in this particular embodiment said method comprises the steps of:

- administering to the patient an initial dose of about 55 mg/m², of the anti-CD19 maytansinoid immunoconjugate, and
- administering to the patient at least 6 subsequent doses of about 55 mg/m² separated in time from each other by about one week of the anti-CD19 maytansinoid immunoconjugate.

This method of treating can comprise a further step of administration of subsequent doses of about 55 mg/m² of anti-CD19 maytansinoid immunoconjugate wherein the doses are separated in time from each other by about two weeks.

In this particular embodiment of this method the administration of the initial dose is followed by the administration of at least 3 doses separated in time from each other by about one week and then by the administration of at least 3 doses separated in time from each other by about two weeks. This embodiment is generally referred to weekly/2 weekly or qw/q2w or even optimized schedule in the present application.

Thus in this particular embodiment said method comprises the steps of:

- administering to the patient an initial dose of about 55 mg/m², of the anti-CD19 maytansinoid immunoconjugate,

- administering to the patient at least 3 subsequent doses of about 55 mg/m² separated in time from each other by about one week of the anti-CD19 maytansinoid immunoconjugate , and
- administering to the patient at least 3 subsequent doses of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate separated in time from each other by about two weeks.

CD19+ B-cell malignancies are defined as any malignancies expressing the CD19 cell surface antigen.

Said CD19+ B-cell malignancies symptom can be a leukemia symptom, such as Acute lymphoblastic leukemia (ALL) symptom or a lymphoma symptom, such as a Non-Hodgkin's lymphoma symptom (NHL) symptom.

The Non-Hodgkin's lymphoma symptom can be a Diffuse Large B-cell lymphoma (DLBCL), a folicullar lymphoma (FL), a Mantle cell lymphoma (MCL), a Marginal zone lymphoma (MZL), a Small lymphocytic lymphoma (SLL) or a Waldenström macroglobulinemia (WM).

In a particular embodiment of this method said Non-Hodgkin's lymphoma symptom is a relapsed or refractory B-cell non-Hodgkin's lymphoma.

In another particular embodiment of this method the said Non-Hodgkin's lymphoma symptom is a B-cell non-Hodgkin's lymphoma expressing CD19.

In another particular embodiment of this method the said patient has already been treated for the Non-Hodgkin's lymphoma symptom. In particular said patient may have failed therapy, and in particular a chemotherapy or a rituximab therapy.
In another particular embodiment of this method the said Non-Hodgkin's lymphoma symptom is a rituximab resistant disease.

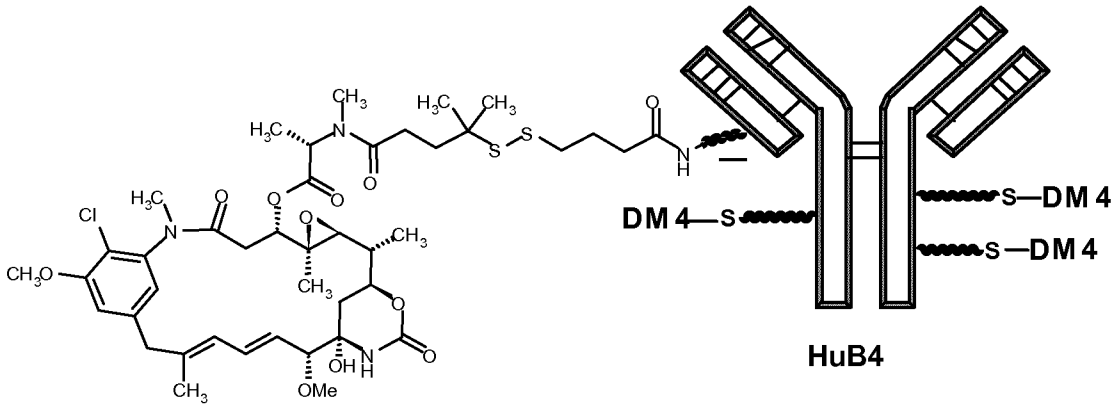
In another particular embodiment of this method the said patient has received a autologous or allogeneic stem cell transplant.

In a particular embodiment of this method the anti-CD19 maytansinoid immunoconjugate comprises an antibody which binds specifically to the CD19 antigen conjugated to DM4.

The antibody which binds specifically to the CD19 antigen can be conjugated to DM4 through a cleavable linker, in particular a N-succinimidyl 4-(2-pyridyldithio)butanoate (SPDB) linker.

In a particular embodiment of this method the anti-CD19 maytansinoid immunoconjugate comprises an antibody which binds specifically to the CD19 antigen conjugated to DM4 through SPDB wherein about 3.5 molecules of DM4 are bound through the SPDB linker to each huB4 molecule.

In a particular embodiment the anti-CD19 maytansinoid immunoconjugate has the following formula:



In an embodiment, the said antibody comprises six complementary determining region (CDR), said CDR having the sequences represented in SEQ ID NOs 1 to 6.

In another embodiment, the antibody comprises a light chain, wherein the sequence of the said light chain has at least 60%, at least 75%, at least 85%, at least 95 % or at least 99% identity with the sequence displayed in SEQ ID NO. 7.

In yet another embodiment, the antibody comprises a heavy chain, wherein the sequence of the said heavy chain has at least 60%, at least 75%, at least 85%, at least 95 % or at least 99% identity with the sequence displayed in SEQ ID NO. 8.

In another embodiment, the antibody of the invention is the humanized antibody huB4 described in Roguska et al. (*Proc. Natl. Acad. Sci. USA*, **91**: 969-973, 1994). The antibody huB4 according to the invention comprises a light chain and a heavy chain, said light chain having the sequence represented in SEQ ID NO. 7, and said heavy chain having the sequence represented in SEQ ID NO. 8. in a particular embodiment the conjugate is the HuB4-DM4 conjugate.

In one aspect the invention provides for anti-CD19 maytansinoid immunoconjugate for treating a human patient diagnosed with a CD19+ B-cell malignancies symptom with a method comprising the steps of administering to the patient an initial dose of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate; and administering to the patient a plurality of subsequent doses of about 55 mg/m², of the anti-CD19 maytansinoid immunoconjugate, wherein the subsequent doses are separated in time from each other by one week.

In one aspect the invention provides for anti-CD19 maytansinoid immunoconjugate for treating a human patient diagnosed with a CD19+ B-cell malignancies symptom with a method comprising the steps of administering to the patient an initial dose of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate; and then administering to the patient a plurality of subsequent doses of about 55 mg/m², of the anti-CD19 maytansinoid immunoconjugate separated in time from each other by one week, and in a further step administering a plurality of subsequent doses of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate separated in time from each other by two weeks.

In another aspect the invention provides for an article of manufacture comprising:

- a packaging material
- an anti-CD19 maytansinoid immunoconjugate, and
- a label or package insert contained within said packaging material indicating that said anti-CD19 maytansinoid immunoconjugate is administered to the patient at an initial dose of about 55 mg/m², and in a plurality of subsequent doses separated in time from each other by one week in an amount that is about 55 mg/m².

In another aspect the invention provides for an article of manufacture comprising:

- a packaging material

- an anti-CD19 maytansinoid immunoconjugate, and
- a label or package insert contained within said packaging material indicating that said anti-CD19 maytansinoid immunoconjugate is administered to the patient at an initial dose of about 55 mg/m², then in a plurality of subsequent doses separated in time from each other by one week in an amount that is about 55 mg/m² and then in a plurality of subsequent doses separated in time from each other by two weeks in an amount that is about 55 mg/m².

In one aspect the invention provides for article of manufacture comprising:

- a packaging material
- an anti-CD19 maytansinoid immunoconjugate, and
- a label or package insert contained within said packaging material indicating that said anti-CD19 maytansinoid immunoconjugate is administered to the patient at a dose of about 55 mg/m² to minimize the risks of toxicity, such as the late and cumulated toxicities and in particular the risks of ocular toxicity.

Such a packaging material indicating that said anti-CD19 maytansinoid immunoconjugate is administered to the patient at a dose of about 55 mg/m² (4 doses separated in time from each other by one week and then 4 subsequent doses separated in time from each other by two weeks) with to limit the accumulation of the drug thought to be the cause –at least in part – of cumulative toxicities or of the increase severity of such toxicities, such as corneal toxicities, peripheral sensory neuropathy and paresthesias.

In a particular embodiment the label or package insert contained within said packaging material indicates that the occurrence of eye related adverse events (all grades) is below 40 %, 30% or 25%.

In a particular embodiment the label or package insert contained within said packaging material indicates that the occurrence of eye related adverse events grade 3/4 is below 13 %, 10% or 5%.

The ocular toxicity is characterized by the eye disorders observed in the patients.

The eye disorders are defined in the Version 3.0 of the document entitled “Common Terminology Criteria for Adverse Events (CTCAE)” Published in May 28, 2009 by the U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES to which the man skilled in the art may refer.

According to this document the eye disorders are classified by adverse events (AE) that are graded depending on their severity.

The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

The anti-CD19 maytansinoid immunoconjugate can be administered within a pharmaceutical compositions comprising:

- an effective amount of anti-CD19 maytansinoid immunoconjugate, and
- a pharmaceutically acceptable carrier, which may be inert or physiologically active.

As used herein, “pharmaceutically-acceptable carriers” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, and the like that are physiologically compatible. Examples of suitable carriers, diluents and/or excipients include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol, and the like, as well as combination thereof. In many cases, it will be preferable to include isotonic agents, such as sugars, polyalcohols, or sodium chloride in the composition. In particular, relevant examples of suitable carrier include: (1) Dulbecco’s phosphate buffered saline, pH ~ 7.4, containing or not containing about 1 mg/ml to 25 mg/ml human serum albumin, (2) 0.9% saline (0.9% w/v sodium chloride (NaCl)), and (3) 5% (w/v) dextrose; and may also contain an antioxidant such as tryptamine and a stabilizing agent such as Tween 20.

In another embodiment, the anti-CD19 maytansinoid immunoconjugate is administered intravenously. However other mode of parenteral administration can be used: e.g. intramuscular, intraperinoneal or subcutaneous.

When the anti-CD19 maytansinoid immunoconjugate is administered intravenously it can be administered as a bolus or by continuous infusion over a period of time that is typically comprised between 10 minutes and 4 hours.

In another embodiment, they are injected by intramuscular, subcutaneous, intra-articular, intrasynovial, intratumoral, peritumoral, intralesional, or perilesional routes, to exert local as well as systemic therapeutic effects. They can be also administered by nebulisation.

The anti-CD19 maytansinoid immunoconjugate may be administered in a variety of forms. These include for example liquid, semi-solid, and solid dosage forms, but the form depends on the intended mode of administration and therapeutic application. Typical compositions are in the form of injectable or infusible solutions.

Sterile compositions for parenteral administration can be prepared by incorporating the anti-CD19 maytansinoid immunoconjugate in the required amount in the appropriate solvent, followed by sterilization by microfiltration. As solvent or vehicle, there may be used water, saline, phosphate buffered saline, dextrose, glycerol, ethanol, and the like, as well as a combination thereof. In many cases, it will be preferable to include isotonic agents, such as sugars, polyalcohols, or sodium chloride in the composition. These compositions may also contain adjuvants, in particular wetting, isotonizing, emulsifying, dispersing and stabilizing agents. Sterile compositions for parenteral administration may also be prepared in the form of sterile solid compositions which may be dissolved at the time of use in sterile water or any other injectable sterile medium.

The anti-CD19 maytansinoid immunoconjugate may be administered with a further therapeutic agent, such a chemotherapeutic agent, as necessary for the particular disorder being treated. Preferably, the anti-CD19 maytansinoid immunoconjugate and the supplementary active agent will have complementary activities that do not adversely affect each other.

Such a chemotherapeutic agent may be administered simultaneously, semi-simultaneously, separately, or spaced out over a period of time so as to obtain the maximum efficacy of the co-administration; it being possible for each administration to vary in its duration from a rapid administration to a continuous perfusion.

The man skilled in the art may refer in particular to EP1651162 to carry out the present invention.

Figures

Figure 1: structure of the HuB4-DM4 conjugate SAR3419.

Figure 2: treatment response by dose level .

Figure 3: treatment response by histology.

Figure 4: tumor shrinkage over time at the MTD.

The following example illustrates a combination according to the invention.

EXAMPLE 1: HuB4-DM4 conjugate administered weekly in Patients With Relapsed/Refractory CD19-positive B-cell Non-Hodgkin's Lymphoma (study TED6829)

STUDY OBJECTIVES

Primary:

. To determine the maximal tolerated dose (MTD) of SAR3419 according to the Dose Limiting Toxicities (DLTs) observed when administered IV, as a single agent, once weekly in patients with relapsed or refractory B-cell NHL.

Secondary:

. To characterize the global safety profile of SAR3419

. To evaluate the pharmacokinetic (PK) profile of SAR3419

. To perform pharmacodynamic (PD) assessments

. To assess the potential immunogenicity of SAR3419

. To assess preliminary evidence of anti-lymphoma activity

METHODS

Study design

. Adult patients with refractory or relapsed B-cell NHL expressing the CD19 antigen were enrolled.

. Dose escalation was based on safety in a 3+3 design.

. The dose-escalation was guided by the occurrence of pre-defined DLT during the initial 3 week period of treatment. Late or cumulative toxicities during the treatment period could also be considered for defining the recommended dose.

. SAR3419 Drug Product was available as a solution for infusion at 25 mg / 25 mL (1 mg/mL) with reference to the active entity supplied in a 30 mL clear glass vial.

. SAR3419 as single agent was administered IV once weekly for 8 doses. Any further treatment that may be of clinical benefit for the patient could be discussed and agreed between the investigators and the sponsor.

. Premedication with diphenhydramine 50mg IV and acetaminophen 650 mg per os was required prior to each infusion.

Evaluations

. Computed Tomography (CT) and / or Positron Emission Tomography (PET) scan performed at study entry, after 8 doses and 42-49 days after the last treatment (EOT). Responders were followed every 3 months for up to 1 year.

. PK and immunogenicity assessments were performed using blood samples collected at baseline, at specific time-points during the treatment and at EOT.

RESULTS

The results are summarized in the following tables 1-7.

Table 1: Baseline Demographics and Disease Characteristic

	N	
Treated Dose escalation / dose expansion	44 28 / 16	
Evaluable for safety	44	
Evaluable for response	43	
Age, median (range)	67 (36-82)	
Male / Female	30/14	
Histology	Initial diagnosis	Study entry*
FL	19 (43%)	15 (34%)
DLBCL	16 (36%)	17 (39%)
MCL, MZL, SLL, mixed	3, 4, 1, 1	4, 0, 1, 1
Stage III/IV at study entry	39 (89%)	
Median number of prior regimens	3 (1-8)	
Patients with prior rituximab therapy	43 (98%)	
Patients with rituximab resistant disease	21 (48%)	
Prior stem cell transplant autologous / allogeneic	18 (41%) / 1 (2%)	

* 6 missing histologies at study entry.

Table 2: Dose escalation

Dose level (mg/m^2/week)	Patients enrolled (intented dose)	Patients enrolled (actual dose)***	Patient with predefined DLT	
			Predefined DLT period	Treatment period
< 10		1	0	0
10	3	3	0	0
14	3	3	0	0
20	4	4	0	0
28	3	3	0	0
40	3	5	0	0
55 **	22	21	0	0
70	6	4	1*	1*

* 1 patient had a DLT after 2 doses: grade 3 neutropenia leading to a 2 week-dose delay.

2 patients treated at 70mg/m2 had late (>5 doses) grade 2 significant toxicities: blurred vision associated with corneal deposits and left bundle branch block which were taken into account for dose escalation.

** The study defined 55mg/m2 as the MTD/RD (Recommended Dose).

*** One investigative site mistakenly did not flush the IV line at each study drug infusion. A 18ml-dead volume of the preparation corresponding to 18mg of study drug was not administered. Eight patients that were enrolled at this site were retrospectively reassigned to their actual dose level. Study results are provided based on the actual dose level.

Table 3: Non heamotological Related TEAE grade 3-4

Adverse Events*	Dose Levels (mg/m^2/week)							
	< 10 (n=1)	10 (n=3)	14 (n=3)	20 (n=4)	28 (n=3)	40 (n=5)	55*** (n=21)	70 (n=4)
Increased gamma-glutamyltransferase							1	
Cholestasis	1					1		
Optic neuropathy							1**	
Paresthesia							2	
Lobar pneumonia							1**	
Alveolitis allergic							1**	
Progressive multifocal leukoencephalopathy			1**					

* Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version3.

** A total of 5 related SAE were reported, with 4 being of grade 3-4.

*** At the MTD, 2 patients of the expansion cohort had reversible grade 3 toxicities after 6-8 weekly doses: optic neuropathy and paresthesia. These late and cumulative toxicities were considered for amending the study protocol in July 2010 and modifying the administration schedule.

Table 4: Hematological toxicity grade 3-4

Laboratory raw data	Dose Levels (mg/m^2/week)							
	< 10 (n=1)	10 (n=3)	14 (n=3)	20 (n=4)	28 (n=3)	40 (n=5)	55 (n=21)	70 (n=4)
Neutropenia	1	1		1			3	1
Leukopenia	1						3	1
Thrombocytopenia							3	
Anemia							5	

Table 5: Related Ocular toxicity

	Dose Levels (mg/m^2/week)							
	< 10 (n=1)	10 (n=3)	14 (n=3)	20 (n=4)	28 (n=3)	40 (n=5)	55 (n=21)	70 (n=4)
Eye disorders grade 1-2*			1			1	6	1
Eye disorders grade 3**							1	

* include blurred vision (5), dry eye (3), conjunctivitis (1), diplopia (2), eye irritation (1), corneal deposits (1), keratitis (1), keratoconjunctivitis (1), scotoma (1)

** Optic neuropathy (with associated grade 3-4 symptoms blurred vision and eye irritation) is the unique ocular toxicity of grade > 2 reported within the study.

Table 6: Anti-lymphoma activity

ORR (CR/PR) at « active doses » *(>10mg//m^2)*	12 / 40 (30%)
Response rate at MTD	7 / 21 (33%)
NHL subtypes at study entry DLBCL FL	 5 / 15 6 / 15
Response duration (weeks)	[5; 55+]*

- 3 patients still responding at the study cut-off date

Table 7: Median (CV% or Min-Max) SAR3419 plasma pharmacokinetic parameters observed after repeated administration of SAR3419 (8-12 doses) in the weekly schedule

Treatment	10 mg/m²	14 mg/m²	20 mg/m²	28 mg/m²	40 mg/m²	55 mg/m²	70 mg/m²
N	1	3	3	3	3	16	1
Week of Treatment (week)	8	8 (8-8)	8 (8-8)	8 (8-8)	12 (8-12)	8 (8-12)	8
Dose (mg/m²)	4.6	14.0 (14.0-16.9)	19.6 (19.6-20.0)	28.2 (27.2-30.4)	45.1 (40.0-45.1)	55.2 (53.2-61.9)	70.5
C_{max} (µg/mL)	2.01	11.4 (30)	14.2 (31)	22.8 (31)	35.3 (30)	47.4 (33)	94.7
t_{max} (day)	0.03	0.03 (0.02-0.06)	0.02 (0.02-0.19)	0.04 (0.03-0.05)	0.06 (0.04-3.89)	0.07 (0.06-1.00)	0.07
t_{last} (day)	15.01	23.0 (22.0-42.0)	42.8 (14.80-48.11)	21.0 (6.89-38.9)	41.9 (6.89-43.95)	20.0 (2.93-48.0)	48.0
AUC_{0-7} (day.µg/mL)	8.07	50.7 (31)	67.3 (44)	84.6 (65)	155 (30)	219(44)	298
$T_{1/2z}$ (day)	5.46	8.72 (9)	13.5 (70)	5.28 (73)	9.8(1)	7.93 (47)	13.0
CLss (L/day)	1.12	0.58 (34)	0.817 (0.435-1.20)	0.79 (75)	0.60 (0.507-0.32	0.32 (49)	0.442
Vss (L)	0.14	5.94 (1)	6.12 (5.96-6.29)	2.20 (95)	3.32 (0.04-6.55)	1.91 (66)	5.03

CONCLUSIONS

Using weekly schedule of SAR3419 for 8 -12 doses, the maximum tolerated dose is 55 mg/m²/week.

. SAR3419 demonstrates encouraging activity in both indolent and aggressive NHL with an ORR of 33% at the MTD.

. Tumor shrinkage was observed in 25 (58%) patients.

. Globally SAR3419 is well tolerated with a median number of doses per patient of 8 overall, and a median relative dose intensity of 0.96 at the MTD. Noteworthy is the lack of significant myelosuppression, making SAR3419 an appealing ADC to be combined with conventional chemotherapy.. .In the weekly schedule, the ocular toxicity (all

grades) is 22% (2% grade 3/4) whereas in the 3 weeks administration regimen the ocular toxicity (all grades) was 43.5% with 15.4% of grade 3/4.

. Paired pre- and post-treatment biopsies allowed to show DM4 accumulation in tumors decrease in CD19 protein expression level and mitosis blockade confirming the mechanism of action of the drug.

. Based on the clinical evidence of two grade 3 toxicities (optic neuropathy and paresthesia) with late onset supported by PK data showing drug accumulation after weekly dosing, the protocol was amended to evaluate an optimized schedule consisting of 4 weekly doses of 55 mg/m² followed by 4 additional doses administered once every 2 weeks.

EXAMPLE 2: HuB4-DM4 conjugate administered weekly and then bi-weekly (qw/q2w schedule) in Patients With Relapsed/Refractory CD19-positive B-cell Non-Hodgkin's Lymphoma (amended clinical trial of study TED6829)

Based on the clinical evidence of two late toxicities with late onset supported by PK data showing that steady state is reached after 3-4 weeks of treatment, the protocol described in EXAMPLE 1 was amended to evaluate an optimized schedule consisting of 4 weekly doses of 55 mg/m² followed by 4 additional doses administered once every 2 weeks (ongoing).

The STUDY OBJECTIVES and METHODS are identical to EXAMPLE 1, except that SAR3419 as single agent was administered IV under a schedule consisting of 4 weekly doses followed by 4 bi-weekly doses at the RD.

Furthermore the SAR3419 Drug Product was available as a concentrate solution for infusion at 125 mg / 25 mL, i.e.5 mg/ml with reference to the active entity supplied in a 30 mL clear glass vial.

The study of EXAMPLE 1 was extended to treat 25 patients with the optimized schedule.

RESULTS

The results are summarized in the following tables 8-12.

Table 8: Baseline Demographics and Disease Characteristic

	N	
Treated	25	
Evaluable for safety *	25	
Evaluable for response *	25	
Eligible for exploratory biomarkers sub-study (biopsy at study entry)	13	
Age, median (range)	70 (37-85)	
Male / Female	12/13	
ECOG PS (0/1/2)	13/9/3	
Histology	Initial diagnosis	Study entry
FL	6 (24%)	7 (28%)
DLBCL	11 (44%)	9 (38%)
MCL, MZL, other	2, 1, 5	2, 2, 5
Ann Arbor stage III/IV at study entry	24 (96%)	
Median number of prior chemotherapy regimens (range)	2 (1-8)	
Patients with prior rituximab-based therapy	24 (96%)	
Patients refractory** to last regimen	7 (28%)	
Last regimen containing rituximab	3	
Prior stem cell transplant autologous	9 (38%)	

* 4 patients were mistakenly underdosed and received 40mg/m^2; 21 patients did actually receive the planned dose 55mg/m^2

* * Refractory status = progressive under treatment or within 6 months after the end of treatment

Table 9: Clinical AE per patient (>10%), whatever the relationship to the study drug (N=25)

	All grades*	Grades 3-4**
Asthenia	7 (28.0%)	1
Diarrhoea	4 (16.0%)	1
Abdominal pain / upper	4 (16.0%)	-
Nausea	3 (12.0%)	-
Constipation	3 (12.0%)	-
Bronchitis	3 (12.0%)	-
Pyrexia	3 (12.0%)	-
Myalgia	3 (12.0%)	-

* reversible grade 1 blurred vision and grade 1 paresthesia were reported in 1 patient each.
** Other gr 3-4 reported in the study (1 event each): uveitis, pyelonephritis, myocardial infarction, lymphoedema.

Table 10: Haematological toxicity (N=25)

Laboratory raw data	All grades	Gr 3	Gr 4
Leukopenia	18	2 (1)*	1
Neutropenia	12	3 (2)*	3 (2)*
Anemia	23	1	-
Thrombocytopenia	16	3 (2)*	1 (0)*

* 2 patients received further anticancer therapy without being censored for haemotological reporting. 1 patient was deviant at study entry and included with grade 3 neutropenia/leukopenia.

Table 11: Anti-lymphoma activity of the qw/q2w schedule

ORR (CR/PR)	7 / 25 (28%) including 3 CRu*
ORR in DLBCL subtype	3 / 9 (33%)
Tumor shrinkage	64%
Response duration (weeks)	[8; 35+]** to be updated

* 1 CRu in a patient refractory to last regimen
** x patients still responding at the study cut-off date

Table 12: Mean (CV%) SAR3419 PK parameters after the first and the last SAR3419 dose

	N	t_{max} *a* (day)	C_{max} (µg/mL)	$AUC_{0-\tau}$ *b* (µg.day/mL)	C_{avg} (µg/mL)	CL_{ss} (L/day)	V_{ss} (L)	$t_{1/2Z}$ (day)
1st SAR3419 administration	20	0.06 [0.04-0.24]	28.6 (19)	107 (22)	15.3 (22)	NA	NA	NA
Last SAR3419 administration (5^{th} to 12^{th} administration)	9	0.06 [0.06-0.22]	41.6 (26)	260 (31)	18.6 (31)	0.438 (56)	4.34 (28)	7.99 (27)

Cmax : maximum observed concentration ; tmax : fist time to reach Cmax ; AUC : area under concentration versus time curve ; Cavg : average concentration over the dosing interval ; CLss : clearance at steady state ; Vss : volume of distribution at steady state ; t1/2z : terminal elimination half-life.

a : Median [min-max] , *b*: τ corresponds to the dosing interval (7 days and 14 days after the 1^{st} and the last administration, respectively) ; NA: Not applicable

CONCLUSIONS

Median number of doses received was 8 as planned with a median relative dose intensity of 1.0 [0.8-1.0] at the RD.

The most frequent related TEAEs were asthenia in 5 (23.8%) patients (1 event being of grade 3) and gastrointestinal disorders in 7 (33%) patients. Reversible grade 1 blurred vision / corneal event occurred in 1 patient. Grade 3-4 haematological toxicities were minimal.

Tumor shrinkage was observed in 16 (64%) patients. Seven (28%) patients, achieved an objective response including 1 CR and 3 Complete Response (CRu). The response rate was essentially preserved in aggressive disease (3/9 DLBCL patients).

In conclusion the schedule consisting of 4 weekly doses followed by 4 bi-weekly doses shows an improved safety profile compared to prior tested schedules, with a clinical efficacy preserved essentially in aggressive lymphoma.

OVERALL CONCLUSIONS

SAR3419 MTD/RD was determined during this study as 55 mg/m² (maximum tolerated dose) whilst the maximum administered dose (MAD) was 70 mg/m².

The optimized administration schedule (55 mg/m² weekly/biweekly) showed an improved safety profile compared to prior tested schedules with apparent clinical control of the incidence and severity of ADC (corneal) / DM4 (neuro-, digestive and hematological) related-toxicities.

Anti lymphoma activity was observed in both schedules of administration, around 30% of patients at the 55 mg/m² MTD/RD, especially in patients with aggressive histology (DLBCL) at that dose in the weekly/biweekly recommended schedule of administration.

CLAIMS

1. A method of treating CD19+ B-cell malignancies symptom in a patient in need thereof, said method comprising administering to said patient therapeutically effective amounts of anti-CD19 maytansinoid immunoconjugate.

2. A method according to claim 1 wherein the immunoconjugate is administered with a dose regimen reducing the toxicity resulting from the treatment.

3. A method according any one of claims 1 and 2 wherein the toxicity is an ocular toxicity resulting in eye related adverse events.

4. A method according to claim 3 wherein the occurrence all grades of eye related adverse events is below 40 %.

5. A method according to claim 3 wherein the occurrence of eye related adverse events grade 3 or 4 is below 13 %.

6. A method of treating CD19+ B-cell malignancies symptom in a patient in need thereof, said method comprising the steps of administering to the patient an initial dose of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate; and administering to the patient a plurality of subsequent doses of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate, wherein the subsequent doses are separated in time from each other by about one week.

7. A method according to claim 6 wherein the administration of the initial dose is followed by the administration of at least 6 doses separated in time from each other by about one week.

8. A method according to any one of claims 6 and 7 wherein the administration of the initial dose is followed by the administration of between 6 and 14 doses separated in time from each other by about one week.

9. A method according to any one of claims 6 and 7 wherein said method comprises the steps of:

    - administering to the patient an initial dose of about 55 mg/m², of the anti-CD19 maytansinoid immunoconjugate, and

- administering to the patient at least 6 subsequent doses of about 55 mg/m² separated in time from each other by about one week of the anti-CD19.

10. A method according to claim 6 wherein said method comprises a further step of administration of subsequent doses of about 55 mg/m² of anti-CD19 maytansinoid immunoconjugate wherein the doses are separated in time from each other by about two weeks.

11. A method according to any one of claims 6 and 10 wherein said method comprises the steps of:
    - administering to the patient an initial dose of about 55 mg/m², of the anti-CD19 maytansinoid immunoconjugate,
    - administering to the patient at least 3 subsequent doses of about 55 mg/m² separated in time from each other by about one week of the anti-CD19 maytansinoid immunoconjugate , and
    - administering to the patient at least 3 subsequent doses of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate separated in time from each other by about two weeks.

12. A method according to any one of claims 1 to 11 wherein said CD19+ B-cell malignancies symptom is a leukemia symptom or a lymphoma symptom.

13. A method according to claim 12 wherein said leukemia symptom is Non-Hodgkin's lymphoma symptom (NHL) symptom.

14. A method according to claim 12 wherein said lymphoma symptom is Acute lymphoblastic leukemia (ALL) symptom.

15. A method according to claim 13 wherein said Non-Hodgkin's lymphoma symptom is a Diffuse Large B-cell lymphoma (DLBCL), a folicullar lymphoma (FL), a Mantle cell lymphoma (MCL), a Marginal zone lymphoma (MZL), a Small lymphocytic lymphoma (SLL) or a Waldenström macroglobulinemia (WM).

16. A method according to claim 13 wherein said Non-Hodgkin's lymphoma symptom is a relapsed or refractory B-cell non-Hodgkin's lymphoma.

17. A method according to claim 13 wherein said Non-Hodgkin's lymphoma symptom is a B-cell non-Hodgkin's lymphoma expressing CD19.

18. A method according to claim 13 wherein said patient has already been treated for the Non-Hodgkin's lymphoma symptom.

19. A method according to claim 13 wherein said patient has failed rituximab therapy.

20. A method according to claim 13 wherein said Non-Hodgkin's lymphoma symptom is a rituximab resistant disease.

21. A method according t to claim 13 wherein said patient has received an autologous or allogeneic stem cell transplant.

22. A method according to any one of claims 1 to 21 wherein the anti-CD19 maytansinoid immunoconjugate is administered intravenously.

23. A method according to any one of claims 1 to 22 which is safe and effective.

24. A method according to any one of claims 1 to 23 which further comprises administering simultaneously or sequentially an effective amount of a chemotherapeutic agent.

25. A method according to any one of claims 1 to 24 wherein the anti-CD19 maytansinoid immunoconjugate comprises an antibody which binds specifically to the CD19 antigen conjugated to a cytotoxic of the maytansinoid family.

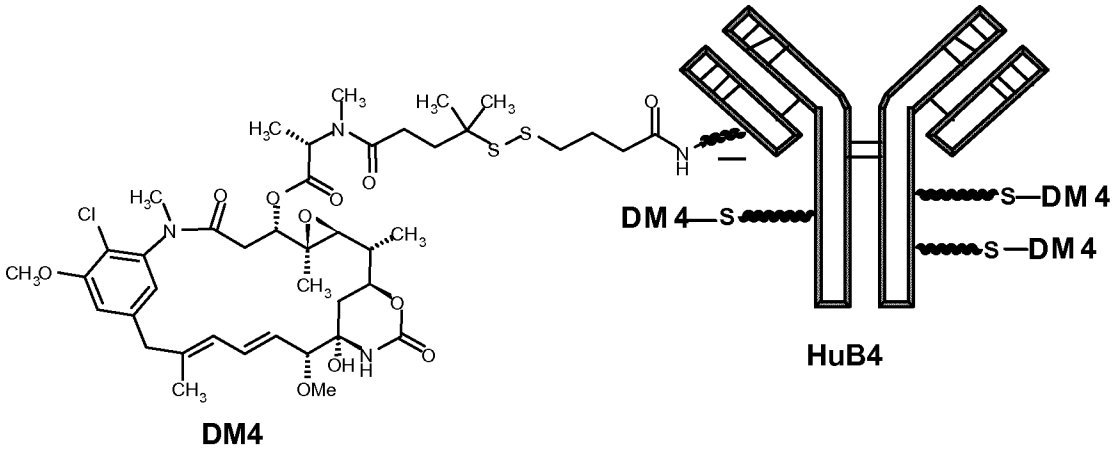
26. A method according to any one of claims 1 to 25 wherein the anti-CD19 maytansinoid immunoconjugate comprises an antibody which binds specifically to the CD19 antigen conjugated to DM4.

27. A method according to any one of claims 1 to 26 wherein the anti-CD19 maytansinoid immunoconjugate comprises an antibody which binds specifically to the CD19 antigen conjugated to DM4 through a cleavable linker.

28. A method according to any one of claims 1 to 27 wherein the anti-CD19 maytansinoid immunoconjugate comprises an antibody which binds specifically to the CD19 antigen conjugated to DM4 through SPDB.

29. A method according to any one of claims 1 to 28 wherein the anti-CD19 maytansinoid immunoconjugate comprises an antibody which binds specifically to the CD19 antigen conjugated to DM4 through SPDB wherein about 3.5 molecules of DM4 are bound through the SPDB linker to each huB4 molecule.

30. A method according to any one of claims 1 to 29 wherein the anti-CD19 maytansinoid immunoconjugate has the following formula:



31. A method according to any one of claims 1 to 30, wherein the anti-CD19 maytansinoid immunoconjugate comprises an antibody and the said antibody comprises six complementary determining region (CDR), said CDR having the sequences represented in SEQ ID NOs 1 to 6.

32. A method according to any one of claims 1 to 30, wherein the anti-CD19 maytansinoid immunoconjugate comprises an antibody and the said antibody comprises a light chain, wherein the sequence of the said light chain has at least 60% identity with the sequence displayed in SEQ ID NO. 7.

33. A method according to any one of claims 1 to 30, wherein the anti-CD19 maytansinoid immunoconjugate comprises an antibody and the said antibody comprises a heavy chain, wherein the sequence of the said heavy chain has at least 60% identity with the sequence displayed in SEQ ID NO. 8.

34. A method according to any one of claims 1 to 30, wherein the anti-CD19 maytansinoid immunoconjugate comprises an antibody and the said antibody comprises a light chain and a heavy chain, said light chain having the sequence represented in SEQ ID NO. 7, and said heavy chain having the sequence represented in SEQ ID NO. 8.

35. A method according to any one of claims 1 to 30 wherein the anti-CD19 maytansinoid immunoconjugate comprises the HuB4 antibody.

36. A method according to any one of claims 1 to 30 wherein the anti-CD19 maytansinoid immunoconjugate is the HuB4-DM4 conjugate.

37. A method according to any one of claims 2 to 30 wherein the dose regimen reduces the toxicity resulting form the treatment with the HuB4-DM4 conjugate.

38. Anti-CD19 maytansinoid immunoconjugate for treating a human patient diagnosed with a CD19+ cell malignancy symptom with a method comprising the steps of administering to the patient an initial dose of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate; and administering to the patient a plurality of subsequent doses of about 55 mg/m², of the anti-CD19 maytansinoid immunoconjugate, wherein the subsequent doses are separated in time from each other by about one week.

39. Anti-CD19 maytansinoid immunoconjugate for treating a human patient diagnosed with a CD19+ cell malignancy symptom with a method comprising the steps of administering to the patient an initial dose of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate; and then administering to the patient a plurality of subsequent doses of about 55 mg/m², of the anti-CD19 maytansinoid immunoconjugate separated in time from each other by about one week, and in a further step administeriong plurality of subsequent doses of about 55 mg/m² of the anti-CD19 maytansinoid immunoconjugate separated in time from each other by about two weeks.

40. An article of manufacture comprising:

a) a packaging material

b) an anti-CD19 maytansinoid immunoconjugate, and

c) a label or package insert contained within said packaging material indicating that said anti-CD19 maytansinoid immunoconjugate is administered to the patient at an initial dose of about 55 mg/m², and in a plurality of subsequent doses separated in time from each other by about one week in an amount that is about 55 mg/m².

41. An article of manufacture comprising:

a) a packaging material

b) an anti-CD19 maytansinoid immunoconjugate, and

c) a label or package insert contained within said packaging material indicating that said anti-CD19 maytansinoid immunoconjugate is administered to the patient at an initial dose of about 55 mg/m², then in a plurality of subsequent doses separated in time from each other by about one week in an amount that is about 55 mg/m² and then in a plurality of subsequent doses separated in time from each other by about two weeks in an amount that is about 55 mg/m².

42. An article of manufacture comprising:

a) a packaging material

b) an anti-CD19 maytansinoid immunoconjugate, and

c) a label or package insert contained within said packaging material indicating that said anti-CD19 maytansinoid immunoconjugate is administered to the patient at a dose of about 55 mg/m² to minimize the risks of toxicity

43. An article of manufacture according to claim 42 wherein the occurrence of eye related adverse events (all grades) is below 40 %.

44. An article of manufacture according to claim 42 wherein the occurrence of eye related adverse events grade 3/4 is below 13 %.