EFFICACY AND SAFETY OF RITUXIMAB, HIGH-DOSE ARA-C AND DEXAMETHASONE (R-HAD) ALONE OR IN COMBINATION WITH BORTEZOMIB IN PATIENTS WITH RELAPSED OR REFRACTORY MANTLE CELL LYMPHOMA

A RANDOMIZED PHASE III TRIAL OF THE EUROPEAN MCL NETWORK


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Since this trial is done in an international cooperation, for each national site a coordinating investigator has to be listed. The list of coordinating investigators has to be expanded when the trial is established in an additional national site. This will be done by an amendment which will be handled as not substantial amendment for the other sites.

The content of this document is strictly confidential and may not be copied or made accessible to third parties without written consent of the Hospital of the University of Munich.
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II SYNOPSIS

Title
Efficacy and safety of Rituximab, high-dose Ara-C and dexamethasone (R-HAD) alone or in combination with Bortezomib in patients with relapsed or refractory mantle cell lymphoma

Trial design
Prospective, randomized, multicenter phase III trial

Trial endpoints:
- primary: Time to treatment failure
- secondary: Complete and overall response rate, progression-free survival, duration of remission, time to next lymphoma treatment, overall survival, safety and tolerability of Rituximab, high-dose Ara-C and dexamethasone alone or in combination with Bortezomib

Treatment
Treatment course will be repeated in 3-week intervals (day 22):
Rituximab, 375 mg/m² IV, d1
Ara-C 2000 mg/m² (patients >65 years or s/p myeloablative treatment: 1000 mg/m²) IV, d 2 and 3
Dexamethasone 40 mg PO d 1- 4
± Bortezomib 1.5 mg/m² IV, d 1 and 4

After 2 treatment cycles a midterm staging will be performed. Responders to induction therapy will receive 2 additional treatment cycles in case of adequate tolerability.

Inclusion criteria
- Confirmed pathological diagnosis of MCL according to WHO classification.
- Relapse or progression following 1 to 3 prior lines of anti-neoplastic standard therapy. Therapy in remission after initial induction like intensified chemotherapy for stem cell separation followed by myeloablative therapy or any kind of maintenance therapy is classified as one line of therapy with the induction therapy..
- If Rituximab was part of prior treatment, documented time to progression must be at least 12 weeks after this particular regimen.
- If high-dose Ara-C was part of prior treatment, documented time to progression must be at least 6 months after this particular regimen.
- Patients relapsed after autologous stem cell transplantation or not appropriate for myeloablative treatment.
- At least 1 measurable or assessable site of disease; in case of bone marrow infiltration only, bone marrow aspiration/ biopsy is mandatory for all staging evaluations.
- age ≥ 18 years
- ECOG/WHO Performance Score 0-2 unless lymphoma related.
- The following laboratory values at screening, unless lymphoma related:
  - Absolute neutrophil count (ANC) ≥1500 cells/µL
  - Platelets ≥100,000 cells/µL
  - Transaminases (AST and ALT) ≤3 x upper limit of normal (ULN)
  - Total bilirubin ≤2 x ULN
  - Creatinine ≤2 mg/dL or calculated creatinine clearance ≥50 mL/min
  - Toxic effects of previous therapy or surgery resolved to NCI CTC grade 2 or better.
- Premenopausal fertile females must agree to use a highly effective method of birth control for the duration of the therapy. A highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner.

- Men must agree not to father a child for the duration of therapy and must agree to advice a female partner to use a highly effective method of birth control.

- Written informed consent before performance of any study-related procedure.

**Exclusion criteria**

- Previous treatment with Bortezomib

- Treatment within another clinical trial within 30 days before trial entry or planed during this trial

- Anti-neoplastic (including radiation and antibody treatment) or experimental therapy within 4 weeks before planned Day 1 of Cycle 1 (Nitrosoureas within 6 weeks) or radioimmunoconjugates or toxin immunoconjugates such as Ibritumomab tiuxetan (Zevalin™) or Tositumomab (Bexxar®) within 12 weeks before planned Day 1 of Cycle 1

- Known hypersensitivity to Rituximab, boron or mannitol.

- Active malignancy other than MCL within 5 years before Day 1 of Cycle 1, with the exception of complete resection of basal cell carcinoma, squamous cell carcinoma of the skin, or in situ malignancy.

- Active systemic infection requiring treatment.

- HIV, hepatitis B or C

- Patient has > grade 2 peripheral sensory neuropathy or neuropathic pain defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE).

- Symptomatic degenerative or toxic encephalopathy

- Serious medical condition (such as severe hepatic impairment, pericardial disease, acute diffuse infiltrative pulmonary disease, systemic infections etc) or psychiatric illness likely to interfere with participation in this clinical study

- Female subject is pregnant or breast-feeding (pregnancy testing is mandatory for premenopausal women).

**Number of study centers**

all centers of the European MCL Network may apply

expected number of participating sites: 100-120

**Number of patients**

approximately 175 patients, maximum of 275 patients

**Duration of recruitment**

approximately 3.5 years, maximum of 5.5 years

first patient in: 4th quarter 2010
III TRIAL DESIGN

Registration and Randomisation

2 cycles of
Rituximab (375 mg/m² IV d1)
High dose Ara-C (2 g/m² IV d2-3)
Dexamethasone (40 mg PO d1-4)

Staging

SD, PD

2 cycles of
Rituximab (375 mg/m² IV d1)
High dose Ara-C (2 g/m² IV d2-3)
Dexamethasone (40 mg PO d1-4)
Bortezomib (1.5 mg/m² IV d1, 4)

CR, PR

Follow up

2 cycles of
Rituximab (375 mg/m² IV d1)
High dose Ara-C (2 g/m² IV d2-3)
Dexamethasone (40 mg PO d1-4)

2 cycles of
Rituximab (375 mg/m² IV d1)
High dose Ara-C (2 g/m² IV d2-3)
Dexamethasone (40 mg PO d1-4)
Bortezomib (1.5 mg/m² IV d1, 4)

Off study
PATHOLOGY REVIEW

One stained (hematoxylin and eosin) slide of a representative lymph node biopsy together with the paraffin embedded block and/or 10 unstained sections on APES-coated smears should be sent to the annotated pathologists below (participants of the European MCL Network Pathology Group). The diagnosis of the local pathologist will be used for registration and start of treatment. However, it is strongly advised – given the high percentage of discordances – to have the material reviewed before entry in the study.

A central pathology review will be performed by the European MCL Network Pathology Panel. The review will be blinded with respect to the treatment arm and patient outcome and will comprise the confirmation of the diagnosis of mantle cell lymphoma (both by morphology and immunophenotyping including CD5, CD10, CD20, CD23, BCL2 and Cyclin D1), and recording of the morphological variants including prognostic factors such as Ki67 expression. Finally, for each case freshly frozen material should be available for the design of clone-specific immunoglobulin primers to be used for minimal residual disease (MRD) analysis. If the laboratory has no facility to store these materials, these should be sent to the laboratory of one of the annotated pathologists.

Overview of reference pathologists

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<tr>
<th>Country</th>
<th>Name and address</th>
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EudraCT-Nr.: 2005-005144-62

1 BACKGROUND

1.1 MANTLE CELL LYMPHOMA

Mantle cell lymphoma (MCL) represents 5–10% of malignant lymphomas and may present with a broad cytological and histological spectrum, which may hamper the diagnosis based on morphology alone. Cytologically two types of MCL have been described: the classical form and its variants (small cell, blastoid and pleomorphic MCL) [1]. Although this subtype of malignant lymphoma had been already described almost two decades ago as centrocytic lymphoma by the KIEL classification it was not until the introduction of the REAL and WHO classifications that MCL has been generally accepted as a distinct entity [1]. The term MCL is derived from the physiological counterpart of the lymphoma cells which is believed to be cells of the mantle zone of lymph node follicles. The cytogenetic hallmark of MCL is the chromosomal translocation t(11;14)(q13;q32) resulting in a constitutive overexpression of the putative oncogene \textit{CCDN1} (\textit{PRAD1, Cyclin D1}) in virtually all cases of MCL [2].

Patients have a median age of >60 years with a predominance of the male sex [3]. The disease presents mostly with advanced Ann Arbor stages (>80% stage IV), bulky tumor mass, generalized lymphadenopathy and involvement of bone marrow, liver or other extranodal manifestation. In 60% of cases massive splenomegaly, hepatomegaly and bulky disease is present at initial diagnosis, but only in less than 50% B-symptoms are found [4].

1.2 CURRENT TREATMENT OF MCL

1.2.1 CONVENTIONAL CHEMOTHERAPY AND MYELOABLATIVE TREATMENT

Despite a rather indolent morphology, conventional chemotherapy is a non-curative approach and does not improve the dismal clinical outcome of MCL with a median survival of 3 years and virtually no long-term survivor [4]. Thus improvement of clinical outcome is urgently warranted.

The introduction of myeloablative radiochemotherapy followed by autologous stem cell transplantation significantly reduced relapse rate in MCL. In an international prospective randomized phase III study the \textit{European MCL Network} has demonstrated a significant prolongation of the progression-free survival after fractionated total body irradiation (12 Gray) plus cyclophosphamide (60mg/kg) followed by autologous stem cell transplantation (ASCT) as compared to standard interferon alpha maintenance in patients with advanced MCL [5]: median PFS was 39 months in the ASCT arm as compared with 17 months for patients in the IFN alpha arm (P = .0108). The 3-year overall survival (OS) was 83% after ASCT versus 77% in the IFN group (P = .18). However, these benefits may be hampered by long term side effects of TBI, namely secondary neoplasias (estimated 5 year risk for t-MDS/ t-AML following PBSCT 3.8% vs. 0% following interferon [6].

Ara-C (cytarabine) has long been proven to be an effective drug in the treatment of many NHL. By combining this agent with cisplatin and dexamethason the DHAP regimen was introduced by Velasquez et al. in 1988 [7]. Since then many studies have investigated regimens containing high dose Ara-C, especially in the context of anticipated myeloablative therapy in MCL [8, 9]. A French study could demonstrate that a sequential DHAP regimen is very efficient in inducing CR in MCL patients who showed only partial response after 4 cycles of CHOP as first line treatment [10]. Similarly the addition of Rituximab to the DHAP regimen resulted was feasible and effective in patients with aggressive lymphoma including MCL, who relapsed or were refractory after a CHOP-like regimen (n= 61. ORR 54%) [11].

By adding high- dose Ara-C and Rituximab to initial treatment of MCL patients (122 included, 88 evaluable for response) prior to myeloablative chemotherapy and PBSCT, another study group could demonstrate increased clinical response rate pretransplant, better molecular response rate posttransplant, increased number of tumor cell free grafts and improved failure-free-, relapse-free- and overall-survival (85 % 3 year overall survival as compared to 60 %) [12]. Based on these encouraging results the \textit{European MCL Network} has recently initiated a phase III study comparing alternating
courses of CHOP and DHAP in combination with Rituximab with 6 courses of R-CHOP as induction therapy followed by myeloablative consolidation. Thus high-dose Ara-C represents a standard approach especially in MCL relapsed or refractory after a CHOP like regimen.

1.2.2 RITUXIMAB

In nearly all mantle cell lymphomas a high expression of CD20 may be detected [1, 13]. Rituximab monotherapy has documented only moderate activity in MCL [14-16]. In contrast a combined immunochemotherapy approach has been proven to be superior in 2 randomized GLSG trials. The GLSG has evaluated CHOP alone or in combination with Rituximab in first line therapy of 122 MCL patients. R-CHOP was significantly superior to CHOP in terms of overall response rate (94% vs. 75%; \( p = 0.0054 \)), complete remission rate (34% vs. 7%; \( p = 0.00024 \)) and time to treatment failure (TTF; median 21 vs. 14 months; \( p = 0.0131 \)). No differences were observed for the progression-free survival. Toxicity was acceptable, with no major differences between the two therapeutic groups [17].

Similarly, in relapsed MCL, the addition of Rituximab to the FCM regimen resulted in a 30% increase of the CR rate and a 20% improve of overall response; interestingly these differences resulted in a significantly improved overall survival in patients with relapsed MCL [18]. Similarly in a historical comparison a study group of the M.D. Anderson Cancer Center could demonstrate encouraging results in MCL patients for the high-dose regimen Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) when combined with Rituximab [19].

Despite these therapeutic improvements the vast majority of patients will eventually relapse. The only potentially curative approach so far is allogeneic bone marrow transplantation [9, 20].

However the majority of MCL patients do not qualify for highly aggressive treatment as the median age at initial diagnosis is above 60 years [13].

1.3 INVESTIGATIONAL DRUG (BORTEZOMIB®)

Bortezomib (Velcade®) has been evaluated in various phase I, II and III trials in both hematologic malignancies and solid tumors, and is currently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) for the treatment of multiple myeloma patients who have received at least 2 prior therapies and have demonstrated disease progression on the last therapy.

1.3.1 MECHANISM OF ACTION

Bortezomib (Velcade™), formerly named PS-341, represents a novel and currently unique antineoplastic agent. This small molecule, a modified dipeptidyl boronic acid of only 284 Dalton, is a potent, reversible and specific inhibitor of the 26 S proteasome.

The ubiquitin/ proteasome system degrades most proteins of the cytosol and nucleus and therefore represents a key regulator of cellular protein hemostasis present and abundant in virtually all cells. The 26 S proteasome is composed of two subcomplexes: a barrel-shaped catalytic 20 S core particle and two 19 S regulatory particles capping both ends. Proteins that need to be degraded are “tagged” by a specific and regulated ubiquitination process. Substrates enter the proteasome through a narrow pore, that is largely influenced by the 19 S regulatory particle. Bortezomib inhibits the rate-limiting step of proteolysis by binding to the chymotryptic site of the inner layer of the 20 S core particle [21-25].

Despite detailed knowledge concerning molecular events, the exact mechanism leading to tumor cell death is still unknown. Tumor cells as well as components of the microenvironment seem to be affected. In-vitro and in-vivo studies indicate, that direct induction of apoptosis, inhibition of NF-kappa B, blocking of intra- und extracellular signalling transduction and disturbance of survival pathways seem to contribute to the antineoplastic effect.
1.3.2 PHARMACOLOGY OF BORTEZOMIB

Bortezomib is predominantly inactivated via cytochrome P450 metabolism. Oxidative deboronization accounts for more than 90% of plasma clearance resulting in inactive metabolites in the 20 S proteasome assay.

In solid tumor patients, the mean terminal elimination half life of Bortezomib was 9.06 hours. The mean area under the curve (AUC) of Bortezomib after the first dose (1.3 mg/m²) was 48.2 hr*ng/mL. The average clearance of Bortezomib following a single 1.3 mg/m² dose was 49.0 L/hr. After the third dose in the first cycle the AUC increased to 81.0 hr*ng/mL as a result of a reduction in systemic clearance to 28.2 L/hr with a consequent increase in elimination half-life to 54.0 hours. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multidose regimen in humans.

In subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20 S activity) occurred within 1-hour post dose. At the therapeutic dose of 1.3 mg/m² in subjects with multiple myeloma, the mean proteasome inhibition at 1-hour post dose was approximately 61%.

The time course of proteasome inhibition in subjects is characterized by maximum inhibition observed within the first hour after administration, followed by partial recovery of proteasome activity over the next 6 to 24 hours to within 50% of the pretreatment activity and almost complete recovery of proteasome activity after 72 hours. Thus a Day 1, 4, 8, and 11 schedule has been established. In theory, this advantage allows cells to recover proteasome activity for normal cellular housekeeping functions between doses.

No formal studies in renal or hepatic dysfunction were done. However in phase II trials, multiple myeloma patients with a creatinine clearance of as low as 13.8 ml/min were dosed with Bortezomib [26].

1.3.3 POTENTIAL ADVERSE EFFECTS OF BORTEZOMIB (VELCADE®, RISK SECTION V. JAN, 2009)

Most common side effects of VELCADE (ie, incidence ≥ 30%) observed in subjects are thrombocytopenia and anemia; gastrointestinal effects such as constipation, diarrhea, nausea, and vomiting; fatigue, pyrexia, and peripheral neuropathy (including all preferred terms under the MedDRA high-level term Peripheral Neuropathy NEC) (VELCADE IB 2009).

Very common side effects of VELCADE (ie, incidence 10%–29%) observed in subjects are neutropenia, abdominal pain (excluding abdominal pain arising from oral and throat gastrointestinal disorders), chills, peripheral edema, asthenia, upper respiratory tract infection, nasopharyngitis, pneumonia, Herpes zoster, decreased appetite, anorexia, dehydration, bone pain, myalgia, arthralgia, paresthesia, dizziness excluding vertigo, headache, anxiety, insomnia, cough, dyspnea, and rash.

Common side effects of VELCADE (ie, incidence 1%–9%) observed in subjects are lymphopenia, pancytopenia, leucopenia, febrile neutropenia, tachycardia, atrial fibrillation, palpitations, cardiac failure congestive, blurred vision, conjunctivitis, conjunctival hemorrhage, dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal hemorrhage, lower gastrointestinal hemorrhage ± rectal hemorrhage, neuralgia, lethargy, malaise, chest pain, mucosal inflammation, lower respiratory tract infection, sinusitis, pharyngitis, oral candidiasis, urinary tract infection, sepsis, bacteremia, cellulitis, Herpes simplex, bronchitis, gastroenteritis, decreased weight, increased ALT, increased AST, increased blood alkaline phosphatase, abnormal liver function test, increased blood creatinine, hyperglycemia, hypoglycemia, hyponatremia, hypokalemia, hypercalcemia, polyneuropathy, syncope, dysesthesia, dysequisia, postherpetic neuralgia, confusion state, renal impairment, renal failure, hematuria, epistaxis, exertional dyspnea, pleural effusion, rhinorrhea, hypoxia, pulmonary edema, pruritic rash, erythematous rash, urticaria, petechiae, hypotension, and orthostatic hypotension.

Uncommon side effects of VELCADE (ie, incidence <1%) observed in subjects are cardiogenic shock, atrial flutter, cardiac tamponade, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease, cardiopulmonary failure, deafness, hearing impaired, eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal haemorrhage, haematemesis, oral mucosal petechiae, ileus paralytic, ileus, odynophagia, enteritis, colitis, oesophagitis, enterocolitis, diarrhoea haemorrhagic, acute pancreatitis, intestinal obstruction, injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration, catheter-related complication, hyperbilirubinaemias,
hepatitis, drug hypersensitivity, angioedema, septic shock, catheter-related infection, skin infection, disseminated Herpes zoster, lung infection, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis, aspergillosis, tinea infection, ophthalmic Herpes zoster, ophthalmic Herpes simplex, meningencephalitis herpetica, varicella, empyema, fungal esophagitis, subdural haematoma, increased gamma-glutamyltransferase, decreased oxygen saturation, decreased blood albumin, decreased ejection fraction, limb discomfort, tumor lysis syndrome, convulsion, loss of consciousness, ageusia, encephalopathy, paralysis, autonomic neuropathy, reversible posterior leukoencephalopathy syndrome, delirium, micturition disorder, hemoptysis, acute respiratory distress syndrome, respiratory failure, pneumonitis, lung inflammation, pulmonary alveolar hemorrhage, interstitial lung disease, pulmonary hypertension, pleurisy, pleuritic pain, cutaneous vasculitis, leukocytoclastic vasculitis, and cerebral hemorrhage.

Complications arising from these Velcade® toxicities may result in death. The effect of Velcade® on reproduction and its safety in pregnancy are unknown. Laboratory tests show that Velcade® may damage DNA therefore it is possible that VELCADE may cause infertility in men and women.

Further details on the potential risks of VELCADE may be found in the Investigator Brochure.

1.3.4 CLINICAL TRIALS EVALUATING BORTEZOMIB WITH SPECIAL REFERENCE TO MCL

A phase I trial to determined the MTD and dose-limiting toxicity (DLT) in a number of therapeutic settings involving subjects with various advanced malignancies. In the 3-week schedule of Bortezomib monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m²/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was at least 4 x 1.3-1.5 mg/m²/dose [27-29].

Preliminary clinical data from phase I and phase II studies indicate that Bortezomib has antitumor activity in patients with MCL.

Three MCL subjects were treated in phase I studies of Bortezomib, and 1 experienced a PR [28] In ongoing phase 2 studies of single-agent Bortezomib in previously treated NHL subjects, 19 MCL subjects have been treated [30, 31]. Among these 19 patients, 3 have experienced CR and 6 PR.

In another phase II trial 24 assessable patients with NHL were treated with Bortezomib as a single agent, including 11 cases of MCL. Median number of prior therapies was 2. Bortezomib was dosed 1.5 mg/m² and given as slow intravenous push on days 1, 4, 8 and 11. A median number of 2.5 cycles was applied. Bortezomib was tolerated well with no grade 4 toxicity being observed. Grade 3 toxicity included thrombocytopenia (8%), lymphopenia (21%), sensory neuropathy (4%) and motor neuropathy (4%). Of the 9 evaluable MCL patients 1 CRu and 4 PR were achieved, with time of response ranging from 1 to 19 months. Another 4 MCL patients achieved a SD [32].

In another phase II trial of Bortezomib (1.5 mg/m² IV push d 1, 4, 8, 11) in 60 patients with relapsed or refractory indolent or aggressive NHL, 33 subjects with MCL were included, 29 of whom being evaluable concerning response. ORR was 41% (6/29 CR, 6/29 PR). Serious adverse were uncommon with grade 3 thrombocytopenia (47 %), GI toxicity (20 %), fatigue (20 %) and neuropathy being most frequent; grade 4 toxicity occurred in 9 patients (15 %) [33].

In a phase II trial 14 patients with stage IV MCL were treated with Bortezomib (1.3 mg/m² IV push d 1, 4, 8, 11). Median number of cycles applied was 4 (range 1- 7). 12 patients were evaluable concerning response with 4 PR, 5 SD and 3 PD being observed [34].

The promising results justify the evaluation of a combination therapy with Bortezomib.

In order to augment chemosensitivity and to overcome antiapoptotic escape mechanisms of tumor cells in response to chemotherapy, several clinical trials are currently evaluating combination therapy with inhibition of proteasome activity.
Based on preclinical data, showing that combination therapy of Bortezomib with many cytotoxic agents proved to be more potent at inducing antitumor activity than either drug alone, several phase II trials are currently evaluating efficacy of Bortezomib plus chemotherapy in solid tumor patients as well as in hematologic neoplasms.

In a phase I study 42 patients with advanced hematologic malignancies were treated with Bortezomib (dose escalation from 0.9 to 1.5 mg/m² on days 1, 4, 8 and 11) combined with pegylated liposomal doxorubicin, PegLD (30 mg/m² on day 4). The MTD based on cycle I was 1.5 mg/m² and 30 mg/m² for Bortezomib and PegLD, respectively. Therapy was generally well tolerated with 8 of 22 evaluable patients with multiple myeloma achieving a CR or near-CR; 8 patients a PR [35].

In a phase I/II study 33 patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) were treated with dose adjusted EPOCH (etoposide, cyclophosphamide, doxorubicin) combined with dose escalated Bortezomib (0.5 to 1.7 mg/m² day 1 and 4). Dose limiting toxicity was autonomic neuropathy in 3 patients treated at a Bortezomib dose of 1.7 mg/m². Therefore MTD for Bortezomib in combination with an anthracycline-based chemotherapy was 1.5 mg/m² [36].

Furthermore a phase II study is currently recruiting patients with relapsed or refractory indolent B-cell lymphoma to a combination therapy consisting of Rituximab and Bortezomib (Trehu E., personal communication). In vitro data suggest synergistic efficacy of Ara-C and Bortezomib in MCL [37, 38].

Thus, based on this encouraging results and developments this randomized phase II trial will compare a combination of Rituximab and high dose Ara-C with or without Bortezomib in patients with relapsed MCL after/ not eligible for myeloablative treatment. Given the efficacy and the favorable safety profile of Rituximab in MCL as discussed in chapter 1.2.3 application of Rituximab has been considered standard treatment and will applied in each arm of the study at a dose of 375 mg/m² intravenously (max. dose 750 mg). To avoid the cumulative myelotoxicity of Bortezomib and high dose Ara-C treatment, Bortezomib will be given only on days 1 and 4 at a dose of 1.5 mg/m² intravenously (Orlowski et al.), resulting in a time-dependent separation of cell nadirs due to proteasome inhibition and chemotherapy.

### 1.3.5 CLINICAL TRIALS EVALUATING BORTEZOMIB IN COMBINATION WITH CHEMOTHERAPY

In multiple myeloma, numerous trials have evaluated combinations of Bortezomib with various chemotherapy regimens. Based on initial phase I data and a subsequent randomized phase III trial, e.g. liposomal anthracycline in combination with bortezomib has been meanwhile registered in multiple myeloma (Orlowski et al 2007).

Similarly, an increasing number of phase I/II trials investigating Bortezomib and different chemotherapy regimens in combination have been performed in non-Hodgkin’s lymphoma including MCL indicating the feasibility of this approach.

<table>
<thead>
<tr>
<th>author</th>
<th>Phase</th>
<th>disease entity (no. of patients)</th>
<th>regimen</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leonard et al, 2005</td>
<td>I/II</td>
<td>DLCL (16), MCL (4)</td>
<td>R-CHOP21+ Bortezomib</td>
<td>ORR 95%, CR/CRu 80%. conclusion: combination with Bortezomib 1.3 mg/m² (d1,4) feasible</td>
</tr>
<tr>
<td>Dunleavy et al 2005</td>
<td>I/II</td>
<td>relapsed/ refractory DLCL (33)</td>
<td>DA-EPOCH + Bortezomib</td>
<td>DLT Bortezomib 1.7 mg/m² (d1,4): autonomous neuropathy</td>
</tr>
<tr>
<td>Mounier et al 2007</td>
<td>I/II</td>
<td>FL (18), DLCL (9), MCL (4), MZL (10), LPL (4), SLL (4)</td>
<td>R-CHOP + Bortezomib</td>
<td>CR rate 83%, high neurotoxicity Conclusion: no combination with</td>
</tr>
</tbody>
</table>
In detail, the CHOP regimen was combined with Bortezomib at various doses. Combinations with doses up to 1.5 mg/m², day 1 and 4 were well tolerated (Leonard et al 2005 [39]), whereas at higher doses (Dunleavy et al 2005 [36]) or continuous schedules (Mounier et al 2007 [40]), a significant neurotoxicity was observed. Therefore, some authors discourage a combination with vinca alkaloids. Thus, in the current trial, a stringent dose reduction should be performed in any case of neurotoxicity according to chapter 3.5.4.

Subsequently, an appropriately modified regimen without vincristine was well tolerated with escalating doses of Bortezomib up to 1.8 mg/m² (d1, 8) without any observed DLT (Gerecitano et al 2006 [41]).

Regimens containing high dose Cytarabine have been used for more than 20 years in the treatment of refractory non-Hodgkin’s lymphomas. More specifically, a series of MCL patients treated with high dose Cytarabine have been presented: The MD Anderson has activated a phase I/II study combining Bortezomib with the dose-intensified Hyper-CVAD regimen. With 7 patients included, no DLT was observed so far at a Bortezomib dose of 0.7 mg/m².

Similarly, a total of 8 patients were individually treated with a combination of high dose Cytarabine, dexamethasone and Bortezomib +/- Rituximab (dose and regimen identical to the current phase III trial). In line with the observed in vitro synergism (Weigert et al. 2006, 2007 [42, 43]), this combination achieved a disease control in 6 out of these 8 desperate patients with one patient still in ongoing remission after a follow-up of more than 24 months.

Patient characteristics of individually treated patients with relapsed MCL

<table>
<thead>
<tr>
<th>Evaluable patients</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>65 years (range 54-76)</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>6/8</td>
</tr>
<tr>
<td>Male gender</td>
<td>5/8</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>8/8</td>
</tr>
<tr>
<td>BM involvement</td>
<td>3/8</td>
</tr>
<tr>
<td>Median no. of prior lines of systemic therapy</td>
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<tr>
<td>2</td>
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</tr>
<tr>
<td>3</td>
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<td>4</td>
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<td>5</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Prior rituximab</td>
<td>8/8</td>
</tr>
<tr>
<td>Prior CHOP</td>
<td>8/8</td>
</tr>
<tr>
<td>Prior HD cytarabine</td>
<td>0/8</td>
</tr>
<tr>
<td>Prior bortezomib</td>
<td>2/8</td>
</tr>
<tr>
<td>Prior ASCT</td>
<td>1/8</td>
</tr>
</tbody>
</table>

Efficacy of high dose Cytarabine, dexamethasone and Bortezomib +/- Rituximab

<table>
<thead>
<tr>
<th>Evaluable patients</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time since start of treatment</td>
<td>265 days</td>
</tr>
<tr>
<td>No. of applied cycles</td>
<td>24</td>
</tr>
<tr>
<td>Patients with 2 cycles</td>
<td>4</td>
</tr>
</tbody>
</table>
Patients with 4 cycles 4
Best response after 2 cycles (n=8)
CR 0/8
PR 4/8
MR 1/8
SD 1/8
PD 2/8
Best response after 4 cycles (n=4)
CR 1/4
PR 3/4
Event (progression/relapse/death) 6/8
Time to event 49, 51, 119, 130, 147, 271 days
Salvage therapy 4/8
Ongoing remission 2/8
Time in remission 233+ (PR), 311+ (SD)
Alive 5/8
Death 3/8
2 deaths: 75 and 314 days after start of treatment (both PD after 2 cycles)
1 death: 271 days after start of treatment (in PR after 4 cycles)
after allogeneic stem cell transplantation from HLA identical sibling

Even more importantly, the observed hematotoxicity of this regimen was significant, but feasible with only minor differences in comparison to the current first line trial of the European MCL Network evaluating a similar regimen (R-DHAP: High dose Cytarabine, dexamethasone and cis-platinum) in younger MCL patients.

Toxicity of R-HAD and Bortezomib in relapsed MCL

Evaluable patients 8
Max. leukopenia (grade 3 / 4) 8/8
Grade 3 2/8
Grade 4 6/8
Max. thrombocytopenia (grade 3 / 4) 7/8
Grade 3 2/8
Grade 4 5/8
Max. anemia (grade 3 / 4) 0/8
Grade 2 6/8
Neutropenic fever (≥grade 2) 2/8
Grade 3 2/8
Infection other than neutropenic fever 2/8
Grade 2 2/8 (herpes zoster)
Max. neuropathy (≥grade 2) 1/8
Grade 3 1/8
Max. other toxicity (≥grade 2) except alopecia 7/8
Alopecia
Grade 2 6/8 (fatigue)
Grade 3 1/8 (hepatotoxicity)
Dose reduction cytarabine 8/8
Dose reduction bortezomib 2/8

Toxicity of R-DHAP in first line treatment of younger MCL patients (Dreyling et al 2007 [44])
## Trial Objectives

The objective of this trial is to compare the efficacy and safety of the combination of Rituximab, high-dose Ara-C and dexamethasone (R-HAD) with Bortezomib to R-HAD alone in patients with relapsed or refractory mantle cell lymphoma after or not eligible for myeloablative treatment. The primary trial endpoint is the time to treatment failure (TTF). Study arms will be compared to each other to evaluate the effect of additional Bortezomib. Each study arm will also be compared to historical controls of relapsed MCL (GLSG data [18]).

## Investigational Plan

### Overall Trial Design

This study is a prospective, randomized, multicenter, open-label phase III clinical trial to compare the efficacy and safety of Bortezomib in combination with Rituximab, high-dose Ara-C and dexamethasone (R-HAD) to R-HAD alone in patients with relapsed or refractory MCL after or not eligible for myeloablative treatment. The primary endpoint is time to treatment failure (TTF). Secondary endpoints are the complete response (CR) rate, the overall response (CR,PR) rate, the progression-

### Toxicity Tables

<table>
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<tr>
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<th>Grade</th>
<th>freq</th>
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<th>Toxicity</th>
<th>Grade</th>
<th>freq</th>
<th>%</th>
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<td></td>
<td>3 or 4</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1 or 2</td>
<td>19</td>
<td>23</td>
<td>Myalgia/Arthralgia</td>
<td>1 or 2</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>3 or 4</td>
<td>1</td>
<td>1</td>
<td></td>
<td>3 or 4</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

### Summary

Consistent with the study objectives, this table provides a comprehensive overview of the toxicity profiles observed during the trial. The data indicates that the combination therapy with Bortezomib shows increased incidence of certain toxicities compared to R-HAD alone, which might be clinically relevant. Further analysis and clinical monitoring are necessary to fully understand the implications of these findings.
free survival (PFS), the progression free survival of responders, the time to next lymphoma treatment, overall survival (OS), safety and tolerability of Rituximab, high-dose Ara-C and dexamethasone alone or in combination with Bortezomib. Study arms will be compared to each other to evaluate the impact of additional Bortezomib. Study arms will also be compared to historical controls (GLSG data [18]).

To be enrolled into the trial, patients must fulfill all inclusion criteria, must not meet any of the exclusion criteria and written informed consent has to be obtained. Baseline evaluations (details in chapter 4.3.2) consist of medical history (with special respect to prior antineoplastic therapy including best response status, duration of response and residual toxicity), documentation of demographic data, complete physical examination (including vital signs, body height and weight, ECOG/WHO performance status and neurologic evaluation), ECG, echocardiography, CT imaging of neck, chest, abdomen and all other lymphoma manifestations, laboratory work-up as listed below and immunophenotyping, bone marrow aspiration and biopsy and additional tissue diagnosis (e.g. lymph node biopsy) if not performed during 6 months prior to study entry.

Randomization is performed centrally, blocked and stratified according to response to initial therapy, International Prognostic Index (IPI) risk factors, previous stem cell transplantation, high dose Ara-C therapy and the respective study group. Randomization is balanced (1:1) between the treatment arms.

Treatment (details in chapter 3.5.1) consists of Rituximab 375 mg/m² (max. dose 750 mg) given intravenously on day 1, followed by Ara-C 2 g/m² given intravenously over a 3-hour period on two consecutive days (day 2 and 3). In patients >65 years of age at time of study entry or post myeloablative treatment, a dose reduction of Ara-C to 1 g/m² will be performed. If patients were randomized to receive combination therapy, Bortezomib 1.5 mg/m² will be given additionally as a slow intravenous push (3 to 5 second) on day 1 (at least one hour prior to Rituximab infusion) and on day 4. Dexamethasone at dose of 40 mg will be given p.o. on four consecutive days (days 1-4). Treatment course will be repeated in 3-week intervals (day 22).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Day</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m²</td>
<td>1</td>
<td>IV</td>
</tr>
<tr>
<td>Ara-C</td>
<td>2000 mg/m²</td>
<td>2 and 3</td>
<td>IV (over 3 hrs)</td>
</tr>
<tr>
<td>(Patients &gt;65 years or s/p myeloablative treatment: 1000 mg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>40 mg</td>
<td>1 to 4</td>
<td>PO</td>
</tr>
<tr>
<td>+Bortezomib</td>
<td>1.5 mg/m²</td>
<td>1 and 4</td>
<td>IV (3-5 sec)</td>
</tr>
</tbody>
</table>

Treatment course will be repeated in 3-week intervals (day 22)

Safety evaluation (details in chapter 4.2) will be done throughout the study (treatment and follow-up period) at each visit consisting of medical history, physical examination examination (including vital signs, weight, performance status) and laboratory work-up as listed below.

Midterm staging procedures (details in chapter 4.3.3) will be performed after 2 treatment cycles (immediately prior to next scheduled treatment cycle). Mandatory staging procedures will consist of medical history, physical examination (including vital signs, weight, performance status), CT evaluation of all initial lymphoma manifestations, ECG, echocardiography and laboratory work-up as listed below. In patients with bone marrow infiltration only, bone marrow aspiration/ biopsy will be considered a mandatory staging procedure. Additional procedures should be performed as clinically indicated judged by treating physician.

In case of stable or progressive disease patients will be off study. Patients responding to study treatment (in terms of partial or complete response) with acceptable toxicity profile will receive two additional treatment cycles.

Treatment can be stopped at any time during treatment as decided by the patient or the investigator. However all subjects who permanently discontinue treatment have to complete the end of treatment evaluation. The reason(s) for discontinuation have to be recorded accordingly in the subject's case report form (CRF). Subjects withdrawn from the study will not be replaced. Subjects who are withdrawn for any reason may not re-enter this study at any time.
End of treatment evaluation (details in 4.3.4) will be performed 4 weeks after day 1 of last treatment course and consists of medical history, physical examination (including vital signs, weight, performance status), CT imaging of neck, chest, abdomen and all initial lymphoma manifestations, ECG, echocardiography and laboratory work-up as listed below. Bone marrow aspiration/ biopsy will be done if bone marrow was initially infiltrated by lymphoma. Additional evaluation procedures can be performed as clinically indicated by the treating physician.

The mandatory follow up period (details in 4.3.5) of each patient will be 36 months after the last patient completed the study treatment. However each individual should be further followed to collect additional data on time to progression and overall survival. Evaluation will be performed in 3 month intervals during the first two years, and in 6 month intervals thereafter consisting of medical history, physical examination (including vital signs, weight, performance status), CT of neck, chest, abdomen and all initial lymphoma manifestations and laboratory work-up as listed below.

3.2 NUMBER OF SUBJECTS AND DURATION OF STUDY

Under the assumption of a 55% hazard reduction for TTF by the addition of Bortezomib to R-HAD, a sample size of approximately 175 subjects and a trial duration of approximately 3.5 years is estimated. The maximum number of events is set to 160 yielding a maximal trial duration of approximately 5.5 years (for further details refer to chapter 8).

3.3 SELECTION OF STUDY POPULATION

3.3.1 INCLUSION CRITERIA

Each subject must fulfill all of the following inclusion criteria before enrollment to the study:
- Confirmed pathological diagnosis of MCL according to WHO classification.
- Relapse or progression following 1 to 3 prior lines of anti-neoplastic standard therapy. Therapy in remission after initial induction like intensified chemotherapy for stem cell separation followed by myeloablative therapy or any kind of maintenance therapy is classified as one line of therapy with the induction therapy.
- If Rituximab was part of prior treatment, documented time to progression must be at least 12 weeks after this particular regimen.
- If high-dose Ara-C was part of prior treatment, documented time to progression must be at least 6 months after this particular regimen.
- Patients relapsed after autologous stem cell transplantation or not appropriate for myeloablative treatment.
- At least 1 measurable or assessable site of disease; in case of bone marrow infiltration only, bone marrow aspiration/ biopsy is mandatory for all staging evaluations.
- age ≥ 18 years
- ECOG/WHO Performance Score 0-2, unless lymphoma related.
- The following laboratory values at screening, unless lymphoma related:
  - Absolute neutrophil count (ANC) ≥1500 cells/µL
  - Platelets ≥100,000 cells/µL
  - Transaminases (AST and ALT) ≤3 x upper limit of normal (ULN)
  - Total bilirubin ≤2 x ULN
  - Creatinine ≤2 mg/dL or calculated creatinine clearance ≥50 mL/min
  - Toxic effects of previous therapy or surgery resolved to NCI CTC grade 2 or better.
- Premenopausal fertile females must agree to use a highly effective method of birth control for the duration of the therapy. A highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner.

- Men must agree not to father a child for the duration of therapy and must agree to advice a female partner to use a highly effective method of birth control.

- Written informed consent before performance of any study-related procedure.

3.3.2 EXCLUSION CRITERIA

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study:

- Previous treatment with Bortezomib.
- Treatment within another clinical trial within 30 days before trial entry or planed during this trial
- Anti-neoplastic (including radiation and antibody treatment) or experimental therapy within 4 weeks before planed Day 1 of Cycle 1 (Nitrosoureas within 6 weeks ) or radioimmunoconjugates or toxin immunonoconjugates such as Ibritumomab tiuxetan (Zevalin™) or Tositumomab (Bexxar®) within 12 weeks before planed Day 1 of Cycle 1
- Known hypersensitivity to Rituximab, boron or mannitol.
- Active malignancy other than MCL within 5 years before Day 1 of Cycle 1, with the exception of complete resection of basal cell carcinoma, squamous cell carcinoma of the skin, or in situ malignancy.
- Active systemic infection requiring treatment.
- HIV, hepatitis B or C
- Patient has ≥ grade 2 peripheral sensory neuropathy or neuropathic pain defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE).
- Symptomatic degenerative or toxic encephalopathy
- Serious medical condition (such as severe hepatic impairment, peridcardial disease, acute diffuse infiltrative pulmonary disease, systemic infections etc) or psychiatric illness likely to interfere with participation in this clinical study.
- Female subject is pregnant or breast-feeding (pregnancy testing is mandatory for premenopausal women).

3.3.3 REMOVAL OF SUBJECTS FROM STUDY TREATMENT

Study treatment is to be permanently discontinued for subjects meeting any of the following criteria:

- Progressive disease
- Unacceptable toxicity
- Concomitant disease
- Decision by subject, investigator or study coordinator
- Severe protocol violation

All subjects who permanently discontinue treatment, whether prematurely or as scheduled, must complete the end of treatment visit and should be followed thereafter.

Subjects will be discontinued from the study for the following reasons:

- Withdrawal of informed consent
- Severe protocol violation
- Loss of follow-up
- Death

The reason(s) for a subject’s discontinuation from the study are to be recorded in the source documents and the subject’s case report form (CRF).
3.4 REGISTRATION AND RANDOMIZATION

Registration and randomization will be done at the national study group or the central data center in Munich via fax:

European MCL data center  
University Hospital Großhadern  
Dept. of Medicine III  
Dr. M. Unterhalt  
Marchioninistr. 15  
81377 München / GERMANY  
Phone: +49-89-7095-4900 -4901  
Fax: +49-89-7095-7900 -7901

Eligible patients will be randomized to receive Rituximab, high-dose Ara-C and Dexamethasone alone or in combination with Bortezomib.

Randomisation will be stratified according to the following factors:

- Response to initial therapy: relapse vs. primary refractory disease
- International Prognostic Index (IPI) with following risk factors:
  - age > 60 years
  - Ann Arbor stage III and IV
  - LDH serum level over normal range of the respective laboratory
  - WHO/ECOG performance-status >1
  - more than 1 extra nodal involvement
  - previous stem cell transplantation: yes vs. no
  - previous therapy with high dose Ara-C: yes vs. no
  - Study group/association of centre:
    - GELA
    - GLSG
    - HOVON
    - Nordic Lymphoma Group
    - Centres not associated to one of these study groups

3.5 TREATMENT SCHEDULE

Study treatment will be administered only to eligible subjects according to inclusion and exclusion criteria after registration and randomization at the data center in Munich.

3.5.1 IMMUNO-CHEMOTHERAPY (R-HAD)

Rituximab 375 mg/m² (max 750 mg) will be given intravenously on day 1. Ara-C 2 g/m² will be given intravenously over a 3-hour on two consecutive days (day 2 and 3). In patients >65 years at time of study entry or post myeloablative treatment, dose reduction of Ara-C to 1 g/m² will be performed. Dexamethasone will be given at a dose of 40 mg p.o. on four consecutive days (days 1 to 4).

Patients randomized to receive combination therapy, Bortezomib 1.5 mg/m² will be given additionally as a slow intravenous push (3 to 5 second) on day 1 (at least one hour prior to Rituximab infusion) and similarly on day 4. Treatment course will be repeated in 3-week intervals (day 22).

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Day</th>
<th>Route</th>
</tr>
</thead>
</table>

EudraCT-Nr.: 2005-005144-62
R-HAD PLUS/MINUS BORTEZOMIB IN RELAPSED/REFRACTORY MCL
A RANDOMIZED PHASE III TRIAL OF THE EUROPEAN MCL NETWORK

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Route</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m²</td>
<td>1</td>
<td>IV</td>
</tr>
<tr>
<td>Ara-C</td>
<td>2000 mg/m² (Patients &gt;65 years or s/p myeloablative treatment: 1000 mg/m²)</td>
<td>2 and 3</td>
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</tr>
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<td>Dexamethasone</td>
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</tr>
<tr>
<td>± Bortezomib</td>
<td>1.5 mg/m²</td>
<td>1 and 4</td>
<td>IV (3-5 sec)</td>
</tr>
</tbody>
</table>

Treatment course will be repeated in 3-week intervals (day 22)

Before each treatment cycle the following laboratory values are required:
- Absolute neutrophil count (ANC) ≥1500 cells/µL
- Platelets ≥100,000 cells/µL
- Creatinine ≤2 mg/dL or calculated creatinine clearance ≥50 mL/min

In case of severe side effects, like severe left ventricular systolic dysfunction treatment has to be withheld and discussed with the study coordinators.

Rituximab 375 mg/m² (max 750 mg) will be given only if the number of circulating lymphoma cells is < 20 x 10⁹/µl to avoid a cytokine release syndrome more frequently observed in leukemic lymphoma. This criteria has to be reconsidered before each consecutive course.

Dose modifications of Rituximab should not be performed. In case of unacceptable toxicity/hypersensitivity to Rituximab, application of Rituximab has to be permanently discontinued. However those patients will be evaluated accordingly (intent to treat).

It is strongly advised to give the first Rituximab infusion in an inpatient setting. If no adverse events have occurred the following infusions can be given in an outpatient ward. A peripheral (IV) line will be established. Vital signs (blood pressure, pulse, respiration, and temperature) should be monitored every 15 minutes during the first hour or until stable and then hourly until the infusion is discontinued and vital signs are stable. Premedication with paracetamol and/or antihistaminics is strongly advised. Dexamethasone 40 mg should be given 1 hour prior to Rituximab (either orally or intravenously). The initial dose of Rituximab should be 50 mg/hr for the first hour. If no adverse event is seen, the dose may be escalated in 30 minutes intervals with increment steps of 50 mg/hr, to a maximum of 400 mg/hr. Patients may experience transient fever and rigors with infusion of chimeric anti-CD20 antibody.

If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The patient should be treated according to the appropriate standard of care. The infusion should be continued at half the previous rate after symptoms have abated.

Ara-C is a pyrimidine antagonist and one of the most active agents in the treatment of leukemia and lymphoma.

In this study Ara-C will be given intravenously over a 3-hour period every 24 hours for two consecutive days (day 2 and 3). In patients >65 years at time of study entry or status post myeloablative treatment, there will be a dose reduction of Ara-C to 1 g/m² respectively.

Doses >1.7 g/m² may produce conjunctivitis which can be ameliorated with prophylactic use of corticosteroid eye drops (e.g. Isoptodex™). Dexamethasone eye drops may be administered at 2-3 drops every 6 hours during days 2-4. Observed toxicities associated with high-dose Ara-C therapy include cerebellar toxicity, corneal keratitis, hyperbilirubinemia, pulmonary edema, pericarditis, and tamponade. Other known adverse events are listed below.

Adverse events to Ara-C (selected)

<table>
<thead>
<tr>
<th>frequency</th>
<th>organ system</th>
<th>adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%:</td>
<td>CNS</td>
<td>cerebellar toxicity (ataxia, dysarthria, and dysdiadochokinesia; dose-related)</td>
</tr>
<tr>
<td></td>
<td>Dermatologic</td>
<td>Oral/anal ulceration, rash</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>Nausea, vomiting, anorexia, stomatitis, mucositis.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Emetic potential at &gt;1-1.5 g: high (&gt;90%); time course of nausea/vomiting:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>onset: 1-3 hours; duration: 3-8 hours</td>
</tr>
</tbody>
</table>

## Hematologic
- Bleeding, leukopenia, thrombocytopenia; myelosuppression occurs within the first week of treatment and lasts for 10-14 days; primarily manifested as granulocytopenia, but anemia can also occur.

## Hepatic
- Hepatic dysfunction, mild jaundice, increased transaminases.

### 1% - 10%:
- **Cardiovascular**: Cardiomegaly
- **CNS**: Dizziness, headache, somnolence, confusion, neuritis, malaise
- **Dermatologic**: Skin freckling, itching, alopecia, cellulitis at injection site
- **Endocrine & metabolic**: Hyperuricemia or uric acid nephropathy
- **Gastrointestinal**: Esophagitis, diarrhea
- **Genitourinary**: Urinary retention
- **Hematologic**: Megaloblastic anemia
- **Hepatic**: Hepatotoxicity
- **Local**: Thrombophlebitis
- **Neuromuscular & skeletal**: Myalgia, bone pain, peripheral neuropathy
- **Respiratory**: Syndrome of sudden respiratory distress progressing to pulmonary edema, pneumonia
- **Infectious**: Sepsis

### <1% (Limited to important or life-threatening)
- Pancreatitis

### 3.5.2 DOSE REDUCTION AND TREATMENT DELAY OF R-HAD

No dose modification of Rituximab, high-dose Ara-C and dexamethasone (R-HAD) will be made in the first course. During the next courses, modifications of the treatment schedule will be made if myelosuppression occurs: if WBC < 3x $10^9$/l or thrombocytes < 100x $10^9$/l after 3 weeks, postpone up to 2 weeks; if after 5 week insufficient recovery or ongoing non-hematological grade III/IV toxicities (except alopecia), adapt according to scheme below.

<table>
<thead>
<tr>
<th>WBC x $10^9$/l</th>
<th>thrombocytes x $10^9$/l</th>
<th>Ara-C</th>
<th>Dexamethasone</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3</td>
<td>&gt;100</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>2-3</td>
<td>75 – 100</td>
<td>75%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>1-2</td>
<td>50 – 75</td>
<td>50%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>&lt;1</td>
<td>&lt;50</td>
<td>0%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Dose reduction will be calculated according to the doses given in the previous cycle. In case of severe myelosuppression with leucocyte counts < 1.0 x $10^9$/l (and/or thrombocyte counts < 25 x $10^9$/l) as assessed on two consecutive measures but recovery WBC >3.0x $10^9$/l (and/or thrombocytes > 100 x $10^9$/l) after 3 weeks, it is strongly advised to reduce the dose of R-HAD to 75% in Ara-C in subsequent cycles. This reduction of dose can be omitted if the severe myelosuppression can be assumed to be the result of an initial significant bone marrow involvement.

In case of any grade 3 non-hematological toxicity despite optimized supportive care (except alopecia and nausea) dose modifications should be discussed with the study coordinators. Reasons have to be recorded in the source documents and the patient’s case report form (CRF).
3.5.3 BORTEZOMIB

Bortezomib (Velcade™), formerly named PS-341, represents a novel class of antineoplastic agents. This modified dipeptidyl boronic acid of only 284 Dalton, is a potent, reversible and specific inhibitor of the 26 S proteasome.

Bortezomib is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling.

If Bortezomib solution contacts the skin, wash the skin immediately and thoroughly with soap, water, and diluted hydrogen peroxide. If Bortezomib solution contacts the mucous membranes, flush thoroughly with water.

In animal studies lethal intravenous dosis were associated with decreased blood pressure, increased heart rate, increased cardiac contractility and terminal hypotension.

No cases of overdosage with Bortezomib were reported during clinical trials. Single doses of up to 2 mg/m² have been administered to adults.

In the event of overdosage, patients should be medically monitored and appropriate supportive care given:
- Keep patient warm,
- support blood pressure and
- avoid dehydration.

There is no specific antidot for Bortezomib overdosage.

Bortezomib will be dosed at 1.5 mg/m²/dose unless adverse events associated with application necessitate dose modification as listed below. Application will be a 3- to 5-second bolus intravenously twice weekly on days 1 and 4 of a 3-week treatment cycle. Due to pharmacodynamic considerations and in order to distinguish possible adverse events, Bortezomib should be administered at least 1 hour prior to Rituximab application.

Bortezomib is a sterile lyophilized powder for reconstitution and is supplied in vials containing Bortezomib and mannitol at a 1:10 ratio. Vials should be stored according to the directions provided on the label. Each vial should be reconstituted within 8 hours before dosing with normal (0.9%) saline, so that the reconstituted solution contains Bortezomib at a concentration of 1 mg/mL. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted Bortezomib should be administered promptly and in no case more than 8 hours after reconstitution.

Bortezomib will be prepared under aseptic conditions. The amount (in mg) of Bortezomib to be administered will be determined based on BSA. The Bortezomib dose will not be corrected for obese subjects. The dose should be calculated on day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle. The appropriate amount of Bortezomib will be drawn from the injection vial and administered as an IV push over 3- to 5-seconds followed by a standard saline flush or through a running IV line.

Potential Adverse Effects of Bortezomib (selected, also refer to 1.3.3)

<table>
<thead>
<tr>
<th>frequency</th>
<th>adverse event</th>
</tr>
</thead>
</table>

### Frequency of Adverse Events

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%</td>
<td>Cardiovascular: Edema (25%), hypotension (12%)</td>
</tr>
<tr>
<td></td>
<td>Central nervous system: Pyrexia (36%), headache (28%), insomnia (27%), dizziness (21%, excludes vertigo), anxiety (14%)</td>
</tr>
<tr>
<td></td>
<td>Dermatologic: Rash (21%), pruritus (11%)</td>
</tr>
<tr>
<td></td>
<td>Endocrine &amp; metabolic: Dehydration (18%)</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal: Nausea (64%), diarrhea (51%), appetite decreased (43%), constipation (43%), vomiting (36%), abdominal pain (13%), abnormal taste (13%), dyspepsia (13%)</td>
</tr>
<tr>
<td></td>
<td>Hematologic: Thrombocytopenia (43%, Grade 3: 27%, Grade 4: 3%); anemia (32%, Grade 3: 9%); neutropenia (24%, Grade 3: 13%, Grade 4: 3%)</td>
</tr>
<tr>
<td></td>
<td>Neuromuscular &amp; skeletal: Asthenic conditions (65%, Grade 3: 18% - includes fatigue, malaise, weakness); peripheral neuropathy (37%, Grade 3: 14%); arthralgia (26%); limb pain (26%); paresthesia and dysesthesia (23%), back pain (14%); bone pain (14%); muscle cramps (14%); myalgia (14%); rigors (12%) Ocular: Blurred vision (11%)</td>
</tr>
<tr>
<td></td>
<td>Respiratory: Dyspnea (22%), upper respiratory tract infection (18%), cough (17%)</td>
</tr>
<tr>
<td>1-10%</td>
<td>Miscellaneous: Herpes zoster (11%)</td>
</tr>
</tbody>
</table>

#### Frequency not defined (Limited to important or life-threatening)
- Agitation, anaphylactic reaction, ascites, ataxia, arrhythmias, bacteremia, bilateral hydronephrosis, bleeding abnormalities (including gastrointestinal), cardiac amyloidosis, cardiac arrest, cardiac failure, coma, congestive heart failure, cranial palsy, deep vein thrombosis, disseminated intravascular coagulation, dysphagia, epistaxis, hyperbilarubinemia, hypersensitivity reaction, hyperuricemia, hypocalcemia, hypokalemia, hyponatremia, hypoxia, intestinal obstruction or perforation, motor dysfunction, myocardial infarction, pancreatitis, paralytic ileus, pericardial effusion, peripheral embolism, pneumonitis, portal vein thrombosis, proliferative glomerular nephritis, pulmonary edema, renal failure, respiratory distress syndrome, respiratory failure, seizure, spinal cord compression, stroke, subdural hematoma, transient ischemic attack, tumor lysis syndrome, urinary retention

### 3.5.4 DOSE REDUCTION AND TREATMENT DELAY OF BORTEZO MIB

If a Bortezomib dose due to toxicity or another reason is missed, then that dose is skipped and treatment continues with next planned dose.

**Observed toxicities, considered by the investigator to be related specifically to Bortezomib** are to be managed as follows:
- If leucocytes are \(< 1.0 \times 10^9/\text{L}\) (and/or platelet counts \(< 25,000 \text{ cells/\muL}\), scheduled Bortezomib application will be skipped until recovery to NCI toxicity \(\leq 2\).
- For any \(\geq\)grade 3 non-hematologic toxicity other than neuropathic pain and/or peripheral sensory neuropathy, considered by the investigator to be related to Bortezomib, scheduled Bortezomib application will be skipped until the toxicity returns to Grade 2 or better.
- If a dose of Bortezomib was skipped due to toxicity then reduce the drug doses as follows:
  - If the patient was receiving 1.5 mg/m\(^2\), reduce the dose to 1.3 mg/m\(^2\).
  - If the patient was receiving 1.3 mg/m\(^2\), reduce the dose to 1.0 mg/m\(^2\).
  - If the patient was receiving 1.0 mg/m\(^2\), reduce the dose to 0.7 mg/m\(^2\).
  - If the patient was receiving 0.7 mg/m\(^2\), discontinue study drug, unless patient is responding, in which case this should be discussed with the study coordinators. Dose reductions below 0.7 mg/m\(^2\) should be avoided, but will be considered if patient is having a good response.
- Patients who experience Bortezomib-related neuropathic pain and/or peripheral sensory neuropathy are to be managed as follows:
Peripheral Sensory Neuropathy (NCI CTCAE Grade)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>No action</td>
</tr>
<tr>
<td>1</td>
<td>Loss of deep tendon reflexes or paresthesia but not interfering with function</td>
<td>No action, ~25% dose reduction*</td>
</tr>
<tr>
<td>2</td>
<td>Objective sensory loss or paresthesia, interfering with function, but not with ADLs</td>
<td>Skip; ~50% dose reduction**</td>
</tr>
<tr>
<td>3</td>
<td>Sensory loss or paresthesia interfering with ADLs</td>
<td>Discontinue VELCADE</td>
</tr>
<tr>
<td>4</td>
<td>Disabling</td>
<td>Discontinue VELCADE</td>
</tr>
</tbody>
</table>

Neuropathic symptoms are more prominent than abnormalities on the clinical examination. The neurotoxicity-directed questionnaire FACT/GOG-Ntx (see attachment, chapter 12.5) is provided as a safety checklist to help determine the presence and intensity of neuropathic pain or peripheral neuropathy using the subjects’ reports. The FACT/GOG-Ntx questionnaire may be completed assist with the evaluation of the onset and intensity of peripheral neuropathy and other neurotoxicities that may possibly require intervention or dose modification.

3.5.5 FOLLOW-UP

After completion of salvage therapy, patients will be followed for at least 36 months. Especially, no maintenance or consolidation therapy should be administered. During that time, regular staging examinations will be performed (see also chapter 4.3.5). If any progress has been detected, patients will be treated by the responsible physician outside of the study according to local guidelines.

ADLs = activities of daily living

Key:
Skip: Interrupt Bortezomib (VELCADE™) until the toxicity returns to Grade 1 or better.
*~25% Dose reduction: VELCADE dose reduction from 1.5 to 1.3 mg/m²/dose, from 1.3 to 1.0 mg/m²/dose or from 1.0 to 0.7 mg/m²/dose.
**~50% Dose reduction: VELCADE dose reduction from 1.5 to 1.0 or from 1.3 to 0.7 mg/m²/dose.
3.6 SUPPORTIVE CARE

All medications and procedures and support therapies administered from screening through the end of treatment must be recorded in the source documents and the subject’s CRF.

Patients should receive full supportive care, including hydration and diureses as needed, transfusions of blood and blood products, antibiotics, anti-emetics, etc. where applicable.

According to a proposed classification of acute emetogenicity of cancer chemotherapy published 1997 by the American Society of Clinical Oncology the emetic potential of Ara-C at doses >1-1.5 g is at level four (i.e. high), indicating a considerable frequency of emesis of up to 90%. Therefore the current antiemetic regimen of choice is a combination of an effective dose of an 5-HT3 receptor antagonist (e.g. ondansetron, granisetron) and previous dosing of dexamethasone within the R-HAD regimen. Additional dopaminergic antagonist should be used as needed.

Use of hematopoietic growth factors is at the choice of each individual investigator. The use of G-CSF might be considered if grade 4 (severe neutropenia) or febrile neutropenia grade III after any cycle of chemotherapy has occurred. G-CSF should be started not before day +5 and continued for 7-10 days, or until the granulocytes have risen to >3x 10^9/l.

The reason(s) for treatment, dosage, and dates of treatment should be recorded on the CRF. Prophylactic antibiotics are not routinely recommended and should be handled according to local standard care.
4 DIAGNOSTIC PROCEDURES

4.1 TABLE OF DIAGNOSTIC TESTS
A schedule of treatment and assessments, that will be carried out during the study is shown.

<table>
<thead>
<tr>
<th>Visit</th>
<th>base-line</th>
<th>each cycle</th>
<th>midterm staging</th>
<th>end of treatment evaluation</th>
<th>2-year follow-up at 3 month-intervals</th>
<th>follow-up thereafter at 6 month-intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vital signs</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>WHO Performance Status</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ECG/Echocardiography</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiological tumor assessment (e.g. CT scan)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic tests</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Serum chemistry</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Flow cytometry</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone marrow biopsy</td>
<td>X(^8)</td>
<td>X(^8)</td>
<td>X(^8)</td>
<td>X(^8)</td>
<td>X(^8)</td>
<td></td>
</tr>
<tr>
<td>Serum Test for HIV, hepatitis B and C</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Serum pregnancy test</td>
<td>X</td>
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<td></td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

1 including prior antineoplastic therapy, best response, duration of response and adverse events
2 including body weight and height
3 Complete blood counts with differential
4 Electrolytes, calcium, creatinine, BUN, uric acid, LDH, CRP, glucose, AST(SGOT), ALT (SGPT), alkaline phosphatase, gamma GT, total bilirubin, total protein, albumin. Add IgG, IgM, IgA, ESR, β2 microglobuline, thymidine kinase at baseline and end of treatment evaluation
5 CD5, CD 19, CD 20
6 only if not performed during previous 3 month of study entry
7 female patients of child bearing potential only
8 only to confirm CR if bone marrow was infiltrated initially or in case of isolated bone marrow infiltration
9 mandatory follow-up period will end at 36 months, however further follow-up is strongly recommended
4.2 SAFETY MEASUREMENTS

Safety evaluation will be done throughout the study, during treatment and follow-up period at each visit:
- Medical history with special emphasis on adverse events.
- Complete physical examination (including vital signs, weight, performance status).
- Laboratory work-up: CBC with differential and platelet count, electrolytes, calcium, creatinine, BUN, uric acid, LDH, CRP, glucose, AST(SGOT), ALT (SGPT), alkaline phosphatase, gamma GT, total bilirubin, total protein, albumin.
- Additional diagnostic studies may be performed according to clinical symptoms based on the judgement of the investigator.

Additional safety evaluation after each therapy cycle:
- The following laboratory work-up must be performed on a weekly base after each cycle: CBC with differential and platelet count, electrolytes, calcium, creatinine, BUN, uric acid, LDH, CRP, glucose, AST(SGOT), ALT (SGPT), alkaline phosphatase, gamma GT, total bilirubin.
- In case of thrombocytopenia grade 4 or neutropenia grade 4 CBC with differential and platelet count should be performed again within four days until recovery from grade 4 toxicity.
- Additional laboratory controls may be performed according to clinical or laboratory symptoms based on the judgement of the investigator.

4.3 EVALUATION OF TREATMENT AND RESPONSE

4.3.1 RESPONSE CRITERIA AND TIME SCHEDULE OF RESPONSE EVALUATION

Response will be evaluated three weeks after the first two cycles of trial therapy and 4 to 6 weeks after the end of trial therapy. Follow-up staging will be performed every three months during the first two years after end of trial therapy and every six months thereafter. Response is always evaluated in comparison to the status before start of trial therapy. Evaluation of response will be done according to the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphoma (see appendix).

4.3.2 BASELINE EVALUATIONS

The following baseline evaluations must be performed and results have to be available prior to start of treatment:
- Written informed consent
- Check of inclusion/exclusion criteria
- Medical history and demographic data
- Prior anti-neoplastic therapy (including best response status and duration of response, residual toxicity)
- Complete physical examination (including vital signs, height and body weight, WHO performance status [refer to appendix], and a neurologic evaluation (preferably done by an experienced neurology consultant)
- ECG, echocardiography
- CT of the cervical region (neck), chest, abdomen and pelvis
- Clinical laboratory examination: CBC with differential and platelet count, electrolytes, calcium, creatinine, BUN, uric acid, LDH, CRP, glucose, AST(SGOT), ALT (SGPT), alkaline phosphatase, gamma GT, total bilirubin, total protein, albumin, IgG, IgM and IgA.
- Erythrocyte sedimentation rate (ESR), β2 microglobuline, thymidine kinase,
- Bone marrow biopsy for cytology, histology and immunophenotyping for lymphoma infiltration (CD19, CD20, CD5 staining) and percentage of involvement if not performed during 3 months prior to study entry.
- Immunophenotyping of peripheral blood by flow cytometry with quantitative determination of the total number of B-lymphocytes and circulating lymphoma cells (including CD19, CD20 and CD5 staining)
- Lymph node biopsy if not performed during 6 months prior to study entry
- Sampling for minimal residual disease (20 ml EDTA blood, 5 ml EDTA bone marrow, 20 ml heparin blood, 5 ml heparin bone marrow, 4 bone marrow smears (air dried, unfixed for FISH), 10 ml clotted serum sample; details in 4.3.6)
- Additional diagnostic studies should be performed according to clinical symptoms based on the judgement of the investigator.
4.3.3 MIDTERM STAGING PROCEDURES

The following diagnostic procedures have to be performed after 2 treatment cycles, prior to next scheduled treatment:

- Medical history with special emphasis on adverse events.
- Complete physical examination (including vital signs, weight, performance status)
- Laboratory work-up: CBC with differential and platelet count, electrolytes, calcium, creatinine, BUN, uric acid, LDH, CRP, glucose, AST(SGOT), ALT (SGPT), alkaline phosphatase, gamma GT, total bilirubin, total protein, albumin, IgG, IgM and IgA.
- ECG, echocardiography.
- CT of all known lymphoma manifestations
- In case of isolated bone marrow involvement a bone marrow aspiration/biopsy is mandatory.
- Additional diagnostic studies may be performed according to clinical symptoms based on the judgement of the investigator.

4.3.4 END OF TREATMENT EVALUATION

The following diagnostic procedures have to be performed 4 to 6 weeks after end of treatment (irrespective of number of applied treatment cycles):

- Medical history with special emphasis on adverse events.
- Complete physical examination (including vital signs, weight, performance status)
- Laboratory work-up: CBC with differential and platelet count, electrolytes, calcium, creatinine, BUN, uric acid, LDH, CRP, glucose, AST(SGOT), ALT (SGPT), alkaline phosphatase, gamma GT, total bilirubin, total protein, albumin.
- Erythrocyte sedimentation rate (ESR).
- Immunphenotyping of peripheral blood by flow cytometry with quantitative determination of the total number of B-lymphocytes and circulating lymphoma cells.
- ECG, echocardiography.
- CT of neck, chest, abdomen and all other known or suspected lymphoma manifestations
- In case of isolated bone marrow involvement a bone marrow aspiration/biopsy is mandatory.
- Sampling for minimal residual disease (20 ml EDTA blood, 5 ml EDTA bone marrow, 20 ml heparin blood, 5 ml heparin bone marrow, 4 bone marrow smears (air dried, unfixed for FISH); details in 4.3.6)
- Additional diagnostic studies should be performed according to clinical symptoms based on the judgement of the investigator.

4.3.5 FOLLOW-UP EVALUATIONS

The following diagnostic procedures have to be performed at 3 months intervals during the 2-year follow-up and in 6 month intervals thereafter. The mandatory follow-up period will end at 36 months, however in case of continuing response thereafter further follow-up in 6 month intervals is strongly recommended:

- Medical history with special emphasis on adverse events.
- Complete physical examination (including vital signs, weight, performance status)
- Laboratory work-up: CBC with differential and platelet count, electrolytes, calcium, creatinine, BUN, uric acid, LDH, CRP, glucose, AST(SGOT), ALT (SGPT), alkaline phosphatase, gamma GT, total bilirubin, total protein, albumin.
- Erythrocyte sedimentation rate (ESR).
- CT of neck, chest, abdomen (and other known or suspected lymphoma manifestations)
- In case of isolated bone marrow involvement or suspected progress/relapse a bone marrow aspiration/biopsy is mandatory.
- Immunphenotyping of peripheral blood by flow cytometry with quantitative determination of the total number of B-lymphocytes and circulating lymphoma cells.
- Sampling for minimal residual disease (at 6 month intervals: 20 ml EDTA blood, 5 ml EDTA bone marrow, 20 ml heparin blood, 5 ml heparin bone marrow, 4 bone marrow smears (air dried, unfixed for FISH); 10 ml clotted serum sample; details in 4.3.6)
- Additional diagnostic studies should be performed according to clinical symptoms based on the judgement of the investigator.
4.3.6 EUROPEAN MCL RESEARCH NETWORK/MINIMAL RESIDUAL DISEASE (MRD)

Based on this previously established European MCL Intergroup Working Party and the European MCL Pathology Panel, in 2000 a European MCL Research Network has been established which focusses especially on the characterisation of molecular and biological risk factors in MCL. In addition minimal residual disease will be systematically performed in all study patients. As a prerequisite for molecular assessment of MRD using RQ-PCR peripheral blood and bone marrow has to be sent before start of any treatment to determine the individual patient-specific DNA-sequence of the malignant clone. Additional FACS and FISH analysis will be performed at every time point of MRD detection. Therefore it is essential to send heparin samples for FACS analysis together with EDTA samples for PCR analysis at every time point of MRD investigation. A 10 ml clotted serum sample will be necessary only at diagnosis.

The results of MRD will be not incorporated into the response evaluation nor influence the management of the patient.

Sample collection

Time points for sample collection for the European MCL Research Network/Biomed II MRD project are:

**Prior treatment:** for all patients before treatment
- 20 ml EDTA blood / 5 ml EDTA bone marrow
- 20 ml heparin blood / 5 ml heparin bone marrow
- 4 bone marrow smears (air dried, unfixed for FISH)
- 10 ml clotted serum sample

**Midterm staging:** after 2 x R-HAD or R-HAD plus Bortezomib
- 20 ml EDTA blood
- 20 ml heparin blood

**End of treatment:** after 4 x R-HAD or R-HAD plus Bortezomib
- 20 ml EDTA blood / 5 ml EDTA bone marrow
- 20 ml heparin blood / 5 ml heparin bone marrow
- 4 bone marrow smears (air dried, unfixed for FISH)

**Follow-up (every 3 months during 2 year follow-up, every 6 months thereafter):**
- at 3-months intervals: 20 ml EDTA blood / 20 ml heparin blood
- at 6-months intervals: 20 ml EDTA blood / 5 ml EDTA bone marrow
- 20 ml heparin blood / 5 ml heparin bone marrow
- 4 bone marrow smears (air dried, unfixed for FISH)
Overview of addresses of a selected list of national reference laboratories:

<table>
<thead>
<tr>
<th>Country</th>
<th>Name and address</th>
</tr>
</thead>
</table>
| Denmark   | Dr. N. Andersen  
Dept. of Hematology Lab. 4041  
Rigshospitalet  
Blegdamsvej, 9  
DK 2100 Copenhagen, Denmark  
Phone: +45-35-451146  
Fax: +45-35-454841 |
| Finland   | Prof. Dr. Elizabeth Macintyre, M.D.  
Laboratoire d’Hematologie Tour Pasteur  
2ème étage, Porte 14  
Hôpital Necker-Enfants Malades  
149, rue de Sevres  
75743 PARIS CEDEX 15 - France  
Phone: +33-1-44494947  
Fax: +33-1-44381745 |
| Norway    | Dr. C. Pott  
University Hospital Kiel  
Dept. of Medicine II  
Chemnitzstrasse 33  
24116 Kiel  
Phone: +49-431-1697-1268  
Fax: +49-431-1697-1264 |
| Sweden    | Dr. J.J.M. van Dongen  
Erasmus University Medical Center Rotterdam  
Immunology/Molecular Unit  
Dr. Molewaterplein 50  
Rotterdam 3015 GE  
The Netherlands  
Phone: +31-10-4088094 |
| Spain     | Dr. E. Campo  
Unitat d’Hematopatologia  
Hospital Clinic  
Villarpel 170  
E-09036 Barcelona  
Phone: +349-322-7-5450/5572  
Fax: +349-322-7-5454 |

Samples with the completed molecular form (Monday to Thursday by express mail) should be sent to the respective national reference labs where samples are centrally collected.
5 TOXICITIES

5.1 ADVERSE EVENTS

Special attention is to be paid to the occurrence of adverse events (AE) throughout every stage of the study.

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (e.g. including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

Investigators should be familiar with potential adverse events which have been observed in association with the application of Rituximab, high-dose Ara-C, dexamethasone and Bortezomib as outlined above.

5.2 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:
- results in death, or
- is life-threatening, or
- requires inpatient hospitalization or prolongation of existing hospitalization, or
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect,
- is a suspected transmission of infectious agents by medicinal product, or
- is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs.

All defined Serious Adverse Events (SAEs) occurred after signature of informed consent up to 30 days after the last study drug administration, whether or not ascribed to the IMP, will be reported to the sponsor. A Serious Adverse Event that occurs after this time, if considered related to the study medication, will be reported.

Any serious adverse event that is not listed in 5.3 has to be reported by fax immediately within 24 hours to the sponsor (contact address for SAE reporting: GELARC, Centre Hospitalier Lyon Sud, Secteur Sainte-Eugénie, pavillon 6D, 165, chemin du Grand Revoyet, 69495 Pierre-Bénite Cedex, France, fax number: +33 3 59 11 01 86, phone number: +33 4 72 66 93 33) and thereafter documented in detail as indicated on the CRF. The following information is required:
- date and time of onset
- duration (date of onset and end)
- peak intensity (according to CTC criteria, see appendix).
- drug relationship of the AE to the investigational product (for definitions, see below)
- outcome of the adverse event (recovered completely / with residual effects, continuing).
- assessment of the seriousness of the event

The investigator has to classify the drug relationship of an SAE according to the following definitions:
- None: The time course between administration of the study drug and occurrence or worsening of the adverse event rules out a causal relationship and/or another cause is confirmed and no indication of involvement of the study drug in the occurrence/ worsening of the adverse event exists.
- Unlikely: The time course between administration of the study drug and occurrence or worsening of the adverse event makes a causal relationship unlikely and/or the known effects of the study drug provide no indication of involvement in the occurrence/worsening of the adverse event and...
another cause adequately explaining the adverse event is known and/or regarding the occurrence/
worsening of the adverse event a plausible causal chain may be deduced from the known effects
of the study drug, but another cause is much more probable and/or another cause is confirmed
and involvement of the study drug in the occurrence/worsening of the adverse event is unlikely.
- **Possible**: Regarding the occurrence/worsening of the adverse event a plausible causal chain
may be deduced from the pharmacological properties of the study drug, but another cause is just
as likely to be involved or although the pharmacological properties of the study drug provide no
indication of involvement in the occurrence/worsening of the adverse event, no other cause can be
identified.
- **Probable**: The pharmacological properties of the study drug and the course of the adverse event
(after rechallenge) and/or specific tests (e.g. positive allergy test, antibodies against study
drug/metabolites) suggest involvement of the study drug in the occurrence/worsening of the
adverse event, although another cause cannot be ruled out.
- **Definite**: The pharmacological properties of the study drug and the course of the adverse event
(after rechallenge) and specific tests (e.g. positive allergy test, antibodies against study
drug/metabolites) indicate involvement of the study drug in the occurrence/worsening of the
adverse event, and no other causes exists

### Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths that occur during the patient’s study
participation will be recorded in the source documents. All SAEs should be monitored until they are
resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent
illness(es).

### Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must
inform her treating physician immediately and permanently discontinue study drug. The study center
must also be contacted immediately by faxing a pregnancy report. The pregnancy must be followed
through delivery for SAEs.

### 5.3 EXPECTED TREATMENT RELATED SAE

Due to the intensity of the treatment, serious adverse events, which are **excluded from immediate
reporting**, are:

Hematological toxicities (anemia, thrombocytopenia, leucopenia, neutropenia), febrile neutropenia,
and nausea requiring hospitalization less than 8 days.

Planned hospital admissions or surgical procedures for an illness or disease which existed before the
patient was enrolled in the study are not to be considered SAEs unless the condition deteriorated in an
unexpected manner during the study (e.g. surgery was performed earlier than planned).

Instead the cases mentioned above should be documented on the respective CRF within the standard
documentation process.

Alopecia toxicity (any grade) will never be reported as AE and as SAE.

Sign, symptoms and physical findings indicative of progression of lymphoma are not to be reported as
AE and as SAE.
6 REASONS FOR GOING OFF PROTOCOL

In the case record form the reason for going off protocol should be documented according to the following listing:

- Progressive disease.
- Unacceptable toxicity.
- Decision by patient, investigator or study coordinator.
- Severe protocol violation as judged by the study coordinator.
- Concomitant disease.
- Death.

7 CAUSES OF DEATH

In the case record form, the cause of death should be documented according to the following listing:

- Mantle cell lymphoma.
- Complication of therapy.
- Intercurrent disease.
- Secondary malignancy.
- Other cause.
8 STATISTICAL METHODS

8.1 STATISTICAL EVALUATION OF THE PRIMARY TRIAL ENDPOINT

The primary endpoint of this trial is the time to treatment failure (TTF) calculated from the date of randomization. Treatment failure is defined as

- progressive disease (PD) or stable disease (SD) following induction therapy or
- relapse or progression after complete or partial remission (CR, CRu, PR) or
- death from any cause,

whichever occurred first. Response to therapy is defined as the staging result after the last cycle of therapy. If no treatment failure has been observed until the time of analysis, TTF is censored at the day of the last follow-up staging.

For ethical reasons, the statistical monitoring of the primary trial endpoint is done with planned interim analyses by means of the truncated sequential probability ratio test as described by Whitehead\textsuperscript{(1)}. The logrank test statistics \( Z \) and its variance \( V \) are calculated according to the formulas (1) and (2) every time when new data with reported events are available.

\[
Z = e - \sum_{i=1}^{k} \frac{o_i r_i C}{r_i} \quad \text{(1)}
\]

\[
V = \sum_{i: r_i > 1} \frac{o_i (r_i - o_i) r_i C r_i E}{r_i^2 (r_i - 1)} \quad \text{(2)}
\]

with

- \( t_1, \ldots, t_k \) the distinct, ascendingly ordered failure times
- \( o_i \) the number of observed events at \( t_i \)
- \( r_i \) the number of patients at risk before \( t_i \)
- \( r_i C \) the number of patients at risk before \( t_i \) in the R-HAD arm
- \( r_i E \) the number of patients at risk before \( t_i \) in the Bortezomib + R-HAD arm
- \( e \) the total number of observed events

If the values of \( Z \) and \( V \) remain within the boundaries of the continuation region (Figure 1), statistical monitoring is continued. If the values of \( Z \) and \( V \) leave the continuation region, the statistical test decides against or in favor of the null hypothesis of no difference in TTF between the two study arms, depending on which boundary is crossed. If the values of \( Z \) and \( V \) cross the upper solid line in Figure 1, the null hypothesis is rejected and Bortezomib + R-HAD considered superior to R-HAD alone. If the values of \( Z \) and \( V \) cross the lower dotted line, the null hypothesis is rejected and Bortezomib + R-HAD considered inferior to R-HAD alone. If the values of \( Z \) and \( V \) cross the dashed line, the null hypothesis is accepted. The christmas tree adjustment for discrete monitoring is performed according to Whitehead\textsuperscript{[45]}. 
For the primary analysis patients are evaluated on an intention-to-treat basis. Thus, all patients are analyzed in the treatment arm they have been randomized to, regardless of which treatment they received and whether further protocol violations have occurred. Patients for whom no staging has been performed during induction therapy have to be excluded from analysis. Patients for whom the diagnosis MCL is rejected by the central pathology review are also excluded from analysis.

A secondary analysis on a per-protocol basis is also performed. Patients are evaluable per protocol if they actually received the treatment they were assigned to by randomization and treatment was not stopped prematurely. Thus, patients with progressive (PD) or stable disease (SD) at the end of therapy have to have received at least two cycles and patients with partial (PR, CRu) or complete remission (CR) have to have received the total number of four cycles of therapy.

8.2 NUMBER OF SUBJECTS AND EXPECTED TRIAL DURATION

For the calculation of the required number of events a hazard reduction to 55% by the addition of Bortezomib to R-HAD is considered as a clinically relevant and achievable goal. The maximum number of events is limited to 160 by truncation. With the significance level set to $\alpha = 0.05$ and a desired power of 95% the average number of events needed to obtain a decision of the statistical test is calculated to 87 for a true hazard ratio of 55% (Table 1).

<table>
<thead>
<tr>
<th>true hazard ratio</th>
<th>55%</th>
<th>74%</th>
<th>100%</th>
<th>182%</th>
</tr>
</thead>
<tbody>
<tr>
<td>average number of events</td>
<td>87</td>
<td>118</td>
<td>76</td>
<td>29</td>
</tr>
<tr>
<td>median number of events</td>
<td>78</td>
<td>136</td>
<td>66</td>
<td>27</td>
</tr>
<tr>
<td>90% quantile of number of events</td>
<td>160</td>
<td>160</td>
<td>147</td>
<td>44</td>
</tr>
</tbody>
</table>

Table 1

To obtain the respective sample sizes, the results of the R-FCM arm of the preceding GLSG trial for relapsed or refractory mantle cell lymphoma are used to estimate the distribution of the TTF in the control arm (Figure 2).
Finally, to calculate the approximate recruiting times, a recruiting rate of 50 evaluable patients with MCL per year is considered to be realistic. The approximate sample sizes and recruiting times assuming equal group size are shown in Table 2. Thus, in the case of a true hazard ratio of 55% of the combination of Bortezomib and R-HAD as compared to R-HAD alone, an approximate recruiting time of 3.5 years with a total sample size of approximately 175 patients is necessary. The truncation of the statistical test to 160 events yields a maximal sample size of approximately 275 patients and a maximal recruiting time of approximately 5.5 years.

The corresponding fixed sample test with no interim analysis would require a total of 146 events (vertical gray line in Figure 1). This number would result in a recruiting time of approximately 5 years and a sample size of approximately 250 patients in the case of a true hazard ratio of 55% (Table 3).

### Table 2

<table>
<thead>
<tr>
<th>true hazard ratio</th>
<th>55%</th>
<th>74%</th>
<th>100%</th>
<th>182%</th>
</tr>
</thead>
<tbody>
<tr>
<td>expected recruiting time (years)</td>
<td>3.5</td>
<td>4</td>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>expected sample size</td>
<td>175</td>
<td>200</td>
<td>150</td>
<td>75</td>
</tr>
<tr>
<td>median recruiting time (years)</td>
<td>3.5</td>
<td>4.5</td>
<td>2.5</td>
<td>1.5</td>
</tr>
<tr>
<td>median sample size</td>
<td>175</td>
<td>225</td>
<td>125</td>
<td>75</td>
</tr>
<tr>
<td>90% quantile of recruiting time (years)</td>
<td>5.5</td>
<td>5</td>
<td>4.5</td>
<td>2</td>
</tr>
<tr>
<td>90% quantile of sample size</td>
<td>275</td>
<td>250</td>
<td>225</td>
<td>100</td>
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</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>true hazard ratio</th>
<th>55%</th>
<th>74%</th>
<th>100%</th>
<th>182%</th>
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<tr>
<td>fixed sample recruiting time (years)</td>
<td>5</td>
<td>4.5</td>
<td>4.5</td>
<td>4</td>
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<tr>
<td>fixed sample size</td>
<td>250</td>
<td>225</td>
<td>225</td>
<td>200</td>
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</tbody>
</table>

### 8.3 STATISTICAL METHODS FOR SECONDARY ANALYSES

The following secondary endpoints are evaluated for interim and final reports.

- **complete remission rate**: the rate of complete remissions (CR) after induction therapy. A CRu is not counted as a complete remission.
- **overall response (OR) rate**: the rate of complete, complete unconfirmed, and partial remissions (CR, CRu, PR) after induction therapy.
- **progression free survival (PFS)**: time from randomization to first documentation of progression or relapse or death from any cause, whichever occurred first. Patients with no event during follow-up are censored at the day of the last follow-up staging.
- **progression free survival of responders (PFS of responders) or response duration (RD)**: time from end of successful (CR, CRu, PR) trial therapy to first documentation of progression or relapse or death.
from any cause, whichever occurred first. Patients with no event during follow-up are censored at the
day of the last follow-up staging.
time to next lymphoma treatment: time from start of trial therapy to the start of next lymphoma
treatment outside the protocol. Patients in which no further treatment has been started are censored at
the day of the last follow-up staging.
overall survival (OS): time from randomization to death. Patients who were alive at the day of the last
contact are censored at that time.
CR-rates and OR-rates are calculated for each treatment arm with the corresponding 95% confidence
intervals. Response rates are compared by means of two-sided Fisher’s exact test. For time to event
variables Kaplan-Meier estimates are calculated with 95% confidence intervals as well as median
event free survival times. Time to event variables are compared between treatment groups by means
of the logrank test.
Secondary efficacy analyses are done both on an intention-to-treat and on a per-protocol basis.
For safety analysis, maximal grades of CTC toxicity during the course of therapy are determined for
each patient. The frequencies of CTC grades 0, 1/2, and 3/4 are calculated for each category and
compared by means of two-sided Fisher’s exact test. For safety analysis patients are evaluated „as
treated”. Thus, patients have to have received at least one cycle of therapy and are evaluated
according to the therapy they actually received.
The primary and secondary endpoints may be additionally analysed in subpopulations according to
age, gender, IPI risk group, and number, kind and response to previous lines of therapy.
The significance level is fixed to $\alpha = 0.05$ for all secondary analyses.

8.4 EVALUATION DURING THE TRIAL
Data about recruitment and pooled data for both arms about response to trial therapy, time to
treatment failure and overall survival are evaluated every 6 months and reported to the study chairman
and co-chairmen. Toxicity is also reported every 6 months in the treatment arms. These data are also
reported at the meetings of the study group and may also be reported about the ongoing trial at
conferences. Beside toxicity data no other data for the comparison of the arms are disclosed before
the decision of the sequential procedure.

8.5 FINAL AND INTERIM REPORTS AND TERMINATION OF THE
TRIAL
The first interim report for the comparison of the arms is done when the sequential procedure
monitoring the trial has accepted or rejected the null hypothesis. At this point the results are first
disclosed at the meeting of the trial steering committee and then to the study group and the
randomization is stopped.
9 ADMINISTRATIVE REQUIREMENTS

9.1 GOOD CLINICAL PRACTICE
The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator’s Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

9.2 ETHICAL CONSIDERATIONS
The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Summary of product characteristics (SmPC), informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be submitted to the IRB/IEC by the sponsor or its designee.

9.3 FINANCING AND INSURANCE
The study will be conducted as “Investigator-Initiated Trial”. Sponsor is the Klinikum of the Ludwig-Maximilians-University of Munich. Patients will not receive any payments for their participation in the study.
For every patient an insurance has been contracted according to national requirements. For detailed information, please see the patient information or ask the relevant national study coordinator.

9.4. PATIENT INFORMATION AND CONSENT
After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). The information for the patients will be adopted by the participating groups in the national language of the patient.

9.5. PATIENT CONFIDENTIALITY
In order to maintain patient privacy, all data capture records, study drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from the sponsor or its designee and regulatory authority(ies) access to the patient’s original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient’s confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

For France: The whole of these procedures will be validated by the National Commission of Data processing and Liberté (CNIL). However the authorized representatives of organizations of regulation will be able to possibly consult the medical files in order to confirm the data collected at the time of this study.

For Germany: All data capture records, study drug accountability records, study reports and communications will identify the patient by assigned unique numbers. However if staff of the sponsor is involved in medical consultations for a patient, they will be given access to the identification data of the patient.

9.6 CHANGES TO THE PROTOCOL AND PROTOCOL COMPLIANCE
The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies).

Amendments to the final protocol will be initiated by the Sponsor. Prior to their implementation, all applicable approvals / favorable opinions will be obtained. Deviations from the protocol and immediate implementation of a proposed protocol amendment should not be made, except when the modification is needed to eliminate an immediate hazard(s) to patients. Any departures from the protocol must be fully documented in the source documents.

9.7 MONITORING
The sponsor will arrange on-site monitoring visits. At these visits, the monitor will compare the data entered into the CRFs with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and investigational staff and are accessible for verification by the sponsor site contact. At a minimum, source documentation must be available to substantiate: subject identification, eligibility and participation; proper informed consent procedures; dates of visits; adherence to protocol procedures; records of safety and efficacy parameters; adequate reporting and follow-up of adverse events; administration of concomitant medication; drug receipt/dispensing/return records; study drug administration information; date of subject completion, discontinuation from treatment, or withdrawal from the study, and the reason if appropriate. Specific items required as source documents will be reviewed with the investigator before the study. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded in the CRF are consistent with the original source data. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents.

9.8 ON SITE AUDITS
Regulatory authorities, the IEC/IRB and/or the sponsor or its designee’s clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. The patient’s confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

9.9 DRUG ACCOUNTABILITY
Accountability for the study drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Drug accountability records indicating the drug’s delivery date to the site, inventory at the site, use by each patient, and disposal of the drug will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers. All used, unused or expired study drug will be disposed of at the study site and documented. All material containing VELCADE will be treated and disposed of as hazardous waste in accordance with governing regulations.

9.10 PREMATURE CLOSURE OF THE STUDY
This study may be prematurely terminated, if in the opinion of the investigator or the sponsor or its designee, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or the sponsor or its designee by the terminating party. Circumstances that may warrant termination include, but are not limited to:
- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the study drug
Should the study be closed prematurely, all study materials must be returned to the sponsor or its designee.

9.11 END OF STUDY
The end of study is defined as the date of the last visit of the last patient undergoing the study. Within 90 days of the end of the study the sponsor will notify the competent authorities and the ethics committees in all Member States where the study is being carried out that the study has ended. If the study is terminated early the sponsor will notify the competent authorities and ethics committees in all Member States within 15 days and explain the reasons for premature termination. Within one year of the end of the study a summary of the clinical trial report will be submitted to the competent authorities and ethics committees in all Member States involved.

9.12 RECORD RETENTION
The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

9.13 PUBLICATION POLICY
All publication procedures must be in line with the protocol and contract. The final publication of the trial results will be written by the Study Coordinator(s) on the basis of the statistical analysis performed at the Data in Munich. A draft manuscript will be submitted to the Data Center and all co-authors for review. After revision by the Data Centre and the other co-authors, the manuscript will be sent to a peer reviewed scientific journal. Authors of the manuscript will include the study coordinator(s), the lead investigators of the major groups, investigators of most recruiting institutions (by order of inclusion), the statistician, and others who have made significant scientific contributions. Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, but no comparisons between randomized treatment arms may be made publicly available before the recruitment is discontinued. Any publication, abstract or presentation based on patients included in this study must be approved by the study coordinator(s). This is applicable to any individual patient registered in the trial, or any subgroup of the trial patients. Such a publication cannot include an analysis of any of the study end-points unless the final results of the trial have already been published.

9.14 NATIONAL REQUIREMENTS
The study will be conducted at different national sites in accordance with the national law and national regulatory requirements. All documents necessary for the initiation of the study at a national site will be conducted in a separate attachment to this protocol.
10 REFERENCES


18. Forstpointner, R., Dreyling, M., Repp, R., et al., *The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate


41. Gereciano, J., Portlock, C., Noy, A., et al., The Schedule Dependent Combination of Bortezomib (Bor) with Rituximab (R), Cyclophosphamide (C) and Prednisone (P) Produces Minimal Toxicity, Even at Relatively High Doses of Proteasome Inhibitor, in Patients with


## 11 ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALAT (SGPT)</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ASAT (SGOT)</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ASCT</td>
<td>Autologous stem cell transplantation</td>
</tr>
<tr>
<td>BUN</td>
<td>Blood urea nitrogen</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CR</td>
<td>Complete response</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>Cru</td>
<td>Complete response/unconfirmed</td>
</tr>
<tr>
<td>CTC</td>
<td>Common toxicity criteria</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>FL</td>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>G-CSF</td>
<td>Filgastrim</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Process</td>
</tr>
<tr>
<td>HAMA</td>
<td>Human anti-murine antibodies</td>
</tr>
<tr>
<td>Hb</td>
<td>Hemoglobin</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>MCL</td>
<td>Mantel cell lymphoma</td>
</tr>
<tr>
<td>MM</td>
<td>Millimole</td>
</tr>
<tr>
<td>PBS</td>
<td>Phosphate buffered saline</td>
</tr>
<tr>
<td>PBSCT</td>
<td>Peripheral blood stem cell transplantation</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>PFS</td>
<td>Progression-free-survival</td>
</tr>
<tr>
<td>PPD</td>
<td>Product of two largest perpendicular diameters</td>
</tr>
<tr>
<td>PR</td>
<td>Partial response</td>
</tr>
<tr>
<td>PS</td>
<td>Performance status</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SC</td>
<td>Stem cell</td>
</tr>
<tr>
<td>SPD</td>
<td>Sum of the products of the greatest diameters</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limits of normal</td>
</tr>
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</table>
12 APPENDIX

12.1 WHO PERFORMANCE CRITERIA

<table>
<thead>
<tr>
<th>Definition</th>
<th>Grade</th>
</tr>
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<tbody>
<tr>
<td>The patient is able to carry out all normal activities without restriction</td>
<td>0</td>
</tr>
<tr>
<td>The patient is restricted in physically strenuous activity but able to carry out light work, patient is ambulatory</td>
<td>1</td>
</tr>
<tr>
<td>Patient is ambulatory and capable of all self-care but unable to carry out any work, patient is out of bed more than 50% of waking hours</td>
<td>2</td>
</tr>
<tr>
<td>Patient is capable of only limited self-care and confined to bed or chair more than 50% of waking hours</td>
<td>3</td>
</tr>
<tr>
<td>Patient is completely disabled; cannot carry out any self-care and is totally confined to bed or chair</td>
<td>4</td>
</tr>
</tbody>
</table>
12.2 ECOG PERFORMANCE CRITERIA

<table>
<thead>
<tr>
<th>Definition</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
<td>0</td>
</tr>
<tr>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
<td>1</td>
</tr>
<tr>
<td>Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
<td>2</td>
</tr>
<tr>
<td>Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours</td>
<td>3</td>
</tr>
<tr>
<td>Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair</td>
<td>4</td>
</tr>
<tr>
<td>Dead</td>
<td>5</td>
</tr>
</tbody>
</table>
12.3 CATEGORIES OF STAGING (ACCORDING TO ANN ARBOR)

**Stage I**

I: Involvement of a single lymph node region  
IE: Localized involvement of a single extralymphatic organ or site

**Stage II**

II: Involvement of 2 or more lymph node regions on the same side of the diaphragm  
IIE: Localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm

**Stage III**

III: Involvement of lymph node regions on both sides of the diaphragm  
IIIE: accompanied by: localized involvement of an extralymphatic organ or site  
IIIS: involvement of the spleen  
IIIS+E: both (IIIS+IIIE).

**Stage IV**

IV: disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.  
IV E: extranodal lymphoid malignancies arise in tissues separate from, but near, the major lymphatic aggregates.

In the absence or presence of fever (> 38°C, not otherwise explained), night sweats (recurrent, drenching) and/or unexplained loss of 10 percent or more of body weight in the six months preceding admission are to be denoted in all cases by the suffix letters A or B, respectively.
12.4 RESPONSE CRITERIA

Evaluation of response will be done according to the International Workshop to Standardize Response Criteria for Non-Hodgkin’s Lymphoma.

In the future, as additional radiographic, laboratory, and functional studies become more widely available and clearly demonstrate predictive value, they may be recommended as well.

CR requires the following:
Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalisation of those biochemical abnormalities (e.g. lactate dehydrogenase (LDH) definitely assignable to NHL.
All lymph nodes and nodal masses must have regressed to normal size (<1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (>20 mm biopsy core). Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time.

CR/unconfirmed (CRu) includes those patients who achieve a complete disappearance of all clinical symptoms or organ involvement, but with one or more of the following features:
A residual lymph node mass greater than 1.5 cm greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia)

PR requires the following:
50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features:
- they should be clearly measurable in at least two perpendicular dimensions,
- they should be from as completed disparate regions of the body as possible, and
- they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- No increase in the size of the other nodes, liver, or spleen.
- Splenic and hepatic nodules must regress by at least 50% in the SPD.
- With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
- Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report and preferably confirmed by immunohistochemistry.
- No new sites of disease.

Stable disease/No change is defined as less than a PR (see above) but is not progressive disease (see below).

Relapsed disease (after CR, CRu) requires the following:
- Appearance of any new lesion or increase by > 50% in the size of previously involved sites.
- >50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.
**Progressive disease** (after PR, non-responders) requires the following:
- >50% increase from nadir in the SPD of any previously identified abnormal node for PRs or non-responders.
- Appearance of any new lesion during or at the end of therapy

Response is currently assessed on the basis of clinical, radiologic, and pathologic (ie, bone marrow) criteria. PET scanning is not accepted as the sole instrument for response measurements.

CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. Radiologic investigations should be performed no later than 4 weeks after the end of treatment to assess response. A bone marrow aspirate and biopsy should only be performed to confirm a CR if they were initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

Table 1. Response Criteria for Non-Hodgkin's Lymphoma

<table>
<thead>
<tr>
<th>Response category</th>
<th>Physical examination</th>
<th>Lymph nodes</th>
<th>Lymph node masses</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>CR&lt;sub&gt;i&lt;/sub&gt;</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>&gt;75% decrease</td>
<td>Normal/indeterminate</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>Normal</td>
<td>Normal</td>
<td>&gt;50% decrease</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>&gt;50% decrease</td>
<td>&gt;50% decrease</td>
<td>Irrelevant</td>
</tr>
<tr>
<td></td>
<td>Increase in liver/spleen</td>
<td>&gt;50% decrease</td>
<td>≥50% decrease</td>
<td>Irrelevant</td>
</tr>
<tr>
<td><strong>Relapse/progression</strong></td>
<td>Enlarged liver/spleen/new sites</td>
<td>New/increased</td>
<td>New/increased</td>
<td>Reappearance</td>
</tr>
</tbody>
</table>

In case of relapse after initial complete remission the following information will be registered:
Date of relapse
Site of relapse
Whether there is histological or cytological confirmation of the relapse.
12.5 FACT-GOG-NTXScales

12.5.1 German Version

Nachfolgend finden Sie eine Liste von Aussagen, die von anderen Personen mit Ihrer Krankheit für wichtig befunden wurden. Bitte geben Sie jeweils an, wie sehr jede der folgenden Aussagen im Laufe der letzten 7 Tage auf Sie zutroffen hat, indem Sie die entsprechende Zahl ankreuzen.

<table>
<thead>
<tr>
<th>ZUSÄTZLICHE FAKTOREN</th>
<th>Überhaupt nicht</th>
<th>Ein wenig</th>
<th>Mäßig</th>
<th>Ziemlich</th>
<th>Sehr</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTX 1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>NTX 2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
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<tr>
<td>NTX 3</td>
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<td>HI 12</td>
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<td>NTX 6</td>
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</tr>
<tr>
<td>NTX 9</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>An 6</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not at all</th>
<th>A little</th>
<th>Some what</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>I have numbness or tingling in my hands</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have numbness or tingling in my feet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel discomfort in my hands</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel discomfort in my feet</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have joint pain or muscle cramps</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I feel weak all over</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble hearing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I get a ringing or buzzing in my ears</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble buttoning buttons</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble feeling the shape of small objects when they are in my hand</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I have trouble walking</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
12.5.3 FRENCH VERSION

Vous trouverez ci-dessous une liste de commentaires que d'autres patients, atteints de la même maladie, ont jugé importants. Veuillez indiquer, en entourant un chiffre sur chaque ligne, dans quelle mesure chacune de ces propositions était vraie en ce qui vous concerne durant ces 7 derniers jours.

**AUTRES SUJETS D’INQUIÉTUDE**

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NTX 1</td>
<td>J'ai les mains qui s'engourdissent ou qui picotent</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NTX 2</td>
<td>J'ai les pieds qui s'engourdissent ou qui picotent</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NTX 3</td>
<td>J'ai une gêne dans les mains</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NTX 4</td>
<td>Je sens une gêne dans mes pieds</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NTX 5</td>
<td>J'ai des douleurs aux articulations et/ou des cramps aux muscles</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HI 12</td>
<td>Je ressens une faiblesse générale</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NTX 6</td>
<td>J'ai du mal à entendre</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NTX 7</td>
<td>J'ai les oreilles qui tintent ou qui bourdonnent</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NTX 8</td>
<td>J'ai du mal à boutonner les vêtements</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>NTX 9</td>
<td>J'ai du mal à palper la forme de petits objets quand ils sont dans ma main</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>An 6</td>
<td>J'ai du mal à marcher</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>