

# Horizon Scanning in Oncology

Bendamustine  
(Ribomustin<sup>®</sup>/Treanda<sup>®</sup>/ Levact<sup>®</sup>)  
for indolent non-Hodgkin's  
lymphoma, chronic lymphocytic  
leukaemia and multiple myeloma



Ludwig Boltzmann Institut  
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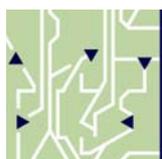
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# 1 Drug description

## Generic/Brand name:

Bendamustine Hydrochloride / Ribomustin® (Germany, Switzerland)

Bendamustine / Levact® (Bendamustine is currently undergoing regulatory review in 12 countries across Europe [1])

Bendamustine Hydrochloride / Treanda® (USA)

**Bendamustine  
Hydrochloride**

**Ribomustin® , Levact® ,  
Treanda®**

## Developer/Company:

Bendamustine (RIBOMUSTIN®) is licensed from Astellas Deutschland GmbH and is marketed in Germany and Switzerland by the Mundipharma independent associated companies (e.g. Mundipharma International). In the United States, bendamustine (TREANDA®) is marketed by Cephalon Inc.

**Mundipharma GmbH  
Cephalon Inc.**

SymBio Pharmaceuticals Ltd holds exclusive rights for developing and marketing bendamustine in Japan (sublicensed to Eisai Co Ltd) and selected Asian countries.

## Description:

Bendamustine, a chemotherapeutic agent for cancer therapy, is a bifunctional mechlorethamine derivative (nitrogen mustard group which contains a purine-like benzimidazole ring). The nitrogen mustard group is structurally similar to cyclophosphamide and chlorambucil and gives the drug its alkylating properties while the benzimidazole ring may be responsible for its antimetabolite properties. The precise cytotoxic mechanism of action remains unclear [2].

**bifunctional alkylating  
agent for cancer therapy**

Bendamustine causes only partial cross-resistance to other alkylating agents and anthracyclines and this has been cited as one advantage over other chemotherapeutic agents [3].

Bendamustine Hydrochloride is available in single-use vials containing either 25 mg or 100 mg of bendamustine hydrochloride as white to off-white lyophilized powder. After reconstitution with sterile water it should be administered by intravenous infusion over 30 (to 60) minutes.

**different regimes and  
dosages ranging from  
60 to 150mg/m<sup>2</sup> for  
NHL, CLL and MM**

The recommended dosage of bendamustine in CLL is 70-100 mg/m<sup>2</sup> in 0.9% NaCl solution (up to 500ml) on Days 1 and 2 of a 28 day cycle for up to 6 cycles (dose depends on use as single agent or in combination) [4, 5].

There are different treatment regimes for its use in indolent non-Hodgkin's lymphomas (NHL). The recommended dosage as single agent is 120 mg/m<sup>2</sup> infused intravenously over 60 minutes on Days 1 and 2 of a 21 day cycle for up to 8 cycles, when used in combination with vincristine and prednisone the dosage is 60 mg/m<sup>2</sup> infused intravenously on Days 1 to 5 [4, 5].

The recommended dosage of bendamustine in multiple myeloma is 120-150 mg/m<sup>2</sup> in 0.9% NaCl solution (up to 500ml) infused intravenously on Days 1 and 2 of a 28 day cycle [5].

## 2 Indication

Bendamustine is indicated for

**indolent NHL, CLL and multiple myeloma**

- indolent non-Hodgkin's lymphomas (NHL)
- chronic lymphocytic leukaemia (CLL)
- advanced multiple myeloma (MM) stage II (with progression) and stage III

## 3 Current regulatory status

**Germany since 2005**  
**USA since 2008**  
**Switzerland since 2009**

Bendamustine was first synthesized in the early 1960s at the Institute for Microbiology and Experimental Therapy in Jena (Germany). It was widely used but never studied systematically in patients until the 1990s. Then German investigators demonstrated its clinical activity in a number of malignancies and bendamustine received its first marketing approval in Germany in 2005, for use as single agent or in combination-chemotherapy regimens for indolent non-Hodgkin's lymphomas (NHL), multiple myeloma (MM) and chronic lymphocytic leukaemia (CLL). Trials conducted outside of Germany led to the approval of bendamustine (TREANDA®) by the FDA in 2008 [2, 6] for the following indications:

- Chronic lymphocytic leukaemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established
- Indolent B-cell non-Hodgkin's lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab containing regimen.

In addition, bendamustine has been approved in Switzerland (RIBOMUSTIN®) for CLL since March 2009 [7].

**decentralised approval procedure**

Moreover, Astellas Pharma GmbH submitted Levact (bendamustine hydrochloride) to the German medicines regulatory agency for a decentralised procedure. This is a procedure where one Member State (the 'reference Member State', in this instance Germany) assesses a medicine with a view to granting a marketing authorisation that will be valid in that country as well as in other Member States (the 'concerned Member States', in this instance Belgium, Denmark, Finland, France, Ireland, Italy, Luxembourg, Norway, Poland, Spain and the United Kingdom). However, the Member States were not able to reach an agreement and the German medicines regulatory agency referred the matter to the CHMP for arbitration on 2 October 2009 [8]. In March 2010 the CHMP concluded that marketing authorisation can be granted in the following indications:

**positive CHMP (EMA) opinion**

- Chronic lymphocytic leukaemia in patients for whom treatment with fludarabine is not appropriate
- Non-Hodgkin's lymphoma in patients who have had a relapse following treatment containing rituximab
- Multiple myeloma in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell

transplantation and cannot be treated with thalidomide or bortezomib

Following the CHMP conclusion, a subsequent European Commission decision, and the granting of national licences, the first launches of bendamustine (LEVACT®) in the European Union are anticipated in mid-2010 in Austria, Denmark, Finland and the UK [9].

## 4 Burden of disease

### Indolent Non-Hodgkin's lymphomas (NHL)

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative disorders originating in B-lymphocytes, T-lymphocytes or natural killer lymphocytes (white blood cells). About 90% of NHLs are B-cell lymphomas and about 10% of NHL cases are T-cell and NK lymphomas. There are many different types of non-Hodgkin's lymphomas. NHL is much less predictable than Hodgkin lymphoma and has a far greater predilection to disseminate to extranodal sites. The prognosis depends on the histological type, stage, and treatment.

NHL can be divided into two prognostic groups: the indolent (slow-growing) lymphomas and the aggressive (fast-growing) lymphomas. Indolent NHL types have a relatively good prognosis with a median survival of 10 years, but they are usually not curable in advanced clinical stages. Early stage (stage I and stage II) indolent NHL can be effectively treated with radiation therapy alone. Most of the indolent types are nodular (or follicular) in morphology. The aggressive type of NHL has a shorter natural history, but a significant number of these patients can be cured with intensive combination chemotherapy regimens. In general, with modern treatment of patients with NHL, overall survival at 5 years is approximately 50% to 60%. Of patients with aggressive NHL, 30% to 60% can be cured. The vast majority of relapses occur in the first 2 years after therapy. The risk of late relapse is higher in patients with a divergent histology of both indolent and aggressive disease [10].

Since 2001 the World Health Organization (WHO) classification is the internationally accepted classification of NHL, which is a refinement of the REAL classification, the Revised European-American Classification of Lymphoid neoplasm. The stages of NHL follow the Ann-Arbor-Staging system. The Ann Arbor staging system with Cotswold modification, originally developed for Hodgkin lymphoma, has been adapted for staging NHL. This staging system focuses on the number of tumour sites -nodal and extranodal-location, and the presence or absence of systemic ("B") symptoms:

- ❖ Stage I refers to NHL involving a single lymph node region (stage I) or a single extralymphatic organ or site (stage IE).
- ❖ Stage II refers to two or more involved lymph node regions on the same side of the diaphragm (stage II) or with localized involvement of an extralymphatic organ or site (stage IIE).
- ❖ Stage III refers to lymph node involvement on both sides of the diaphragm (stage III), or with localized involvement of an extralymphatic organ or site (stage IIIIE) or spleen (stage IIIS), or both (stage IIIES).

**heterogeneous group of disorders**

**two prognostic groups:  
indolent NHL,  
aggressive NHL**

**Ann Arbor Staging system**

- ❖ Stage IV refers to the presence of diffuse or disseminated involvement of one or more extralymphatic organs (eg, liver, bone marrow, lung), with or without associated lymph node involvement.
- ❖ The presence or absence of systemic symptoms should be noted with each stage designation. (A = asymptomatic. B = presence of fever (>38 degrees C), sweats, or weight loss >10 percent of body weight over six months.

Since NHLs most frequently disseminate haematogenously, this staging system has proven to be much less useful than for Hodgkin lymphoma, which disseminates principally by contiguous lymphatic extension. It is generally accepted that there is little therapeutic benefit in distinguishing between stages III and IV disease in NHL, since treatment options are nearly identical. Thus, staging is undertaken in NHLs to identify the small numbers of patients with "early stage disease" who can be treated with local therapy or combined modality treatment, and to stratify within histological subtypes in order to determine prognosis and assess the impact of treatment [11].

**incidence of 7.6 per  
100,000 in 2007**

According to Statistik Austria 514 people died of NHL disease and 1057 new cases were diagnosed in 2007 in Austria. Thus, in 2007 the incidence of NHL was 7.6 per 100,000 (9.5 for men and 6.1 for women) [12].

Multiple studies have demonstrated that prognosis is far more dependent upon histopathology, being only secondarily influenced by clinical parameters including age, presence of extranodal disease, performance status, and stage (I/II versus III/IV). Since stage usually depends only upon the location and number of disease sites, it is not a true measure of tumour burden, which is clearly an important prognostic determinant in non-Hodgkin lymphoma, and may also affect the overall treatment program employed [11].

### **Chronic Lymphocytic Leukaemia (CLL)**

**most common  
leukaemia in Western  
countries**

Chronic lymphocytic leukaemia (CLL) is one of the chronic lymphoproliferative disorders (lymphoid neoplasm). It is characterized by a progressive accumulation of functionally incompetent lymphocytes. CLL is considered to be identical (i.e., one disease at different stages) to the mature (peripheral) B-cell neoplasm small lymphocytic lymphoma (SLL), one of the indolent non-Hodgkin lymphomas.

**incidence was  
7.6 per 100,000 in 2007**

CLL is the most common leukaemia in Western countries. The disorder is more common in men with a male to female ratio of approximately 1.7:1.

In Austria the overall incidence of all forms of leukaemia was 7.6 per 100,000 and the overall death rate of all forms of leukaemia was 4.6 per 100,000 in 2007. Within men, the death rate was 6.0 per 100,000 and within women it was 3.6 per 100,000 in 2007 [13].

CLL is considered to be mainly a disease of the elderly, with a median age at diagnosis of 70 years; however, it is not unusual to make this diagnosis in younger individuals from 30 to 39 years of age. The incidence increases rapidly with increasing age.

Patients with CLL have a wide range of symptoms and physical and laboratory abnormalities at the time of diagnosis. Most patients consult a physician because they have noted painless swelling of lymph nodes. Approximately 25 percent of patients feel entirely well with no symptoms when a routine blood count reveals an absolute lymphocytosis, leading to a diagnosis of CLL [14].

The natural history of CLL is extremely variable, with survival times from initial diagnosis that range from 2 to 20 years, and a median survival of approximately 10 years. Although patients with early stage disease have a greater than 10 year life expectancy, patients with more advanced disease have a median survival of 18 months to 3 years and those who have fludarabine refractory disease have a median survival of less than one year. Advances in the therapy for CLL, particularly "chemoimmunotherapy" regimens combining cytotoxic agents such as alkylating agents and purine nucleoside analogs with monoclonal antibodies such as rituximab, have improved initial overall response (OR) rates, complete response (CR) rates and progression free survival (PFS). Despite these advances, CLL remains incurable with standard therapies [15].

There are two classification systems for the clinical staging of CLL, the Rai Classification and the Binet staging system. The Rai classification distinguishes low (formerly Rai stage 0), intermediate (formerly Rai stage I or II) and high (formerly Rai stage IV and V) risk disease, whereas the Binet staging is subdivided into stage A, B and C [16].

**Binet staging or  
Rai classification**

### **Multiple Myeloma**

Multiple myeloma (MM, plasmacytoma), one of the mature B-cell lymphoid neoplasms, is characterized by the accumulation of malignant plasma cells in the bone marrow compartment, increased production of a monoclonal immunoglobulin (Ig), and bone destruction. MM is an incurable disease and the cause of multiple myeloma is unknown. MM is a disease of older adults. The median age at diagnosis is 66 years; only 10 and 2 percent of patients are younger than 50 and 40 years, respectively [17].

**Multiple Myeloma or  
plasmacytoma an  
incurable disease**

MM accounts for approximately 1 percent of all cancers and slightly more than 10 percent of hematologic malignancies in Austria. The incidence of MM was about 2.5 per 100,000 (2.8 for men and 2.1 for women) in 2007 in Austria. In absolute numbers 180 men and 198 women were diagnosed with plasmacytoma in Austria in 2007. The incidence appears to be stable [18].

**incidence in 2007:  
2.5 per 100,000**

MM is considered to be very sensitive to cytotoxic drugs. However, no curative treatment approach for this disease exists yet. At diagnosis smouldering (asymptomatic) and active (symptomatic) disease can be distinguished. Further, the symptomatic disease is classified according to stages following the Durie-Salmon staging system (based upon factors correlating with tumour cell mass) or the International Staging System (ISS) which incorporates data on the levels of serum beta-2 microglobulin (B2M) and serum albumin alone to divide disease burden into three stages with prognostic significance. Both staging systems have three different levels (stage I-III) and Durie-Salmon uses the letters A (normal renal function; serum creatinine level <2.0 mg/dL) and B (serum creatinine level ≥2.0 mg/dL) for sub-classification within the different stages, whereas ISS has the following classification:

**Durie-Salmon staging or  
International Staging  
System (ISS)**

- ❖ Stage I — B2M <3.5 mg/L and serum albumin ≥3.5 g/dL
- ❖ Stage II — neither stage I nor stage III
- ❖ Stage III — B2M ≥5.5 mg/L

The median overall survival for patients with ISS stages I, II, and III are 62, 44, and 29 months, respectively [19, 20].

## 5 Current treatment

### Indolent Non-Hodgkin's lymphomas (NHL)

While indolent NHL is responsive to radiation therapy and chemotherapy, a continuous rate of relapse is usually seen in advanced stages. Patients, however, can often be retreated with considerable success as long as the disease histology remains low grade. Patients who present with or convert to aggressive forms of NHL may have sustained complete remissions with combination chemotherapy regimens or aggressive consolidation with marrow or stem cell support [10].

different therapeutic  
approaches for indolent  
NHL

The most common subtypes of indolent (slow growing) B-cell NHL include chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL), follicular lymphoma and Marginal Zone lymphoma. Different therapeutic approaches exist in the treatment of these types of lymphoma and the following substances are used in different chemotherapy regimes:

- Fludarabine
- Chlorambucil
- Cyclophosphamide
- Vincristine
- Mitoxantrone
- Rituximab

### Chronic Lymphocytic Leukaemia (CLL)

CLL is an extremely heterogeneous disease and not all patients require treatment at the time of diagnosis. Therapy is indicated for patients with advanced stage disease, high tumour burden, severe disease-related "B" symptoms, or repeated infections.

Among patients with newly diagnosed early stage asymptomatic CLL, observation is recommended rather than immediate treatment

Prior to the initiation of active therapy for patients with symptomatic disease, patients with CLL should undergo a pre-treatment evaluation to determine the extent of disease, patient performance status, and assessment of co-morbidities that are likely to have an impact on treatment options.

fludarabine-based  
regime for most  
patients

For patients with localized (stage I) SLL, treatment with involved-field radiation therapy is recommended alone rather than systemic chemotherapy. Patients with stage II or more advanced SLL are treated with chemotherapy regimens used for symptomatic CLL. There is no agreed upon standard treatment regimen for symptomatic CLL or advanced SLL. There are several initial treatment options for patients with symptomatic CLL or advanced SLL. Treatment options include purine analogs (e.g., fludarabine, pentostatin), alkylating agents (e.g., chlorambucil, bendamustine), monoclonal antibodies (e.g., rituximab, alemtuzumab), or combinations of these agents. Most have not been directly compared. The use of fludarabine-based regimes is suggested for most patients. While overall survival rates with the different available regimens are similar, they differ in their rates of complete remission (CR), time to progression, and associated toxicities. A choice between these therapies is made based upon patient characteristics and goals

of therapy. Median overall survival with each of these regimens is approximately five years.

The National Cancer Institute Working Group (NCI/WG) and the International Workshop Group on CLL (IWCLL) have developed joint formal criteria for evaluating disease response. The goals and duration of therapy for CLL are poorly defined, and there is no evidence that intensification or maintenance therapy is of benefit [15, 21].

### **Multiple Myeloma (MM)**

The initial therapy of patients with symptomatic myeloma varies depending on whether patients are eligible for autologous hematopoietic cell transplantation (AHCT). If a patient is not a candidate for AHCT, the only treatment option is chemotherapy alone. The present choices for induction therapy for transplant candidates include bortezomib-, lenalidomide- or thalidomide-based regimens. All these regimens are also options for non-transplant candidates. Alkylating agents compromise stem cell reserve, and thus are options only for non-transplant candidates: Melphalan and prednisone has been standard treatment for MM since 1960. The addition of bortezomib or thalidomide is recommended by the NCCN myeloma panel since studies reported superior responses compared to melphalan/prednisone alone [19].

**melphalan and prednisone as standard treatment**

## **6 Evidence**

A literature search and contact with Mundipharma GmbH Austria about further information, as yet unpublished, on bendamustine have revealed three phase III trials for indolent NHL: two full publications, and one ASH meeting abstract; one phase III trial for CLL; and one phase III clinical trial for MM. In addition, six phase II trials of bendamustine in indolent NHL have been published, in addition to one phase II trial in CLL. No full publication of phase II trials in MM was identified.

**5 phase III trials for NHL, CLL and MM**

For indolent NHL, one trial compared bendamustine in combination with vincristine and prednisone (BOP) to cyclophosphamide with vincristine and prednisone (COP) in patients with advanced indolent non-Hodgkin's lymphoma and mantle cell lymphoma [22].

**3 phase III trials in indolent NHL:**

**2 full publications, one meeting abstract**

Kahl et al. investigated bendamustine monotherapy in patients with rituximab-refractory, indolent B-cell NHL in a single arm clinical trial [23].

The third clinical phase III trial was presented by Rummel et al. in 2009 at the Annual Meeting of the American Society in Hematology (ASH) [24] and compared bendamustine plus rituximab to CHOP plus rituximab as first-line treatment in patients with advanced follicular, indolent, and mantle cell lymphomas. Primary endpoints in these trials were overall response rate (ORR), duration of response (DOR), complete remission rate (CR) or progression-free survival. Overall survival (OS) was only secondary endpoint in two trials [22, 24].

**6 single-arm phase II studies**

Six single-arm phase II trials investigated bendamustine either as monotherapy in pre-treated low-grade NHL [25] or in rituximab-refractory indolent and transformed NHL [26], bendamustine in combination with vincris-

tine and prednisolone (BOP) in relapsed and refractory low grade NHL [27] or bendamustine plus rituximab in indolent NHL [28-30].

#### one phase III trial in CLL

In patients with CLL, bendamustine was investigated in a phase III trial published by Knauf et al. in 2009 [31]. Bendamustine was compared to chlorambucil in 319 patients with previously untreated CLL, primary endpoints were overall response rate and progression-free survival, no comment was made on overall survival due to short follow-up.

Additionally, a fully published single-arm phase II trial of bendamustine monotherapy in advanced and refractory CLL is available, primary endpoint was complete remission [32].

Other phase II trials, such as the combination of bendamustine with rituximab or the comparison of bendamustine to fludarabine in CLL, are only available as meeting abstracts and therefore not further discussed in this review.

#### one phase III trial in MM

Only one phase III trial of bendamustine in MM was identified in the literature search. Pönisch et al. investigated bendamustine in combination with prednisone compared to melphalan and prednisone in patients with newly diagnosed multiple myeloma [33]. Primary endpoint was time-to-treatment failure whereas overall survival, on of the secondary endpoints, did not differ significantly between treatment groups.

Further information and detailed results of all mentioned phase III and phase II trials is described in sections 6.1. and 6.2 which follow:

## 6.1 Efficacy and safety - Phase III studies

Table 6.1-1. Evidence table of phase III trials in indolent NHL

Reference	Kahl et al. 2010 [23]	Rummel et al., ASH Meeting Abstract 2009 [24]	Herold et al. 2006 [22]
Sponsor	Research support was provided by Cephalon Inc	Honoraria by Mundipharma	Supported by a grant from Ri-bosepharm GmbH, Germany
Country	USA, Canada	Germany	Germany
Design	Single-arm, open-label, phase III multicenter clinical trial	randomized, phase III multicenter clinical trial	Randomised, open-label, phase III multicenter trial
Participants characteristics	100 pts with rituximab-refractory, indolent B-cell NHL median age 60 years (range 31-84)	549 pts (513 randomized pts for the final analysis (I=260 pts; C: =253 pts), median patient age: I 64 years, C 63 yrs (range 31-83) Most patients were in stage IV and stage III. Histologies (I vs C: follicular 55% and 56%, mantle cell 18% and 19%, and other indolent lymphomas 27% and 24%	162 pts (advanced, previously untreated indolent NHL and mantle cell lymphoma I 82 pts, mean age 58.1 years C 80 pts, mean age 58.4 years

<b>Treatments</b>	<p><b>I(ntervention):</b> bendamustine 120 mg/m<sup>2</sup> on days 1 + 2 every 21 days, intravenously infused over 60 to 120 minutes</p> <p><b>No control group!</b></p>	<p><b>I(ntervention):</b> Rituximab 375 mg/m<sup>2</sup> (day 1) plus Bendamustine 90 mg/m<sup>2</sup> (days 1+2) every 28 days</p> <p><b>C(ontrol):</b> Rituximab 375mg/m<sup>2</sup> (day 1) plus standard CHOP regimen every 21 days (both for a maximum of 6 cycles)</p>	<p><b>I(ntervention):</b> BOP: bendamustine 60 mg/m<sup>2</sup> i.v. on days 1-5, vincristine 2mg on day 1 and prednisone 100 mg/m<sup>2</sup> on days 1-5 i.v. (the protocol originally specified bendamustine 70 mg/m<sup>2</sup>, but after 25 pts had been enrolled, significantly higher platelet toxicity was observed with the BOP regime compared to COP, and bendamustine dose was reduced to 60 mg/m<sup>2</sup>)</p> <p><b>C(ontrol):</b> COP: cyclophosphamide 400 mg/m<sup>2</sup> i.v on days 1-5, vincristine 2mg on day 1, and prednisone 100 mg/m<sup>2</sup> on days 1-5 i.v</p>
<b>In-/exclusion criteria</b>	<p><b>Inclusion:</b> ≥18 years of age, documented rituximab-refractory, indolent B-cell lymphoma WHO performance status ≤2; patients received 1-3 previous chemotherapy regimens</p> <p><b>Exclusion:</b> Chemotherapy, immunotherapy, radioimmunotherapy or investigational therapy within 28 days before the start of cycle 1, myeloid growth factor treatment within 14 days, concurrent treatment with therapeutic doses of systemic steroids within 14 days, transformed disease, concurrent, active malignancy, CNS lymphoma, serious infection, expected survival &lt;3 months</p>	<p>first-line therapy, follicular lymphoma, indolent and mantle cell lymphoma</p>	<p><b>Inclusion:</b> 18-75 years of age, previously untreated Histological confirmed follicular lymphoma, mantle cell lymphoma or lymphoplasmocytic lymphoma No longer suitable for primary radiotherapy</p> <p><b>Exclusion:</b> Previously treated with chemotherapy or radiotherapy WHO performance status &gt;2 Secondary NHL Positive HIV status Severe concomitant disease Chronic airway disease Non-lymphoma related renal or liver insufficiency</p>
<b>Follow-up</b>	median follow-up: 11.8 months	median observation time was 32 months	5 years (median follow up 44 months)
<b>Outcomes</b>	<p><b>Primary:</b> overall response rate (ORR), duration of response (DOR)</p> <p><b>Secondary:</b> safety, progression-free survival</p>	<p><b>Primary:</b> median progression-free survival (PFS)</p> <p><b>Secondary endpoints:</b> overall survival (OS), event-free survival (EFS), time to next treatment (TTNT), safety</p>	<p><b>Primary:</b> complete remission rate</p> <p><b>Secondary:</b> time to progression, time to treatment failure (event-free survival), overall survival, toxicities</p>
<b>Key results</b>	<p><b>Primary:</b> ORR: 75% (95% CI: 65-83%) median DOR: 9.2 months (95% CI: 7.1 – 10.8 months)</p> <p><b>Secondary:</b> Median progression-free survival: 9.3 months (95% CI: 8.1 – 11.9 months)</p>	<p><b>Primary:</b> median PFS: I 54.8 months vs. C 34.8 months, p=0.0002, HR = 0.577 (95%CI 0.429 to 0.768)</p> <p><b>Secondary:</b> EFS: I 54 months vs. C 31 months, p=0.0002, HR = 0.601, 95% CI 0.452 to 0.785 OS did not differ between both groups at time of analysis (after median observation time of 32 months)</p>	<p><b>Primary:</b> complete remission rate: I 22% vs. C 20%, p=0.812</p> <p><b>Secondary:</b> Median time to progression: I 84 months vs. C 28 months, p=0.0369 Time to treatment failure (responders only): I 27 months vs. C 21 months, p= 0.05 Median survival time: I 76 months vs. C 54 months, p=0.2</p>

<b>Adverse effects</b>	27 patients discontinued treatment early due to adverse events, 24 pts had dose reductions because of adverse events (neutropenia, thrombocytopenia were most common) Grade 3: neutropenia 38%, thrombocytopenia 19%, infections 15% , fatigue 12% Grade 4: neutropenia 23%, thrombocytopenia 6%, infections 6% , fatigue 2% Overall Grade 3/4: in 61% of patients Secondary malignancies in 2 pts 2 episodes of tumor lysis syndrome	Hematologic toxicities: neutropenia grade 3/4: I 10.7% vs. C 46.5% leukocytopenia grade 3/4: I 12.1% vs. C 38.2% Infectious complications: I 95 pts vs. C 121 pts deaths: I 34 pts vs. C 33 pts	Most common and most severe toxicities included leucopenia, thrombocytopenia, decreased haemoglobin, nausea and vomiting, fever, alopecia and infection Leucopenia grade 3/4: I 19% vs. C 34% Alopecia grade 3/4: I 32% vs. C 84% Thrombocytopenia more frequent in BOP treatment related deaths: I 2 pts vs. C 0 pts secondary neoplasias: I 4 pts vs. C 2 pts
<b>Commentary</b>	Overall survival was not an endpoint of the study	Overall survival was not primary endpoint of the study Only meeting abstract, no full publication available;	No statistically significant difference in treatment arms for primary endpoint Overall survival was not primary endpoint, no difference in overall survival

*pts – patients; CI – confidence interval; I – intervention ; C – control ; HR – hazard ratio ;*

#### 442 patients overall in bendamustine group

In these three phase III trials bendamustine was investigated overall in 442 patients. Due to different study designs (randomized controlled trial vs. single-arm trial), patient characteristics (previously untreated NHL vs. rituximab-refractory NHL) and treatment options (bendamustine monotherapy vs. bendamustine combination with rituximab), these trials can not be compared to each other. In addition, bendamustine was administered in three different doses ranging from 60 mg/m<sup>2</sup> to 120 mg/m<sup>2</sup>. Overall survival was either not considered as an endpoint in the trial or analysed as a secondary endpoint. No difference between treatment arms at time of analysis was shown.

#### no significant difference in primary endpoint

Herold et al. [22] compared bendamustine combination therapy to the COP regime which has been considered as standard treatment for patients with indolent NHL but did not detect a significant difference in complete remission rate (primary endpoint) between both treatment groups. Although a benefit for the bendamustine combination (BOP) over COP was shown in some secondary endpoints, its role in these patients remains unclear. There is no other equal clinical trial comparing this bendamustine-based regime versus COP available.

#### meeting abstract PFS significantly longer in bendamustine group single-arm phase III study overall response rate of 75%

Rummel et al. [24] investigated bendamustine in combination with rituximab versus CHOP plus rituximab in previously untreated patients (first-line treatment) and showed the final results at the ASH Annual Meeting in 2009. The median progression-free survival (primary endpoint) was significantly longer in the bendamustine group (54.8 months versus 34.8 months in control group, p=0.0002). This is the only phase III trial of bendamustine in combination with rituximab as first-line treatment in patients with indolent NHL. The full final publication remains to be seen.

The third phase III trial [23] was as single-arm study investigating bendamustine monotherapy in rituximab-refractory indolent NHL. An overall response rate of 75% (65-83%, 95%CI) was observed which is comparable with the result of a previous phase II trial [26] by Friedberg et al. (ORR = 77%). This phase III trial was one of the relevant studies considered by the FDA for the approval of bendamustine monotherapy in rituximab-refractory indolent NHL in the USA in 2008.

The most common adverse events in these trials were grade 3 or 4 neutropenia, thrombocytopenia, anaemia, infection, nausea and other non-haematological adverse events as described in table 6.1-1.

**mainly haematological adverse events**

Table 6.1-2. Evidence table of phase III trial in Chronic Lymphocytic Leukaemia (CLL)

<b>Reference</b>	Knauf et al. 2009 [31]
<b>Sponsor</b>	Supported by grants from Ribosepharm GmbH Germany and Mundipharma International
<b>Country</b>	Multicenter (45 centers in Austria, Bulgaria, France, Germany, Italy, Spain, Sweden and UK)
<b>Design</b>	randomized, open-label, parallel-group, phase III multicenter trial
<b>Participants characteristics</b>	319 previously untreated patients with advanced (Binet stage B or C) CLL Intervention: 162 pts, mean age 63 years, Binet stage B: 116 pts and stage C 46 pts Control: 157 pts, mean age 63.6 years, Binet stage B: 111 pts and stage C 46 pts Comparable WHO performance status in both groups
<b>Treatments</b>	<b>I(ntervention):</b> Bendamustine at a dose of 100 mg/m <sup>2</sup> /d on days 1 and 2 every 4 weeks as intravenous infusion over 30 min  <b>C(ontrol):</b> Chlorambucil orally at a dose of 0.8 mg/kg on days 1 and 15 every 4 weeks
<b>In-/exclusion criteria</b>	<b>Inclusion:</b> Previously untreated patients, Age up to 75 years, Binet stage B or C, WHO performance status of 0 to 2, Life expectancy of at least 3 months  <b>Exclusion:</b> Patients with second malignancy, Patients with manifest immune haemolysis or thrombocytopenia, Richter's syndrome, Hepatic or renal dysfunction, Mental disorders, HIV infection, Major surgery within 30 days before start of trial
<b>Follow-up</b>	Median observation time 35 months (range 1 to 68)
<b>Outcomes</b>	<b>Primary:</b> overall response rate, progression-free survival  <b>Secondary:</b> time to progression, duration of remission, overall survival, safety
<b>Key results</b>	<b>Primary:</b> overall response rate (CR or PR): I 68% vs. C 31%, p<0.0001 median progression-free survival: I 21.6 months vs. C 8.3 months, p<0.0001  <b>Secondary:</b> median duration of response: I 21.8 months vs. C 8.0 months, p<0.0001 time to progression not reported; no difference in overall survival at time of analysis
<b>Adverse effects</b>	Withdrawal due to toxicities: I 18 pts vs. C 5 pts AEs grade 3/4: Neutropenia/granulocytopenia: I 23% vs. C 10.6% Leukopenia: I 14.3% vs. C 1.3% Thrombocytopenia: I 11.8% vs. C 7.9% Infections: I 8% vs. C 3% More adverse events (all grades) in bendamustine group: hypersensitivity reactions, hematologic events (neutropenia, thrombocytopenia, anemia, leukopenia) and GI events (nausea, vomiting), severe infections, two reports on tumor lysis syndrome in bendamustine group
<b>Commentary</b>	ITT analysis (6 patients randomly assigned to chlorambucil and one to bendamustine were not treated), safety population 312 pts treated Overall survival was not primary endpoint, no difference in overall survival after median observation time of 35 months Adverse events in bendamustine group more frequent although manageable

pts – patients; I – intervention; C – control; CR – complete response; PR – partial response; AEs – adverse events; ITT – intention to treat;

**bendamustine compared to chlorambucil**  
**PFS significantly longer in bendamustine group**

This phase III randomized clinical trial compared bendamustine to chlorambucil in a total of 319 previously untreated patients with advanced (Binet stage B or C) CLL. A complete response was achieved in 31% bendamustine-treated patients and in 2% of chlorambucil-treated patients, the median progression-free survival was 21.6 months in the bendamustine group and 8.3 months in the chlorambucil group ( $p < 0.0001$ ) but no significant difference in overall survival has yet been observed.

**more grade 3/4 AEs in bendamustine group**

18 patients from the bendamustine and 5 from the chlorambucil group were withdrawn from the study due to unacceptable toxicity. In general, more grade 3/4 adverse events were observed in bendamustine-treated patients, especially neutropenia and leukopenia, hypersensitivity and infections. In addition, two reports on tumor lysis (although not fatal) were observed in the bendamustine group, none in the control group.

No other phase III clinical trial of bendamustine in patients with CLL has been published so far.

*Table 6.1-3. Evidence table of phase III trial in Multiple Myeloma (MM)*

<b>Reference</b>	Pönisch et al. 2006 [33]
<b>Sponsor</b>	East German Study Group of Hematology and Oncology (OSHO) – sponsored by Mundipharma (Ribosepharma GmbH Germany)
<b>Country</b>	Germany
<b>Design</b>	Prospective, open-label, randomized, multicenter, phase III trial
<b>Participants characteristics</b>	131 pts (previously untreated patients) I: 68 pts; median age 62 yrs (range 38 – 76 years); stage II with progression MM: 7 pts; stage III MM: 61 pts C: 63 pts; median age 62 (range 42 – 80 years); stage II with progression MM: 4 pts; stage III MM: 59 pts
<b>Treatments</b>	<b>I(ntervention):</b> Prednisone (60 mg/m <sup>2</sup> intravenously or orally) on days 1-4 in combination with bendamustine (150 mg/m <sup>2</sup> in 500ml NaCl 0.9% as intravenous infusion over 30 min) on days 1 and 2  <b>C(ontrol):</b> Prednisone (60 mg/m <sup>2</sup> intravenously or orally) on days 1-4 in combination with melphalan (15 mg/m <sup>2</sup> in 100 ml NaCl 0.9% intravenously over 30 min) on day 1  Treatment was administered every 28 days until maximum remission or disease progression was observed. Patients had to receive at least two cycles of chemotherapy for efficacy to be evaluated.
<b>In-/exclusion criteria</b>	<b>Inclusion:</b> Stage II with progression or stage III MM (Durie & Salmon System), Quantitatively measurable myeloma proteins, Leukocyte count $\geq 2,000/\mu\text{l}$ , Platelet count $\geq 50,000/\mu\text{l}$ , Karnofsky performance status of $\geq 60\%$ , Life expectancy of $\geq 3$ months, Nor prior chemotherapy or radiotherapy  <b>Exclusion:</b> Nonsecretory and local plasmacytoma, HIV or Hbs-AG positivity or active hepatitis, Secondary malignancy, Serious concomitant diseases
<b>Follow-up</b>	until maximum remission or disease progression
<b>Outcomes</b>	<b>Primary:</b> time to treatment failure (TTF) <b>Secondary:</b> survival, remission rate, toxicity, quality of life

<b>Key results</b>	<p><b>Primary:</b> TTF: I 14 months vs. C 10 months, <math>p &lt; 0.02</math></p> <p><b>Secondary:</b> median overall survival: I 32 months vs. C 33 months, NS Overall remission rate (CR and PR): I 75% vs. C 70%, NS CR: I 32% vs. C 13%, <math>p = 0.007</math> PR: I 43% vs. C 57% , NS QoL: I superior in global status of health and emotional functioning at 4 and 6 months</p>
<b>Adverse effects</b>	<p>Grade 3/4: nausea and vomiting: I 12% vs. C 0% anaemia: I 24% vs. C 24% leukocytopenia: I 40% vs. C 31% thrombocytopenia: I 10% vs. C 15%</p>
<b>Commentary</b>	<p>Overall survival was not primary endpoint, no difference in overall survival No ITT analysis (136 patients enrolled, 131 pts evaluated for analysis) Crossover to alternative treatment in case of progression was allowed, but no crossover analysis</p>

*MM - multiple myeloma; TTF - time to treatment failure, CR - complete remission, PR - partial remission, pts - patients, NS - not significant, ITT -intention to treat; I – intervention ; C – control ; QoL – quality of life;*

There is only one randomized phase III clinical trial of bendamustine in patients with multiple myeloma published. Pönisch et al. compared bendamustine with prednisone to the standard therapy of melphalan with prednisone in patients with previously untreated MM (first-line therapy).

Of the 136 enrolled patients, only 131 patients were analyzed for the primary endpoint ‘time to treatment failure (TTF)’, which was 14 months in the bendamustine group and 10 months in the control group ( $p < 0.02$ ). They did not observe any differences in the median overall survival. The study design allowed crossover to the alternative treatment in the case of disease progression during therapy or within the 3-month therapy-free interval: 9 patients of the bendamustine group and 13 patients of the melphalan group changed the treatment, but no cross-over analysis was performed.

Although haematological toxicities were comparable in both arms, more patients in the bendamustine group required a dose reduction due to adverse events such as leukocytopenia and thrombocytopenia. Grade 3/4 nausea and vomiting was observed in 12% of patients in the bendamustine group, but in no case in the control group.

Although the study assessed quality of life as secondary endpoint, only a small proportion of questionnaires were available for analysis (23 out of 68 in bendamustine group, 19 out of 63 in melphalan group). A positive effect was seen 4 months after treatment and remained so beyond 6 months, but nothing was mentioned about the effect at a later point of time.

**bendamustine with prednisone compared to melphalan with prednisone**

**no difference in median overall survival**

**comparable toxicities in both arms**

**limited results for quality of life**

## 6.2 Efficacy and safety - further studies

### Indolent NHL

additionally six  
phase II trials

In addition to the three phase III studies of bendamustine in patients with indolent NHL, we identified six non-randomized phase II clinical trials investigating bendamustine either in monotherapy or in different combination therapy regimes for patients with pre-treated relapsed or refractory indolent (low-grade) NHL.

#### Bendamustine Monotherapy

bendamustine as  
salvage therapy

- Bremer et al. 2002 [25] conducted a phase II single arm study of bendamustine as salvage therapy in 102 pre-treated low-grade NHL patients (with different histological subtypes). The overall remission rate was 76.5% (78/102 patients), the median overall survival was 29 months. Serious non-haematological side effects ( $\geq$  grade 3 or 4) were less frequent than haematological toxicity such as leukopenia (25%), thrombocytopenia (more than 20%) and anaemia (about 30%).

median PFS 8.3 months

- Friedberg et al 2008 [26] conducted a phase II multicenter study to evaluate bendamustine monotherapy in patients with B-cell NHL refractory to rituximab. 76 patients with a median age of 63 years were treated. The overall response rate was 77%, the median progression-free survival was 8.3 months (95% CI, 6.6 to 10.9), The observed adverse events were grade 3 or 4 neutropenia (54%), anemia (12%) and thrombocytopenia (25%) and non-hematological adverse events like nausea, vomiting and fatigue.

#### Bendamustine in combination with other cytotoxic agents or rituximab

combination with  
vincristine and  
prednisolone

- Kath et al. 2000 [27] conducted an open phase II study of bendamustine in combination with vincristine and prednisolone in patients with relapsed and refractory low grade NHL. 22 patients with a median age of 61.5 years were treated with bendamustine as salvage therapy. Objective remission was achieved in 86% (19/22 patients), haematological adverse events were the most frequent ones and a decline of the CD4/CD8 (ratio was observed in more than 50% of patients).

combination with  
rituximab

median PFS 24 months

- Rummel et al 2005 [29] conducted an open label phase II multicenter trial of bendamustine in combination with rituximab in patients with mantle cell or low grade NHL in first to third relapse or refractory to previous treatment. 63 patients with a median age of 64 years were treated. The median progression-free survival was 24 months (range 5 to 44+ months) for all patients. Leukocytopenia was the major toxicity.

combination with  
mitoxantrone and  
rituximab

overall response rate  
89%

- Weide et al. 2007 [28] conducted a multicenter phase II study of bendamustine in combination with mitoxantrone and rituximab in patients with stage III/IV relapsed or refractory indolent NHL and mantle cell lymphoma with or without prior rituximab containing treatment. 57 patients were treated with a median age of 66 years. The overall response rate was 89% and the estimated progression-free survival was 19 months. The most frequent adverse events were

grade 3 or 4 leukocytopenia (78%), granulocytopenia (46%), thrombocytopenia (16%) and anaemia (10%).

- Robinson et al. 2008 [30] conducted a multicenter, open-label, single-arm phase II study of bendamustine with rituximab in patients with relapsed, indolent B-cell or mantle cell lymphoma. 66 patients with a median age of 60 years were treated. The overall response rate was 92% and the median progression-free survival was 23 months (95% CI, 20 to 26 months). The most common adverse events were leukopenia (94%), neutropenia (79%), anaemia (77%), thrombocytopenia (62%), nausea (70%) and infection (64%).

**combination with  
rituximab**

**median PFS 23 months**

At present, other phase II studies of bendamustine in patients with indolent NHL are only available as meeting abstracts. They will be considered for evidence as soon as full publications are available.

### Chronic Lymphocytic Leukaemia

In addition to the phase III study mentioned above (Knauf et al. 2009), one fully published small phase II trial investigating bendamustine monotherapy in patients with advanced, refractory or relapsed CLL was identified. The single-centre phase II study determined the activity and toxicity of monotherapy with bendamustine in 23 patients (median age 62 years) with previously treated (n=10) and untreated (n=13) CLL [32]. A complete or partial remission was achieved in 15/20 patients (75%), including six patients with complete response. Median overall survival was calculated as 13.6 months. WHO grade 3/4 leukocytopenia was very frequent and resulted in treatment-related deaths in 3/23 patients. A decline of the lymphocyte CD4/CD8 ratio which could lead to additional immunosuppression with subsequent infectious complications was observed in all patients.

**one additional phase II  
trial in CLL**

**median OS 13.6 months**

As above, other phase II studies of bendamustine in patients with CLL are only available as meeting abstracts. They will be considered for evidence as soon as full publications are available.

### Multiple Myeloma

No published phase II clinical trial was identified by the literature search. Other investigations (e.g. phase I trials, clinical observations) in patients with recurrent, advanced or refractory relapsed multiple myeloma are only available as meeting abstract. Two phase II trials in patients with MM are currently ongoing, results are expected for 2012 (see chapter 8 – ongoing research).

**no other fully published  
clinical trial in MM**

## 7 Estimated costs

One vial Ribomustin® (Bendamustine) 25mg costs € 44,- whereas one vial Ribomustin 100mg costs € 267,-. The costs of Levact® (bendamustine) which is currently undergoing regulatory review in 12 countries across Europe are not known. [34]

Assuming an average body surface of 1.7 m<sup>2</sup> for NHL, CLL and MM patients and considering the recommended dosages, the costs per cycle for these indications would be

costs per cycle for NHL,  
CLL and MM range from  
€622,- to €1.335,-  
up to 6 cycles

- € 1,335,- (Bendamustine in combination therapy; 60 mg/m<sup>2</sup>, Days 1-5); € 1,068,- (Bendamustine monotherapy; 120 mg/m<sup>2</sup>, Days 1+2) in NHL treatment
- € 622,- to € 798,- (€ 1,068,-, if only 100mg vials of bendamustine are used) - (Bendamustine 70 - 100 mg/m<sup>2</sup>, Days 1+2) in CLL treatment
- € 1,068,- to € 1,244,- (Bendamustine 120 - 150 mg/m<sup>2</sup>, Days 1+2) in MM treatment

costs for LEVACT® not  
known yet

Since Bendamustine is an old drug belonging to the group of alkylating agents, treatment costs are low compared to newer targeted anticancer therapies like monoclonal antibodies. Nevertheless the costs for Levact®, Mundipharma's new bendamustine product, have to be awaited.

## 8 Ongoing research

According to ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)), a registry of federally and privately supported clinical trials conducted in the United States and around the world and a service of the U.S. National Institutes of Health, several clinical trials of bendamustine are currently being conducted in patients with different cancer diseases.

### Indolent NHL

four phase III studies in  
indolent NHL are  
ongoing

Four phase III trials are investigating the efficacy of bendamustine in patients with indolent NHL. The trials either use bendamustine monotherapy or bendamustine in combination with different antibodies:

- One study (NCT00139841), sponsored by Cephalon, was completed only recently in May 2010. It is a multicenter phase III non-randomized study which investigated the safety and efficacy of Treanda® (Bendamustine HCl) in patients with indolent Non-Hodgkin's Lymphoma (NHL) who are refractory to rituximab. The study started in 2005; primary endpoint was overall response rate. The results have not been published yet.
- An open-label, randomized, parallel-group phase III study (NCT00877006), again sponsored by Cephalon, is investigating bendamustine hydrochloride and rituximab (BR) compared to ri-

tuximab, cyclophosphamide, vincristine, and prednisone (R-CVP) or to rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in the first-line treatment of patients with advanced indolent Non-Hodgkin's Lymphoma (NHL) or Mantle Cell Lymphoma (MCL). The study started in 2009 and will be completed in 2017; primary endpoint is complete response rate.

- One study (NCT01077518), sponsored by GlaxoSmithKline and starting June 2010 will evaluate the safety and efficacy of ofatumumab (Arzerra®) and bendamustine combination therapy in patients with indolent B-cell NHL that did not respond to rituximab or a rituximab-containing regimen during or within 6 months of the last rituximab treatment. The study will last until 2022. Ofatumumab is a monoclonal antibody targeting CD20.
- One study (NCT01059630), sponsored by Genentech, is an open-label, randomized phase III trial investigating the efficacy and safety of GA101 combined with bendamustine compared to bendamustine alone in patients with rituximab-refractory, indolent Non-Hodgkin's lymphoma (NHL). RO5072759 (GA101) is the first humanized and glycoengineered monoclonal anti-CD20 antibody. The study lasts until 2015.

## CLL

Bendamustine in patients with CLL is currently being investigated in one phase IV and one phase III clinical trial:

**one phase III and one phase IV study in CLL are ongoing**

- The phase IV study (NCT01056510), sponsored by Hoffmann La-Roche, is a randomized study to assess the effect on response rate of MabThera (Rituximab) added to a standard chemotherapy, bendamustine or chlorambucil, in patients with Chronic Lymphocytic Leukaemia. The study will be completed in 2013.
- A randomized, open-label phase III clinical trial (NCT00769522), by the German CLL Study Group, is investigating combined immunochemotherapy with fludarabine, cyclophosphamide and rituximab (FCR) versus bendamustine and rituximab (BR) in patients with previously untreated Chronic Lymphocytic Leukaemia. The primary outcome is the progression-free survival rate after 24 months. The study will be completed in 2018.

Several ongoing phase II trials in patients with NHL and CLL are listed on the ClinicalTrials website. These trials investigate bendamustine in combination with various other anticancer drugs (e.g. bortezomib, alemtuzumab, ofatumumab, rituximab, mitoxantrone) and in different stages or therapy lines of NHL and CLL.

## Multiple Myeloma

There is no phase III clinical trial of bendamustine in multiple myeloma listed at clinicaltrials.gov, but phase II and phase I/II studies are currently investigating bendamustine either in combination with bortezomib or lenalidomide in patients with MM. The phase II trials are listed here:

**no phase III, but two phase II in MM are ongoing**

- A non-randomized, phase II trial (NCT01045681) by Intergroupe Francophone du Myelome is investigating bendamustine, bortezomib (Velcade®) and Dexamethasone (BVD) in the treatment of elderly patients ( $\geq 65$  Years) with multiple myeloma in 1st relapse or refractory to first-line therapy. The primary outcome is overall response rate. The study will be completed in 2012.
- A phase II study (NCT01056276) by Sarah Cannon Research Institute and sponsored by Cephalon and Millenium Pharmaceuticals Inc. is investigating bendamustine, bortezomib and dexamethasone (BBD) in the first-line treatment of patients with Multiple Myeloma who are not candidates for high dose chemotherapy. The trial lasts until 2012.

### Other Cancer Types

**bendamustine for ovarian cancer, SCLC, AML / MDS, breast cancer and soft tissue sarcoma**

Bendamustine is currently being investigated in several other indications in oncology within phase I/II or phase II clinical trials, e.g. ovarian cancer, small cell lung cancer (SCLC), acute myeloid leukaemia (AML), breast cancer and soft tissue sarcoma.

## 9 Commentary

Due to disagreement among several EU member states, the EMA was contacted by the German medicines regulatory agency within the decentralised approval procedure for bendamustine (Levact®). EMA's CHMP concluded in March 2010 that marketing authorisation for bendamustine can be granted in Germany and 12 other member states of the EU for three indications (CLL, NHL and MM). The FDA, on the other hand, approved bendamustine (Treanda®) only for CLL and NHL in 2008.

**evidence-based use and balancing benefits and risks**

Although drug costs of bendamustine are considered to be low compared to other especially newer targeted cancer therapies, its use in patients with indolent NHL, CLL and MM should be evidence based. The benefits and risks of bendamustine-based therapy have to be balanced carefully and have to be assessed out of a patients' perspective. The current evidence and recommendations for bendamustine in these indications, based on the identified trials mentioned above, are summarized subsequently.

### Bendamustine in Patients with Indolent Non-Hodgkin's lymphomas (NHL)

Although several phase III as well as phase II studies which assessed bendamustine for the treatment of NHL were found, the heterogeneity of NHL and the differences in treatment regimens (i.e. first- vs. second-line therapy, differing dosing regimens, differing combinations) make it difficult to conclusively judge the potential clinical benefit associated with bendamustine therapy. Despite data indicating improvements in progression-free survival, overall response rate or overall remission rate, to date no trial has demonstrated increases in overall survival or quality of life (QoL).

The NCCN guidelines ‘Non-Hodgkin’s Lymphomas’ include bendamustine with or without rituximab as an option for second-line therapy for patients with relapsed or refractory NHL. This recommendation is only based on low-level evidence (2B recommendation) because only limited data are available for this indication [35].

Due to current reported data, its reasonable safety profile and its low costs, bendamustine can be seen as an additional therapeutic option for some patients with indolent NHL but further trials are needed. The results of these trials will help to better identify the role of bendamustine among treatment options for indolent NHL. In addition, the optimal dose and schedule have to be defined and toxicities (mainly grade 3/4 haematological adverse events) have to be monitored when bendamustine is used.

**therapeutic option for some patients with NHL**

**further trials are needed**

### Bendamustine in Patients with Chronic Lymphocytic Leukaemia (CLL)

To date one phase III randomized clinical trial (Knauf et al. 2009) comparing bendamustine with chlorambucil for first-line therapy in patients with CLL is published. Although the primary endpoints overall response rate (68% versus 31%,  $p < 0.0001$ ) and median progression-free survival (PFS = 21.6 months versus 8.3 months,  $p < 0.0001$ ) were favoured in the bendamustine group, no difference in overall survival was observed between both arms at time of analysis (after median observation time of 35 months). However, the approval of bendamustine for CLL patients was based on this phase III trial. Adverse events especially hematologic toxicity and infections were more frequent in the bendamustine group. Since fludarabine-based regimens are considered as standard choice for most patients with CLL, trials comparing bendamustine with fludarabine are necessary to further investigate the role of bendamustine in patients with previously untreated CLL.

Regarding other treatment regimes, the role of bendamustine in combination with rituximab for first-line therapy or bendamustine-based treatment for patients with relapsed or refractory CLL remains still unclear, since there are no randomized clinical trials available.

**no comparison to fludarabine-based regime**

The CHMP recommended granting marketing authorisation within EU member states for “bendamustine for CLL in patients for whom treatment with fludarabine is not appropriate”. In addition, although bendamustine is approved by FDA for CLL patients and the NCCN guidelines ‘Non-Hodgkin’s Lymphomas’ include bendamustine as single-agent for first-line therapy and as single-agent or in combination with rituximab for second-line therapy, these recommendations are based on limited evidence [35]. Efficacy of bendamustine compared to other therapies than chlorambucil has not yet been established in randomized clinical trials and full publications on efficacy and safety are still required.

In summary, the use of bendamustine for first-line therapy in patients with CLL is currently based on one published randomized phase III trial and results of other clinical trials have to be seen to evaluate its role in second-line CLL therapy. Despite preliminary evidence based on meeting abstracts or published non-randomized trials, bendamustine can be seen as salvage therapy for patients with CLL. The observation of hematologic toxicity and a decline in the CD4/8 ratio (possibly responsible for higher infection rate) in bendamustine treated patients which require dose reduction, end of bendamustine treatment or additional therapy should led to carefully balancing

**salvage therapy for patients with CLL**

the risks and benefits of bendamustine therapy. Further trials investigating bendamustine-based treatments are necessary to clearly define its role in patients with CLL.

### Bendamustine in Patients with Multiple Myeloma (MM)

**no strong advantage  
over standard treatment**

Evidence of bendamustine in patients with MM is still limited. Only one study (RCT) of bendamustine in patients with multiple myeloma has been published. This phase III clinical trial compared bendamustine to a melphalan-based standard treatment in 131 patients newly diagnosed MM, 68 patients were treated with the bendamustine-based regime (see table 6.1-3). Although the primary endpoint ‘time to treatment failure’ was significantly longer in the bendamustine group, no difference in overall survival was observed. The toxicities in the two arms were comparable. In summary, the trial did not show a clear advantage of bendamustine over melphalan-based standard treatment. No other randomized trials are available. The two ongoing phase II trials of bendamustine in patients with MM are non-randomized, single-arm studies and investigate a different treatment regime - bendamustine in combination with bortezomib. The results of these trials are not conclusive with regard to the role of bendamustine compared to standard treatment for first-line therapy of patients with MM.

**salvage therapy for  
patients with MM**

In summary, evidence for bendamustine in patients with MM is limited and its value in MM treatment remains unclear. The NCCN ‘Multiple Myeloma’ guideline recommends bendamustine as salvage therapy (based on low-level evidence, category 2B) [19] and the European Medicines Agency (EMA) indicates bendamustine “for the treatment of multiple myeloma in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and cannot be treated with thalidomide or bortezomib” [1]. Bendamustine is not approved by the FDA for the treatment of MM. Further trials are needed to demonstrate efficacy of bendamustine in patients with MM and to address issues such as overall survival and quality of life.

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