Product monograph

Levact® i.v. (bendamustine HCl)

Levact®
bendamustine HCl

www.napponcology.co.uk

Prescribing information can be found on Page 62

Chapter one: An introduction to *Levact*® i.v.

Levact i.v. (bendamustine hydrochloride) is an alkylating anti-tumour agent with unique activity[1,2] licensed for:

- first-line treatment of chronic lymphocytic leukaemia (CLL, Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate;
- indolent non-Hodgkin's lymphomas (NHL) as monotherapy in patients who have progressed during, or within 6 months following, treatment with rituximab or a rituximab-containing regimen;
- front line treatment of multiple myeloma (MM, Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib-containing treatment.

Bendamustine was developed in the 1960s by East German pharmacologists with the aim of combining the 2-chloroethylamine group of the nitrogen mustard derivatives with the benzimidazole ring system of purine analogues.[3] It entered clinical practice in 1969 to treat MM[4] and reached the German market in the early 1970s.[5] Bendamustine was marketed in Germany from 1971 to 1992 as Cytostasan and from 1993 to present as Ribomustin. In 2005, after formal clinical development programmes were conducted in the US (for NHL) and in Europe, it was formally reapproved in Germany for treating patients with indolent NHL, CLL and MM. Bendamustine is currently marketed in the US as Treanda for the treatment of CLL and relapsed or refractory indolent NHL.

This product monograph introduces evidence supporting ***Levact*** i.v. as an important addition to the oncological armamentarium in the first-line treatment of CLL, indolent NHL in rituximab-refractory patients, and advanced MM. For further information please contact our Medical Information Department (oncologymedinfo@napp.co.uk or 01223 424444) or visit our website (www.napponcology.co.uk).

Chemical structure

The bendamustine molecule is comprised of three structural elements:[2]

- A 2-chloroethylamine group that bendamustine shares with other nitrogen mustard derivatives, including cyclophosphamide, chlorambucil and melphalan. The chloroethylamine group is largely responsible for bendamustine's alkylating action.
- A butyric acid side chain, which bendamustine shares with chlorambucil.
- A benzimidazole central ring system, which is shared with purine analogues such as fludarabine and cladribine.

Figure 1 shows the structure of bendamustine compared with cladribine and alkylators.

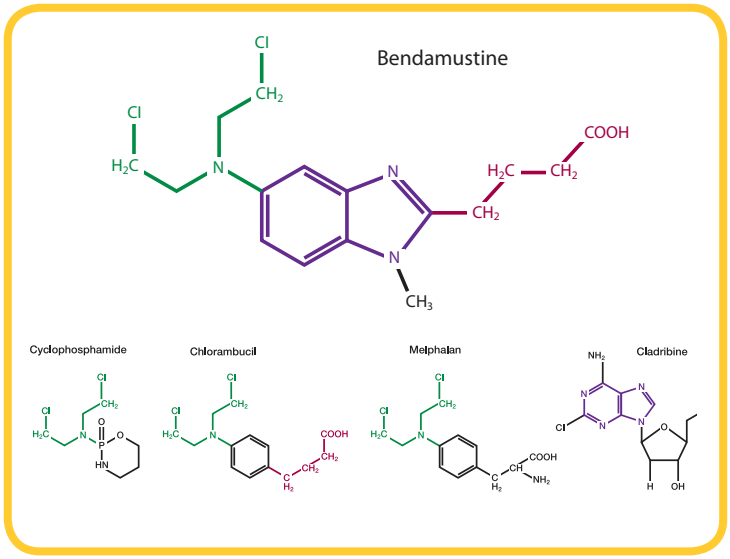

Figure 1: The structure of bendamustine

Mechanism of action

The three structural elements in the bendamustine molecule result in ***Levact*** i.v. having a unique mechanism of action that is distinct from other chemotherapeutics.

Computer programs that identify similarities between the structure and function of thousands of clinically used and experimental anti-cancer drugs can predict whether two compounds are likely to share a mechanism of action. Function in these terms is based on growth inhibitory activity in 60 cell lines.

Using this approach, melphalan, chlorambucil and cyclophosphamide's active metabolites have shown similar patterns to numerous other compounds (25, 25 and 23, respectively), most of which are DNA-alkylating agents.[2] In contrast, bendamustine did not strongly correlate with any other anti-cancer compounds, including other alkylating agents. "These results suggest that bendamustine has a unique mechanistic profile compared with most conventional alkylators."[2]

DNA strand breaks

Like other alkylating agents, bendamustine has been shown to cross-link DNA and produce single or double strand breaks in experimental systems using human ovarian and breast carcinoma cell lines.[6] However, it has been shown to produce more extensive and more durable single and double-strand breaks than cyclophosphamide, cisplatinum (cisplatin), or carmustine.[6]

Induction of apoptosis

Bendamustine induces apoptosis (programmed cell death) in several *in vitro* tumour models through three complementary mechanisms:

- Bendamustine seems to induce numerous genes that trigger apoptosis, including those linked to p53.[2]
- Bendamustine seems to regulate genes controlling expression of receptors that are members of the tumour necrosis factor (TNF) super-family.[2]
- Bendamustine has been shown to lead to an 8-fold up-regulation of Ser^{15}-phosphorylated p53 in NHL cells. Phosphorylation of p53 at Ser^{15} is a key event in triggering apoptosis. Chlorambucil produces only minor increases in phosphorylation, whereas cyclophosphoramide has no effect.[2]

"These results suggest that bendamustine has a unique mechanistic profile compared with most conventional alkylators."[2]

Effect on DNA repair pathways

Bendamustine induces a 'fingerprint' of DNA repair pathways in NHL cell lines that differs from other alkylating agents. For example:

- Bendamustine has been shown to increase expression of exonuclease-1 (EXO1) 2.5-fold. In contrast, phosphoramide mustard (a metabolite of cyclophosphamide) and chlorambucil increased EXO1 expression only 1.5- and 1.8-fold, respectively.[2]
- In contrast to phosphoramide, bendamustine induces a repair pathway in a Burkitt's lymphoma cell line that uses base excision.[2]
- In two lymphoma cell lines, conventional alkylating agents induce a repair mechanism that uses alkyltransferase. Bendamustine does not seem to influence the alkyltransferase repair mechanism in these cells.[2]

Variations in DNA repair pathways may contribute to the different activity and resistance profiles between bendamustine and conventional alkylating agents.[2]

Inhibition of mitotic checkpoints and mitotic catastrophe

The cell cycle includes several checkpoints that send abnormal cells either for repair, or along an apoptotic pathway. Mitotic catastrophe is a necrotic form of cell death that occurs during metaphase and is morphologically distinct from apoptosis. Hallmarks of this process are chromatin condensation and micronucleation. It has been shown to occur *in vitro* in the absence of p53 or in cells where caspase-dependent apoptosis is inhibited. Mitotic catastrophe may destroy cancer cells that are resistant to apoptosis following exposure to previous chemotherapeutics.[2]

In addition to damaging DNA, bendamustine seems to inhibit certain cell cycle checkpoints in certain cell lines. Therefore, it may allow cells with heavy DNA damage (such as that produced by alkylation) to enter the next stage in the cell cycle. This may trigger mitotic catastrophe. Two key strands of evidence support this suggestion:

- Flow cytometric analysis of the effect of several chemotherapeutic agents (used in equitoxic doses) on cell cycle progression in an NHL cell line showed that bendamustine increased the proportion of cells in S phase (DNA replication). Compared with a control rate of 37%, 60% of bendamustine-treated cells entered S phase. Figures for chlorambucil and phosphoramide were 45% and 37%, respectively.[2]
- Chromatin condensation and micronucleation are hallmarks of mitotic catastrophe. One study treated multi-drug resistant breast and colon cancer cell lines with pan-caspase (apoptotic) inhibitors. In these cells, bendamustine induced such morphological changes in 26% of cells, compared with 6% of untreated (DMSO) controls.[2]

The apparent ability of bendamustine to cause mitotic catastrophe in certain cell lines, as well as apoptosis, may help account for bendamustine's effectiveness in drug-resistant cells.[2]

Indications

Levact i.v. is indicated for:

- first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate;
- indolent NHL as monotherapy in patients who have progressed during, or within 6 months following, treatment with rituximab or a rituximab-containing regimen;
- front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib-containing treatment.

Presentation

Levact i.v. is supplied in single-use brown glass vials, containing either 25 mg or 100 mg of white, microcrystalline powder for concentrate for solution for infusion (see Figure 2). The shelf life is 3 years.

Pack sizes available are:

25 mg – 5 vials
25 mg – 20 vials
100 mg – 5 vials

Reconstitution and dilution

Aseptic technique should be used for these procedures:

Reconstitution

- Reconstitute each vial of ***Levact*** i.v. containing 25 mg bendamustine hydrochloride in 10 ml water for injection by shaking.
- Reconstitute each vial of ***Levact*** i.v. containing 100 mg bendamustine hydrochloride in 40 ml water for injection by shaking.

The reconstituted concentrate contains 2.5 mg bendamustine hydrochloride per ml and appears as a clear, colourless solution.

Dilution

As soon as a clear solution is obtained (usually after 5 – 10 minutes), dilute the total recommended dose of ***Levact*** i.v. immediately with 0.9% NaCl solution to produce a final volume of about 500 ml. **Do not** dilute with any other injectable solution.

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25°C/60% RH and 2 days at 2°C to 8°C in polyethylene bags. From a microbiological point of view, the solution should be used immediately.

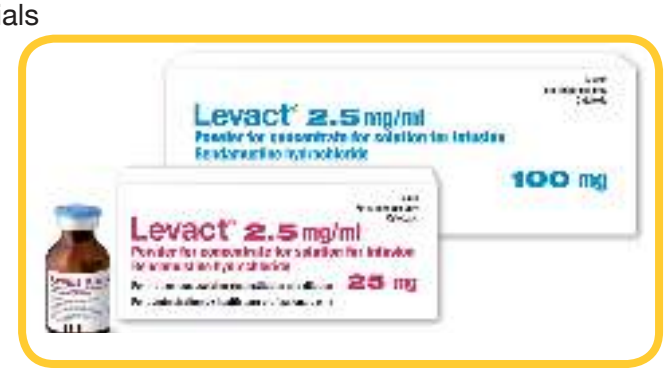

Figure 2: Presentation of ***Levact*** i.v.

Administration

The solution should be administered by intravenous infusion over 30 – 60 minutes. ***Levact*** i.v. must be administered under the supervision of a physician qualified and experienced in the use of chemotherapeutic agents.

Pharmacokinetics

Table 1 summarises the key pharmacokinetic parameters for ***Levact*** i.v.[1,7]

Bendamustine is more than 95% protein bound, mainly to albumin. The relatively short $t_{1/2}$ reflects the rapid metabolism and excretion.[1] Bendamustine binds strongly to DNA, forming carbonium ions, and extending its antineoplastic action[8] beyond the duration of the drug's presence in plasma.

Levact i.v. metabolism

Metabolism of bendamustine is mainly by CYP1A2, which produces two metabolites: monohydroxybendamustine and dihydroxybendamustine (see Figure 3, Page 7). The C_{max} and AUC for these metabolites are approximately 3% of the respective values for bendamustine.[7] Another major route of metabolism involves conjugation with glutathione.[1]

The metabolic route means that clinicians need to be cognisant of theoretical potential interactions between ***Levact*** i.v. and concurrent drugs that inhibit or induce CYP1A2. However, no *in vivo* interaction studies have been performed.

Parameter	Value
$t_{1/2}$ (elimination half life)	28.2 minutes (mean)
t_{max}	29.6 minutes (mean)
C_{max}	11.8 µg/ml
AUC (area under the concentration time curve)	11.7 hr*µg/ml
V_d (volume of distribution)	19.3 L
V_d under steady state	15.8 - 20.5 L
Cl (clearance)	639 ml/min

Table 1: Typical pharmacokinetic values for ***Levact*** i.v.

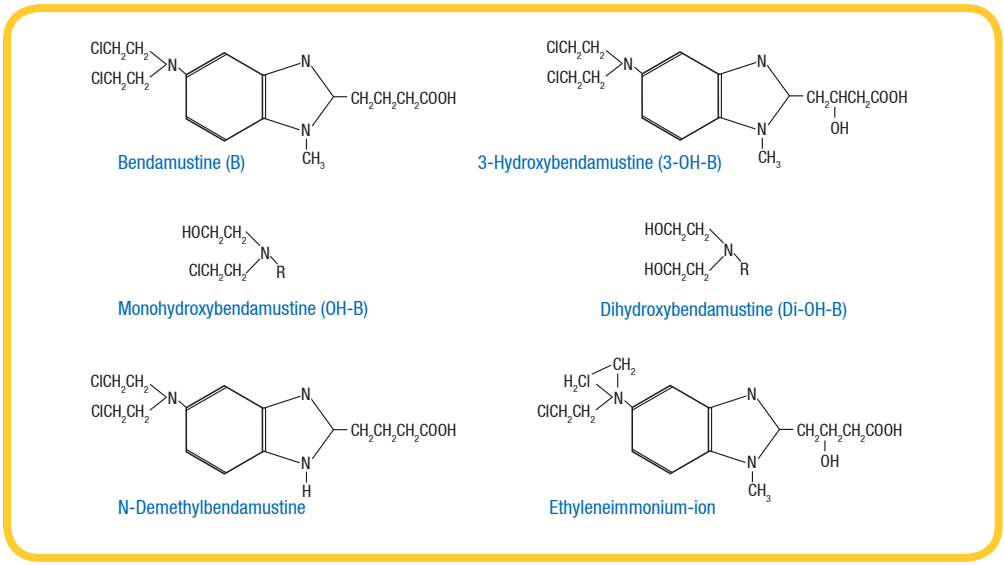

Figure 3: Structure of bendamustine and the main metabolites produced by CYP1A2

Excretion of *Levact* i.v.

Bendamustine and the two cytochrome metabolites undergo type II metabolism to form cysteine S-conjugates. Most (96%) of a single bendamustine dose is excreted in the bile. Urine excretion only accounts for between 3.8% and 16.3%.[9]

Pharmacokinetics of *Levact* i.v. in renal impairment

No significant differences have been observed with respect to t_{max}, C_{max}, AUC, $t_{1/2\beta}$, volume of distribution, and clearance in patients with creatinine clearance >10 ml/min (including dialysis patients) compared with patients with normal renal function.[1,7] No dose adjustment is necessary in patients with creatinine clearance of >10 ml/min.[1]

Experience in patients with severe renal impairment is limited. Bendamustine is dialyzable[1] – further details and trial data in patients on dialysis should be requested from Napp Pharmaceuticals Limited as the data supporting dosage and use in such patients are limited.

Pharmacokinetics of *Levact* i.v. in hepatic impairment

Pharmacokinetic parameters (C_{max}, t_{max}, AUC, $t_{1/2\beta}$, volume of distribution and clearance) are not changed in patients with 30 – 70% tumour infestation of the liver and mild hepatic impairment (serum bilirubin <1.2 mg/dL).[7] Therefore, no dose adjustment is necessary in patients with mild hepatic impairment.[1] A dose reduction of 30% is recommended in patients with moderate hepatic impairment (serum bilirubin 1.2 – 3.0 mg/dl).[1]

No data are available in patients with severe hepatic impairment (serum bilirubin >3.0 mg/dl). ***Levact* i.v. is therefore contra-indicated in these patients.**[1]

Paediatric patients

There is no experience with ***Levact*** i.v. in children or adolescents.[1]

Elderly patients

Subjects up to 84 years of age were included in pharmacokinetic studies. Age does not influence the pharmacokinetic profile of bendamustine. There is no evidence that dose adjustments are necessary in elderly patients.[1]

Dosage

Monotherapy for CLL

100 mg/m^2 body surface area bendamustine hydrochloride on Days 1 and 2, every 4 weeks.[1]

Monotherapy for indolent NHLs (rituximab-refractory)

120 mg/m^2 body surface area bendamustine hydrochloride on Days 1 and 2, every 3 weeks.[1]

Advanced MM

120 – 150 mg/m^2 body surface area bendamustine hydrochloride on Days 1 and 2, 60 mg/m^2 body surface area prednisone i.v. or per os on Days 1 to 4, every 4 weeks.[1]

Treatment should be terminated or delayed if leukocyte and/or platelet values drop to <3,000/µl or <75,000/µl, respectively. Treatment can be continued after leukocyte values have increased to >4,000/µl and platelet values to >100,000/µl.[1]

The leukocyte and platelet Nadir is reached after 14 – 20 days with regeneration after 3 – 5 weeks. During therapy-free intervals, strict monitoring of the blood count is recommended.[1]

In case of non-haematological toxicity, dose reductions should be based on the worst CTC grades in the preceding cycle. A 50% dose reduction is recommended in cases of CTC grade 3 toxicity. An interruption of treatment is recommended in the case of CTC grade 4 toxicity.[1]

If a patient requires a dose modification, the individually calculated reduced dose must be given on Days 1 and 2 of the respective treatment cycle.[1]

Interactions

No *in vivo* interaction studies have been performed. Bendamustine metabolism involves the cytochrome P450 (CYP) 1A2 isoenzyme. Therefore, potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, acyclovir and cimetidine exists.[1]

When ***Levact*** i.v. is combined with myelosuppressive agents, its effect and that of co-administered medicinal products on the bone marrow may be potentiated. Any treatment affecting the patient's performance status or impairing bone marrow function can increase the toxicity of ***Levact*** i.v.

Combination of ***Levact*** i.v. with cyclosporine or tacrolimus may result in excessive immunosuppression with risk of lymphoproliferation.[1]

Cytostatics can reduce antibody formation following live virus vaccination and increase the risk of infection which may lead to a fatal outcome. The risk is increased in subjects who are already immunosuppressed by their underlying disease.

Chapter two: First-line treatment of chronic lymphocytic leukaemia

Introduction

CLL is the most common leukaemia among adults in industrialised countries[10] and accounts for 40% of all leukaemias in individuals over the age of 65 years.[11,12] CLL is extremely rare below the age of 30 years. Between 20% and 30% of the patient population are aged less than 55 years.[11] The median age at diagnosis in the UK is between 65 and 70 years.[12] CLL is currently incurable. Therefore, treatment aims to prolong survival and enhance quality of life.

The overall incidence of CLL is approximately 3 per 100,000 annually[12] with approximately 2,500 new cases diagnosed in the UK each year.[13] CLL is 20 to 30 times more common in European, Australasian and North American white and black populations than in Chinese, Indian and Japanese.[12] Across all populations, men are roughly twice as likely to develop CLL as women.[12]

Prognosis shows marked inter-patient variation, but depends largely on the stage at diagnosis. Survival is generally up to approximately 10 years with stage A. Survival for stages B and C at diagnosis is generally up to 5 years, and approximately 3 to 5 years, respectively.[11]

Commonly used first-line treatment options in the UK (excluding patients with the 17p deletion) are:

- fludarabine + cyclophosphamide (FC) ± rituximab (FCR) for physically fit patients;
- chlorambucil, which is better tolerated in the elderly and unfit patients, but less effective than FC and FCR.

Against this background, bendamustine is also effective in first-line treatment of CLL, offering superior efficacy to chlorambucil as demonstrated by the following pivotal Phase III trial upon which the licensed indication for ***Levact*** i.v. is based.

NB: When this trial was started, the only licensed comparator for first-line treatment was chlorambucil. It should be noted that ***Levact*** i.v. is licensed only for first-line treatment of patients for whom fludarabine combination chemotherapy is not appropriate.

Summary

- This was an open-label, randomised trial to compare the safety and efficacy of bendamustine with chlorambucil in treatment-naïve patients.
- The total number of patients treated in this trial was 312.
- The overall response rate (ORR) showed that bendamustine was significantly superior to chlorambucil (68% *vs.* 31%, respectively; $P<0.0001$).
- More patients experienced a complete response (CR) with bendamustine (31%) than with chlorambucil (2%). This was also the case for nPRs (11% *vs.* 3%, respectively).
- Patients with Binet stage C disease had a higher likelihood of CR with bendamustine than with chlorambucil (20% *vs.* 0%).
- Progression-free survival (PFS) was significantly longer with bendamustine than with chlorambucil (median 21.6 *vs.* 8.3 months).
- The median duration of response (DoR) in the bendamustine and chlorambucil groups were 21.8 months and 8.0 months, respectively.
- At 54 months, responders showed a significant overall survival advantage over non-responders ($P<0.001$).
- Overall, 34% of patients in the bendamustine group and 31% of patients in the chlorambucil group required at least one dose reduction, principally due to neutropenia and thrombocytopenia.

Phase III, open-label, randomised, multicentre efficacy and safety study of bendamustine hydrochloride *vs.* chlorambucil in treatment-naïve patients with (Binet stage B/C) B-CLL requiring therapy[14-17]

Trial methodology

Trial design

This was an open-label, multicentre, international study. Patients were randomised 1:1 to receive either intravenous bendamustine or oral chlorambucil (stratified by centre and Binet stage).

An interim tumour assessment was performed after three treatment cycles. Further treatment was dependant on each patient's status, as follows:

- Patients showing progressive disease (PD) were discontinued from the trial.
- Patients showing stable disease (SD) or no change (NC) received a maximum of three additional treatment cycles.
- Patients showing partial response (PR), near partial response (nPR) or CR received another two or three further treatment cycles for consolidation (to a maximum of six cycles).

A final assessment was performed at the end of treatment. Responders and NC patients were followed for progression at 3-month intervals. Patients with SD or PD were followed for survival at 3-month intervals (see Figure 4).

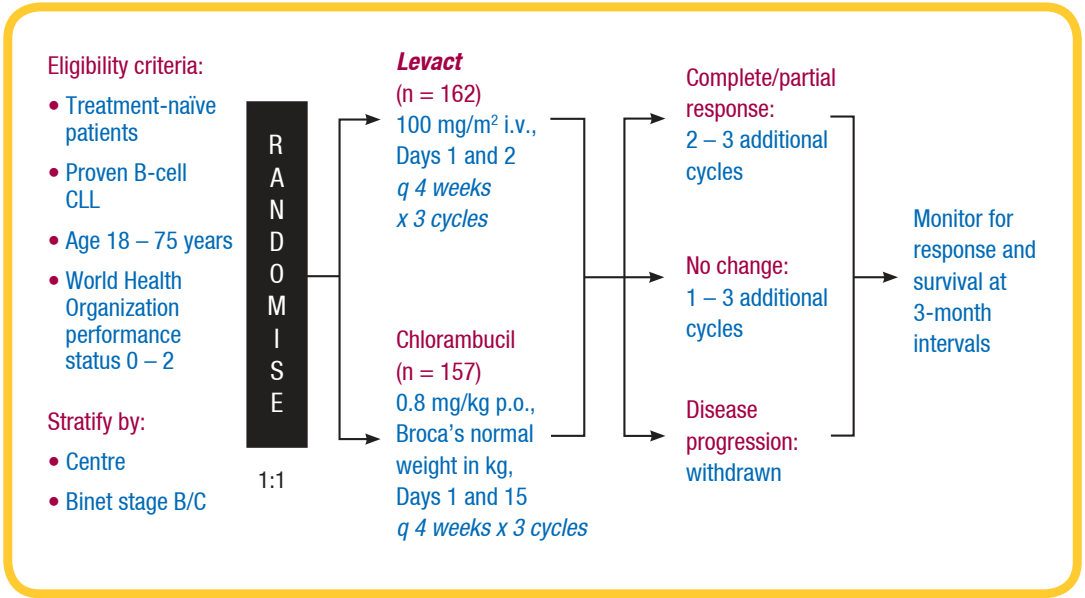

Figure 4: Study design 02CLLIII

Inclusion criteria

General inclusion criteria

- Treatment-naïve, legally competent adult patients <75 years of age capable of following study instructions.
- Had given written informed consent.
- WHO Performance Status 0-2.
- Life expectancy >3 months.
- Contraception for at least 6 months after therapy.
- Confirmed chronic B-cell lymphocytic leukaemia (co-expression of CD5, CD23 and either CD19 or CD20 or both).
- Symptomatic Binet stage B or Binet stage C disease.

Need-to-treat criteria

- Haematopoietic insufficiency with non-haemolysis-induced haemoglobin <10 g/dL

and/or

- thrombocytopenia <100 x 10^9/L (equivalent to Binet stage C)

and/or

- B symptoms defined as:
  - unexplained >20% weight loss in the last 6 months;
  - persistent or recurrent pyrexia of unknown origin >38°C;
  - night sweats

and/or

- rapidly PD (such as rapid lymphoma growth, rapid increase in lymphocyte count, rapid fall in haemoglobin or platelet count not due to autoimmune phenomena)

and/or

- risk of organ complications from bulky lymphomas (e.g. vascular compression).

Exclusion criteria

- Previous treatment with other cytotoxic drugs.
- Participation in another clinical trial within 4 weeks prior to, or during, this study.
- Mental disorders, drug or alcohol dependence, or any other disorder suggesting compliance problems or limited ability to co-operate in the study.
- History of a second malignancy (except cured basal cell carcinoma or cured cervical cancer).
- Manifest immune haemolysis that could be treated with glucocorticoids alone.
- Manifest immune thrombocytopenia that could be treated with glucocorticoids alone.
- Richter's syndrome or transformation to pro-lymphocytic leukaemia.
- Hepatic dysfunction: bilirubin >2.0 mg/dL and/or transaminases >3 x upper limit of normal.
- Renal dysfunction (creatinine clearance <30 mL/min, calculated).
- Any of the following concomitant diseases:
    - Overt heart failure.
    - Cardiomyopathy.
    - Myocardial infarction within the last 6 months.
    - Severe, uncontrollable diabetes mellitus.
    - Severe, uncontrollable hypertension.
    - Active infection that required systemic antibiotic therapy.
    - Uncontrollable infection.
    - Clinically manifest cerebral dysfunction.
- Known HIV infection.
- Major surgery within 30 days before the start of the trial.
- Pregnancy, lactation.
- Hypersensitivity to any of the study drugs.
- Women of childbearing potential without adequate contraception.

Study drug

Drug	Administration
Bendamustine	100 mg/m^2/day intravenously over 30 minutes on Day 1 and 2 of a 28-day treatment cycle. The next cycle started on Day 29
Chlorambucil	0.8 mg/kg (Broca's normalised weight*) orally on Days 1 and 15 or, if necessary, given as divided doses on Day 1 and 2 and Day 15 and 16 of a 20-day treatment cycle. The next cycle started on Day 29

Table 2: Bendamustine and chlorambucil administration. *Broca's weight in kg = height in cm minus 100

Dose adjustments

Dose adjustment in the case of haematological and disease-related toxicity was mandated as outlined below. For toxicity assessment, the value observed at the start of the next cycle was the basis for dose reduction. The final decision concerning the dose reduction was at the discretion of the treating investigator.

Patients experiencing haematological and/or non-haematological toxicities could subsequently have their dose increased to the original level, if they had tolerated the reduced dose. If therapy was delayed by more than 4 weeks, the patient was removed from the study.

Dose adjustment in the case of haematological toxicity

Therapy was suspended if:

- platelets fell to less than 20 x 10^9/L;
- haemoglobin fell to less than 7.0 g/dL, or
- absolute neutrophil count fell to less than 0.5 x 10^9/L.

The dose modifications in Table 3 were applied in cases where decreased values were outside normal range.

In case of therapy-induced myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils were monitored at least weekly, and treatment was not continued until:

- white cell count had returned to >2.5 x 10^9/L or baseline;
- neutrophil count had returned to >1.5 x 10^9/L or baseline;
- haemoglobin had returned to >10.0 g/dL or baseline;
- platelet count had returned to >100 x 10^9/L or baseline.

Percent fall in Hb or platelets *vs.* baseline	**Absolute neutrophil count (x10^9/L)**	**Recommended dose adjustment (relative to last dose)**
0 - 24% (grade 0 - 1)	>1.5 (grade 0 - 1)	No dose reduction
25 - 49% (grade 2)	>1.0 and <1.5 (grade 2)	50% reduction
50 - 74%	>0.5 and <1.0 (grade 3)	75% reduction
>75% (grade 4)	<0.5 (grade 4)	Interruption of treatment until recovery to grade 1

Table 3: Dose modifications for haematological toxicities

Dose adjustment in the case of non-haematological toxicities

Dose reduction (see Table 4) was based on the worst common toxicity criteria (CTC) grades in the preceding cycle. If a patient required a dose modification, the individually calculated reduced dose was given on Days 1 and 2 of the respective treatment cycle.

If patients experienced therapy-induced >CTC grade 2 non-haematological toxicities (except nausea, vomiting, and alopecia), they were to be monitored at least weekly, and treatment not resumed until symptoms had returned (decreased) to baseline intensity or were <CTC grade 2.

CTC grade	Percent of total dose
0 - 2 (and grade 3 nausea/vomiting and alopecia)	100%
3 (except nausea/vomiting and alopecia)	50% or off study (the decision whether or not to stop therapy depended on the nature of the toxicity and at the investigator's discretion)
4	Off study

Table 4: Dose modification guidelines for haematological toxicities

Allowed and disallowed concomitant therapy

A prophylactic anti-hyperuricaemic (e.g. allopurinol) was recommended during the first three cycles to prevent uric acid-induced nephropathy. Thereafter, prophylaxis was at the investigator's discretion. Immunoglobulins, prednisone and growth factors were avoided, whenever possible.

Primary outcome

There were two primary outcomes:

1. ORR - includes CR, PR and nPR.
2. Progression-free survival (PFS).

Responses were assessed by the investigators and also by an independent blinded committee.

Complete response

Response to treatment was defined using the National Cancer Institute Working Group Criteria.[18] All of the following criteria had to be met for a duration of at least 8 weeks:

- Enlarged lymph nodes are no longer detectable by palpation (X-ray or ultrasound were optional).
- Absence of hepatomegaly or splenomegaly, confirmed by palpation (CT and ultrasound were optional).
- No disease symptoms (B-symptoms).
- Blood counts:
  - Lymphocytes $\leq 4.0 \times 10^9$/L.
  - Neutrophils $\geq 1.5 \times 10^9$/L.
  - Platelets $>100 \times 10^9$/L.
  - Haemoglobin >11 g/dL (without blood transfusion).
- Bone marrow biopsy (histology and cytology) was to be performed 8 weeks after meeting the above criteria. The bone marrow had to be at least normocellular for age, with less than 30% lymphocytes.

Nodular partial response

Patients with nPR had to fulfil all criteria for CR with lymphocytes being less than 30% in the bone marrow sample but still showing focal infiltration.

Partial response

All of the following criteria had to be met for a duration of at least 8 weeks:

- ≥50% decrease in peripheral blood lymphocyte count from the pre-treatment baseline value;
- ≥50% reduction of enlarged lymph nodes (total of affected lymph nodes);

and/or;

- 50% reduction of hepatomegaly and/or splenomegaly;

plus at least one of the following criteria:

- Neutrophils $\geq 1.5 \times 10^9$/L or 50% improvement *vs*. baseline;
- Platelets $>100 \times 10^9$/L or 50% improvement *vs*. baseline;
- Haemoglobin >11 g/dL or 50% improvement *vs.* baseline (without blood transfusion).

Progression-free survival

PFS was defined as the time from the start of therapy to first PD or relapse after inter-current remission or CLL-related death.

Patients were classified as 'non-responders', if neither PR nor CR were confirmed or their tumour response was not evaluable. A patient had SD if CR, PR, and PD criteria were not met.

Secondary efficacy endpoints

- Time to progression (TTP): the time from the start of therapy to PD or relapse after inter-current remission. Patients were censored at the time of death if it was due to causes other than CLL.
- DoR/remission: the time from first observation of any response (CR, nPR, or PR) to PD or death. Non CLL-related deaths that occurred during remission were censored at the time of death.
- OS: the time from start of therapy to death from any cause.

Trial results

A total of 319 patients were randomised: 162 to bendamustine and 157 to chlorambucil. Six patients randomised to chlorambucil and one to bendamustine were not treated. Thus the intention-to-treat (ITT) population included all 319 randomised patients and the safety population included 312 treated patients. Figure 5 shows the flow of patients through the study.

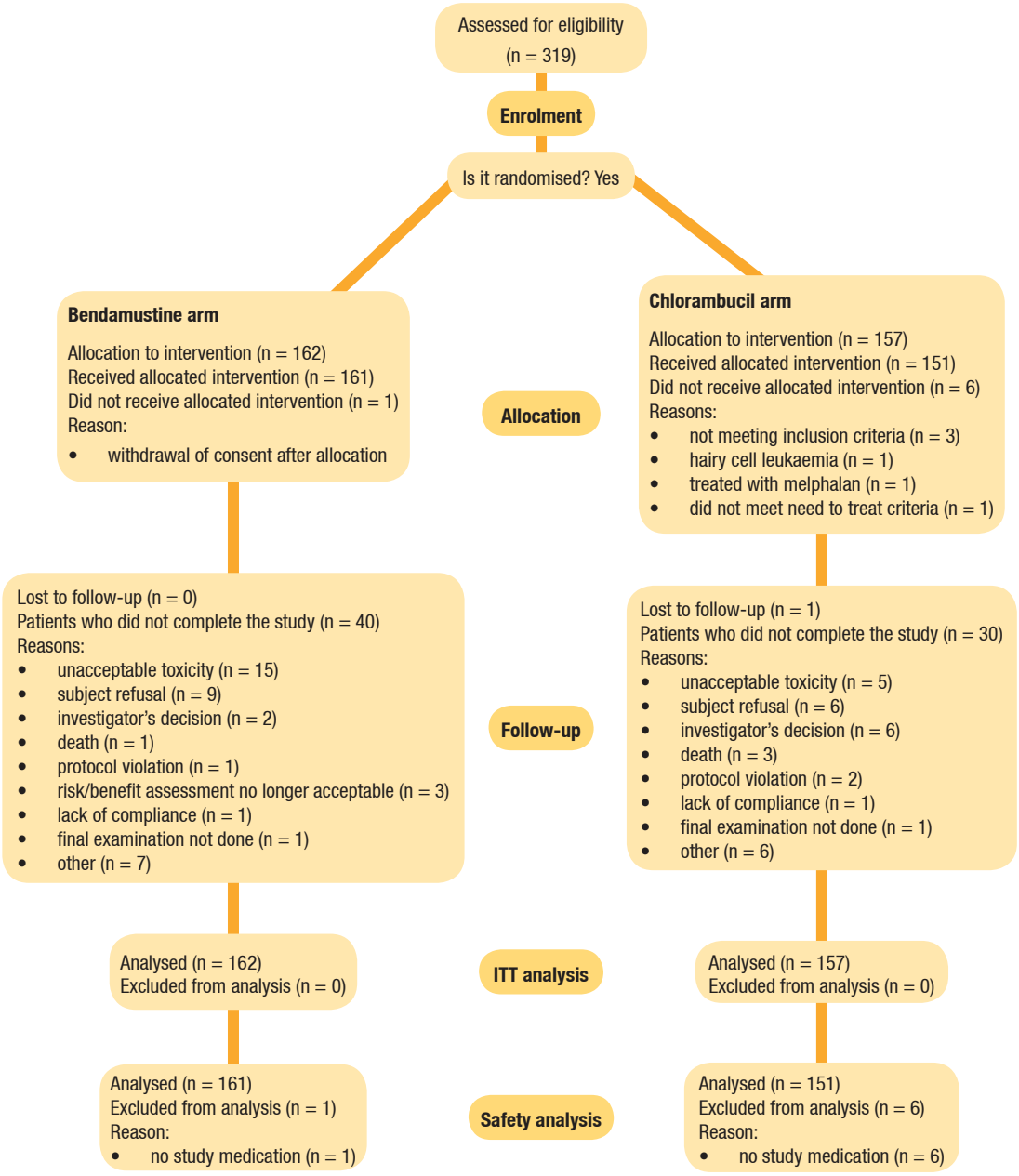

Figure 5: Patient disposition

Baseline demographics

Overall, patient characteristics were well balanced between the groups (see Table 5). A total of 116 (72%) in the bendamustine group and 111 (71%) in the chlorambucil group had Binet stage B disease, whereas 46 (28%) and 46 (29%), respectively, had stage C disease. The mean (± SD) time from initial diagnosis to registration in the trial was 18.8 ± 32.3 months in the bendamustine group and 24.6 ± 33.9 months in the chlorambucil group (P = 0.12).

		Bendamustine (n = 162)	Chlorambucil (n = 157)
Gender [number (%) of patients]	Male	102 (63)	95 (61)
	Female	60 (37)	62 (39)
Age [mean (SD) years]		63 (7.5)	63 (8.8)
Binet stage [number (%) of patients]	B	116 (72)	111 (70)
	C	46 (28)	46 (29)
WHO performance status [number (%) of patients]	WHO 0	113 (70)	102 (65)
	WHO 1	43 (27)	45 (29)
	WHO 2	3 (2)	5 (3)

Table 5: Baseline demographics

Primary outcome analysis

Overall response rate

For ORR, bendamustine was significantly superior to chlorambucil (68% *vs.* 31%, respectively; P<0.0001). The proportion of patients with a CR was higher with bendamustine than with chlorambucil (31% *vs.* 2%) as was the proportion of patients with nPR (11% *vs.* 3%; see Figure 6).

Patients with stage C disease showed a higher likelihood of CR with bendamustine than with chlorambucil (20% *vs.* 0%).

The median number of treatment cycles per patient was six in both arms. The mean (± SD) number of treatment cycles per patient was 4.9 ± 1.7 with bendamustine and 4.9 ± 1.7 with chlorambucil.

Overall, 54 (34%) patients in the bendamustine group and 46 (31%) in the chlorambucil group required at least one dose reduction. The principal reasons for dose reduction in both groups were neutropenia and thrombocytopenia.

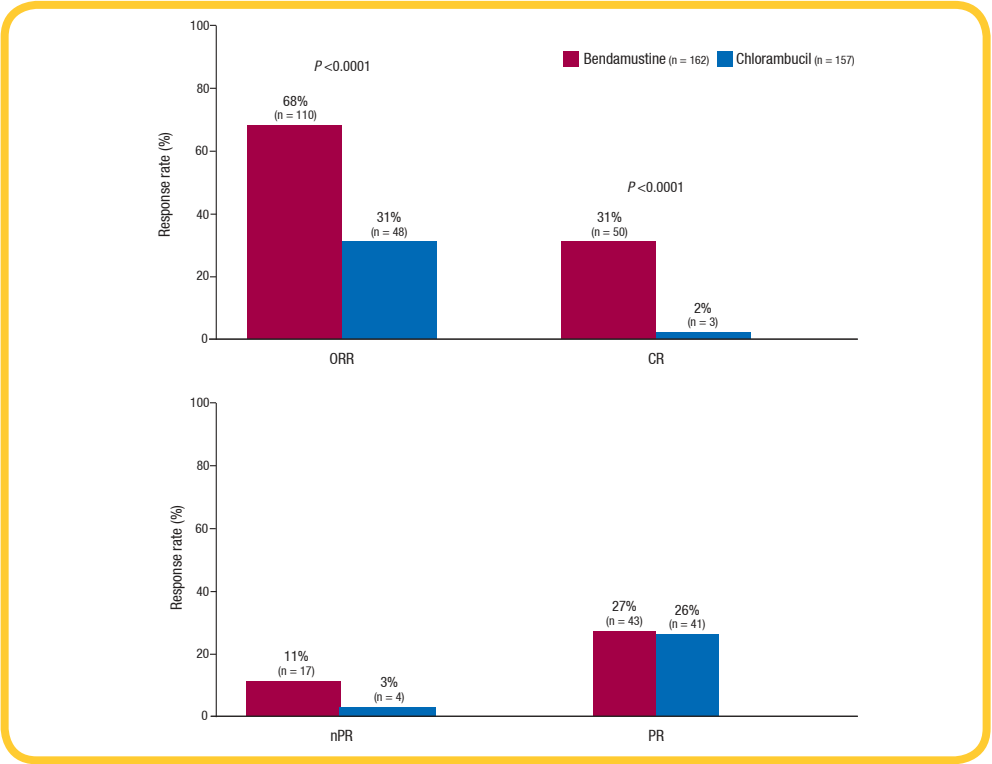

Figure 6: Response rates

Progression-free survival

PFS with bendamustine was significantly longer than with chlorambucil (median 21.6 months *vs.* 8.3 months, *P*<0.0001), as shown in Figure 7. This difference was evident in patients with Binet stage B disease (21.4 months *vs.* 9.0 months) as well as in stage C disease (25.4 months *vs.* 6.3 months).

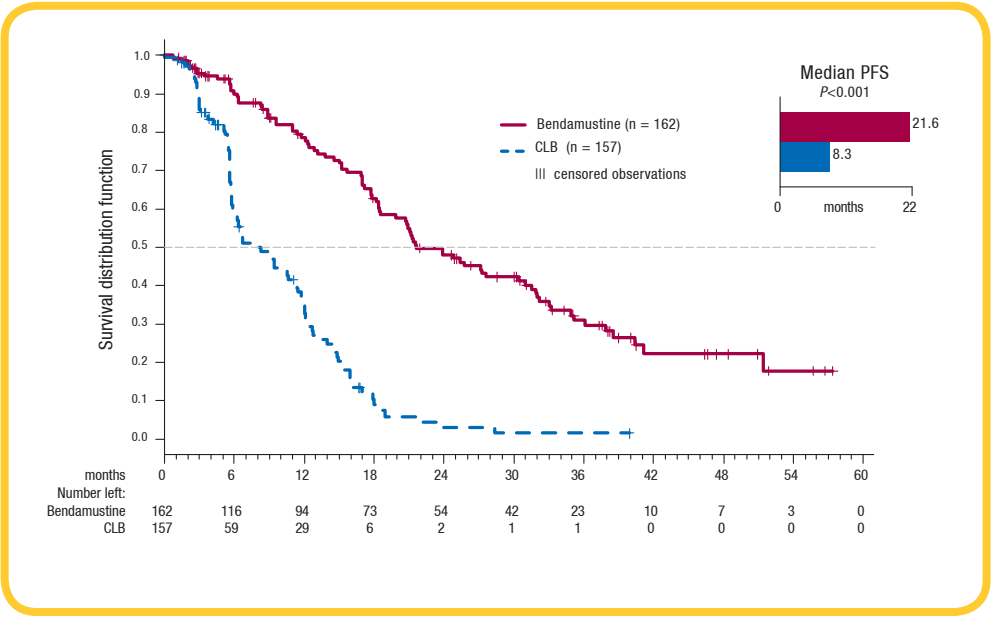

Figure 7: PFS based on ICRA assessment. The median observation time was 35 months (range 1 – 68) at the time of this analysis.

Secondary analyses

Duration of response

The median DoR in the bendamustine and chlorambucil groups were 21.8 months and 8.0 months, respectively (see Figure 8). The median duration of CR in bendamustine-treated patients was 29.3 months. The median duration of PR was 17.4 months with bendamustine and 8.0 months with chlorambucil.

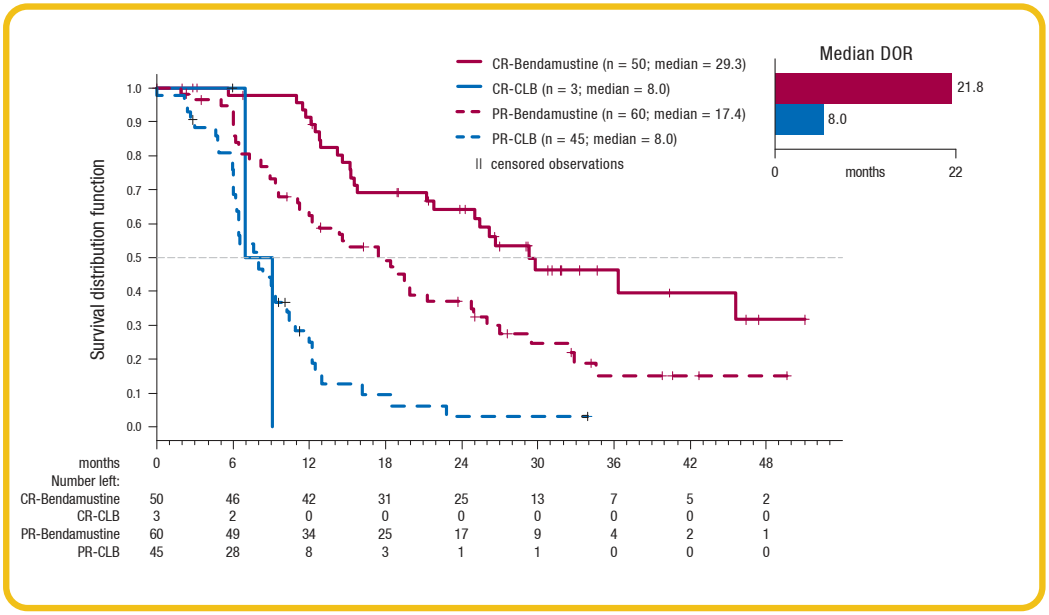

Figure 8: Duration of response

Time to progression

TTP was significantly longer for bendamustine than for chlorambucil (21.2 months *vs.* 8.9 months, respectively, *P*<0.001 - see Table 6).[15]

	Bendamustine		Chlorambucil	
Median TTP (ICRA assessment)	n = 139	21.2 months	n = 125	8.9 months
Median TTP (investigator's assessment)	n = 139	21.7 months	n = 125	9.3 months

Table 6: Median TTP

At the American Society of Hematology meeting in 2009, Dr Knauf presented a further analysis of this study showing that the clinical superiority of bendamustine over chlorambucil was maintained in the elderly sub-population (age >65 years). Table 7 shows the quality of responses by age.[16]

Quality of response	Number (%) of patients							
	Bendamustine				Chlorambucil			
	Age <65 n = 88		Age >65 n = 74		Age <65 n = 74		Age >65 n = 83	
Complete response	31	(35.2)	19	(25.7)	2	(2.7)	1	(1.2)
Nodular partial response	12	(13.6)	5	(6.8)	1	(1.4)	3	(3.6)
Partial response	20	(22.7)	23	(31.1)	18	(24.3)	23	(27.7)
Overall response rate	63	(71.6)	47	(63.5)	21	(28.4)	27	(32.5)

Table 7: Quality of response by age

Overall survival by treatment group and response

Overall survival data were presented at the American Society of Hematology meeting in 2010. The median duration of follow-up at the time of this analysis was 54 months.[17]

There was no significant difference when overall survival was analysed by treatment group (P = 0.18; see Figure 9).

This was not unexpected given the number of patients who went on to receive subsequent therapies (Table 8).

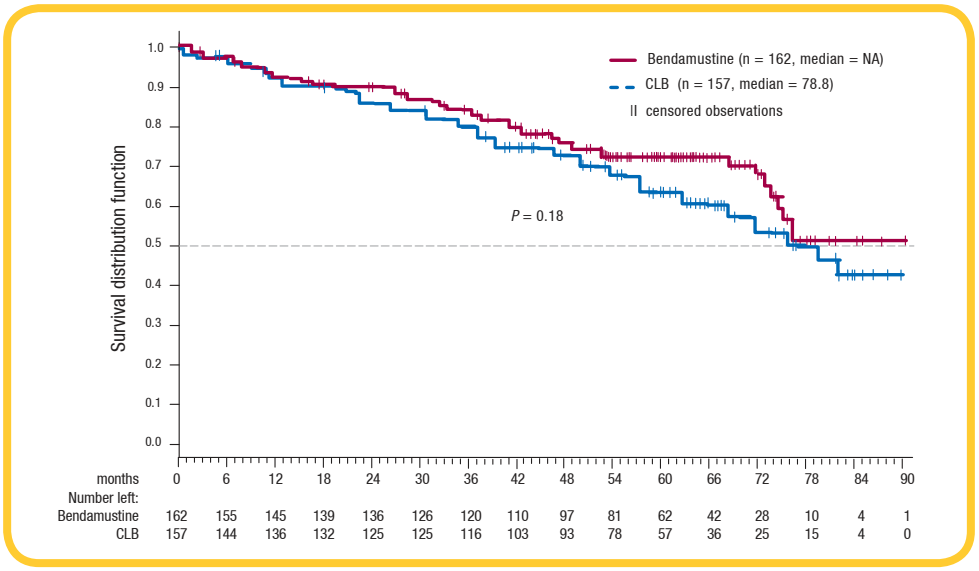

Figure 9: Overall survival by treatment group

Second or further lines?	Number (%) of patients		*P*-value
	Bendamustine (n = 162)	Chlorambucil (n = 157)	
No	59 (36)	34 (22)	0.004
Yes	103 (64)	123 (78)	

Table 8: Patients receiving subsequent therapies

When overall survival was analysed by response, responders (CR and PR) had a significantly longer overall survival than non-responders, irrespective of their treatment type (median not reached *vs*. 68.3 months, respectively; see Figure 10).

Overall survival was significantly longer for patients in CR than for all other patients (*P* = 0.0018; see Figure 11). Fifty of the 53 patients with a CR were in the bendamustine group.

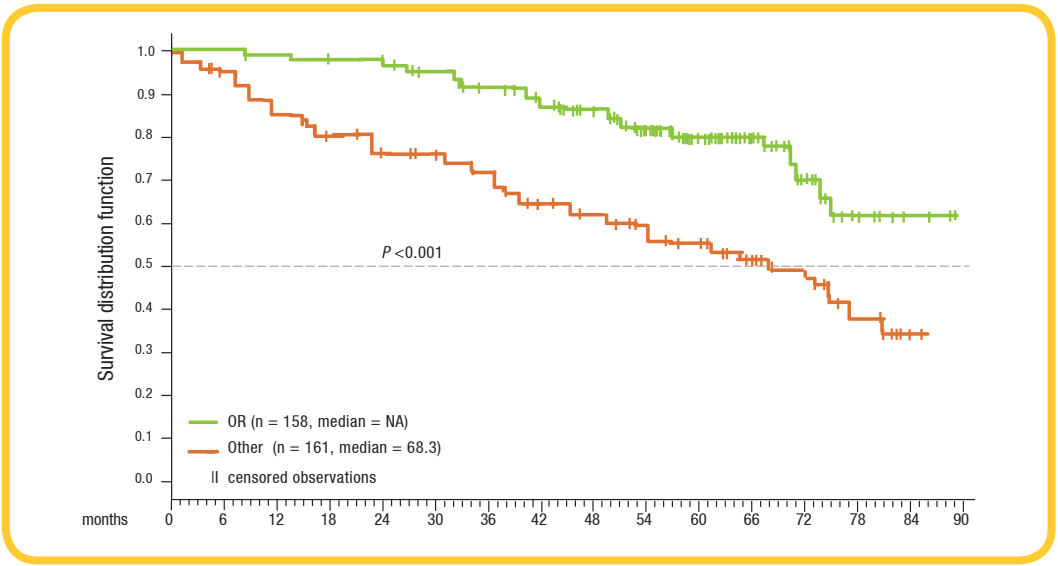

Figure 10: Overall survival by response: responders compared with all others

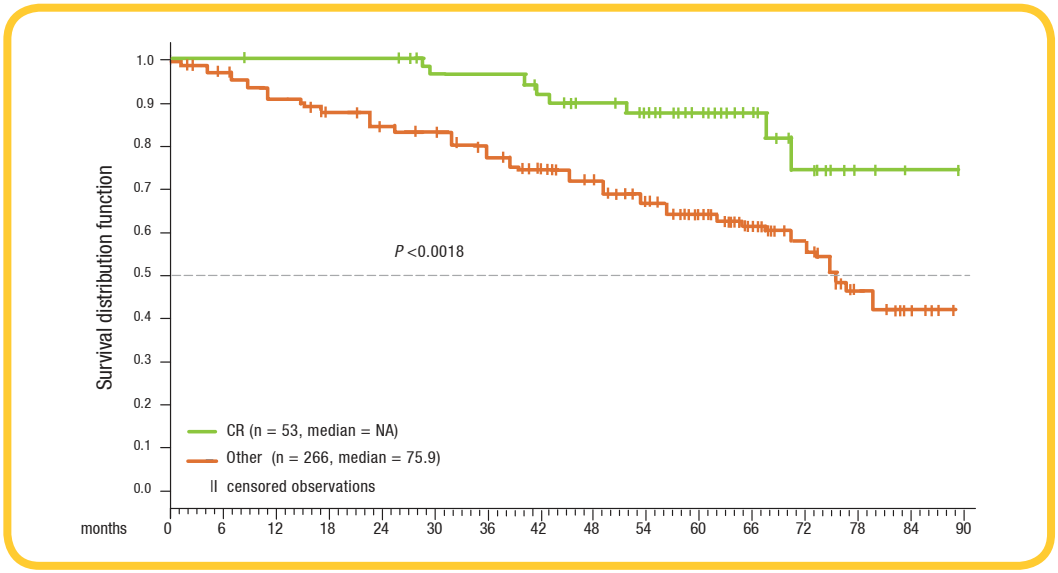

Figure 11: Overall survival by response: patients with complete response compared with all others

Time to next treatment

Time to next treatment (TTNT) was also presented at the American Society for Hematology meeting in 2010. Median TTNT was 31.7 months for bendamustine and 10.1 months for chlorambucil (*P*<0.001; see Figure 12).[17]

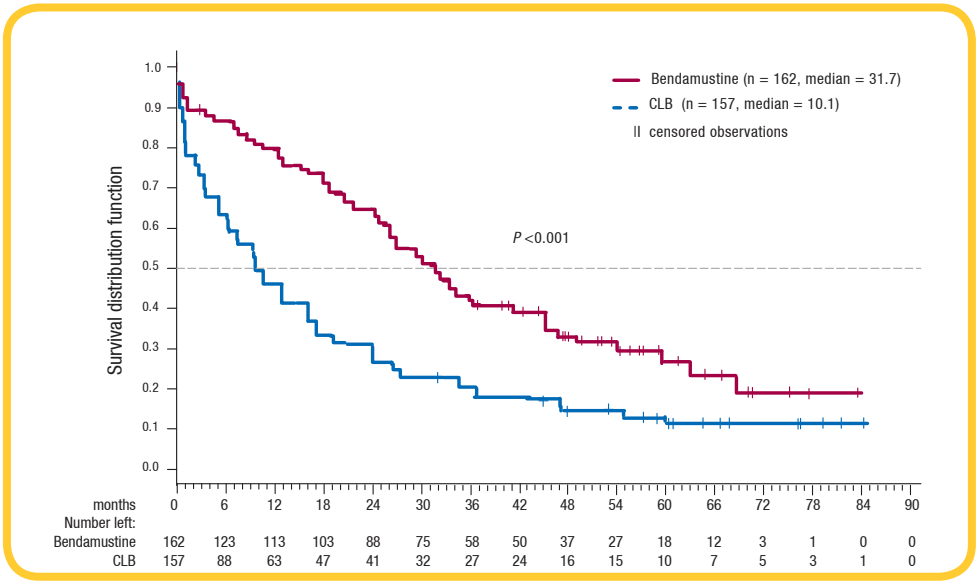

Figure 12: Time to next treatment

Toxicity and tolerability

Table 9 shows the adverse events occurring in >5% of patients in this trial. The dose of bendamustine was reduced in 34% of patients. Treatment with bendamustine was discontinued in 11% of patients, and 3% of patients treated with chlorambucil due to unacceptable toxicity. Severe infections of grade 3 or 4 occurred in 8% and 3% of treated patients in the bendamustine and chlorambucil arms, respectively. No grade 4 hypersensitivity reactions occurred.[14] The number of documented, treatment-related hospitalisations during the study were nine for bendamustine and three for chlorambucil.[15]

	Number (%) of patients			
	Bendamustine (n = 161)		Chlorambucil (n = 151)	
	All grades	Grade 3/4	All grades	Grade 3/4
Anaemia	35 (22)	4 (3)	21 (14)	0 -
Leukopenia	28 (17)	23 (14)	5 (3)	2 (1)
Neutropenia	44 (27)	37 (23)	21 (14)	16 (11)
Thrombocytopenia	40 (25)	19 (12)	31 (21)	12 (8)
Nausea	31 (20)	1 (<1)	21 (14)	1 (<1)
Vomiting	25 (16)	2 (1)	10 (7)	0 -
Pyrexia	40 (25)	3 (2)	8 (5)	2 (1)

Table 9: Adverse events during the study

Bendamustine combined with rituximab (BR) in first-line therapy of advanced CLL: a multicentre, Phase II trial of the German CLL Study Group (GCLLSG)[19]

Summary

- This was a Phase II study to investigate the efficacy and toxicity of bendamustine in combination with rituximab in previously untreated CLL patients.
- The total number of patients treated in this trial was 117.
- The ORR was 90.9%, with 32.7% patients achieving a CR.
- After 18 months, 75.8% patients were still in remission and the median PFS had not been reached.
- Encouraging response rates were seen in patients in the genetic subgroups 11q-, +12, 17p- and unmutated IgV_H.
- The most frequent adverse events were myelosuppression and infection.
- The German CLL Study Group concluded that BR is effective in first-line treatment of CLL, with an acceptable toxicity profile.

Introduction

On behalf of the German CLL Study Group, Dr Fischer presented data on bendamustine combined with rituximab in the first-line treatment of CLL at the 2009 annual American Society of Hematology meeting.[19] One hundred and seventeen patients with previously untreated CLL requiring treatment received bendamustine at a dose of 90 mg/m^2 on Days 1 and 2 of a 28-day cycle, combined with rituximab 375 mg/m^2 for the first cycle and 500 mg/m^2 for subsequent cycles. A maximum of six cycles were administered. Blood samples were taken for analysis by fluorescence *in situ* hybridisation (FISH), and to determine the IgV_H mutational status and expression of ZAP70/CD38. Minimal residual disease (MRD) was evaluated in peripheral blood and bone marrow by 4-colour cytometry.

A total of 110 patients were evaluable for response, with a median follow up of 15.4 months. The median age was 64 years. The GCLLSG concluded that BR is effective in first-line treatment of CLL, with an acceptable toxicity profile. Based on these results, they are presently investigating the efficacy of BR compared with FCR in the first-line treatment of CLL.

Trial methodology

Trial design

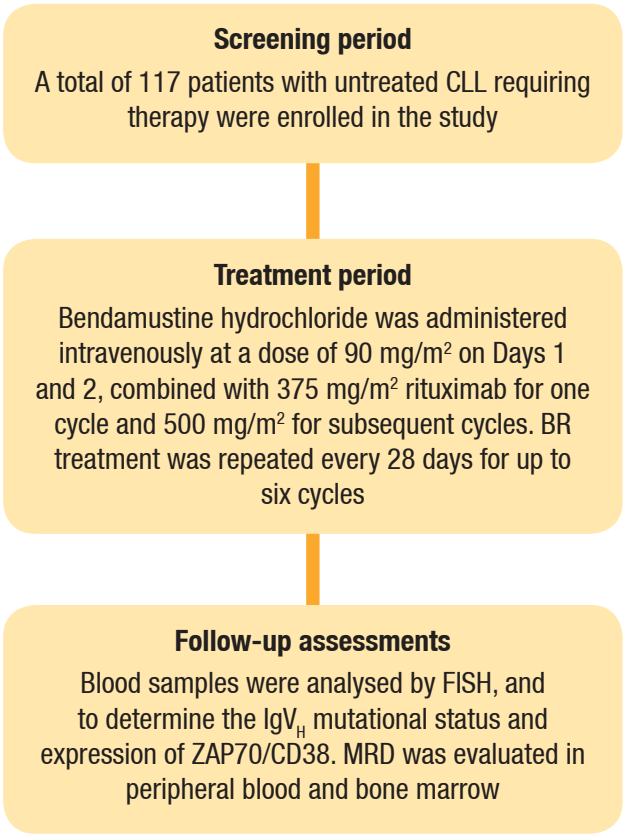

Figure 13: The overall study schema

Study drugs

Patients were given bendamustine intravenously at a dose of 90 mg/m² on Days 1 and 2, combined with 375 mg/m² rituximab for one cycle and 500 mg/m² for subsequent cycles. BR treatment was repeated every 28 days for up to six cycles.

Trial results

Patient disposition

Between March 2007 and September 2008, 117 patients with untreated CLL requiring therapy were enrolled in this study. A total of 114 patients were evaluable for toxicity, 110 for response and 113 for PFS. BR treatment was administered every 28 days up to a maximum of six cycles.

Baseline demographics

Table 10 shows the baseline demographics for patients who enrolled in this trial.

Characteristics	Number	%
Median age (range) in years	64	
Disease stage (Binet)		
A	13	11.1
B	48	41.0
C	56	47.9

Table 10: Baseline demographics

Primary outcome analysis

The ORR was 90.9% with 32.7% (36 patients) achieving a clinical CR. A nPR was achieved in 2.7% (three patients) and a PR in 55.5% (61 patients). A total of 9.1% (10 patients) had SD, but none of them experienced PD. After 18 months, 75.8% patients were still in remission and a median PFS had not been reached (n = 113). MRD negativity below 10E-4 was observed in peripheral blood of 29 of 50 evaluable patients after therapy completion and in the bone marrow of 7 of 25 patients.

Encouraging response rates were seen in patients in the following genetic subgroups: 11q- (9 CR and 10 PR; ORR 90.5%), +12 (three CR, 14 PR; ORR 89%), 17p- (three PR; ORR 43%) and unmutated IgV_H (89%).

Adverse events/toxicity

A total of 114 patients were evaluable for toxicity. The most frequent adverse events based on 583 cycles were myelosuppression and infection; grade 3/4 leucopenia in 14.6%, neutropenia in 6.5%, thrombocytopenia in 6.1% and anaemia in 4.9% of all given courses, respectively. Twenty-nine episodes of CT grade >3 infections were documented (5.1% of all courses). Treatment-related mortality occurred in 2.6% of patients; one liver failure after attempted suicide, one fatal pneumonia and one sepsis in neutropenia.

Chapter three: Rituximab-refractory indolent non-Hodgkin's lymphoma

Introduction

In the UK, around 10,500 cases of NHL are diagnosed each year, equivalent to 4% of all cancers.[20] Males are more likely to develop NHL than females:[21] the age-standardised incidence rates per 100,000 of the population are 16.3 and 11.7, respectively. The incidence of NHL increases sharply in people over 50 years of age and 70% of cases occur in people over 60 years of age.[22]

NHL caused more than 4,500 deaths in the UK in 2007. However, infections cause most deaths among people with NHL and the statistics may underestimate mortality.[23] Three-quarters of deaths from NHL occurred in people aged 65 years and over and a third in those aged over 80 years.[23] Age-standardised mortality increased by an average of approximately 3% per year until the mid 1990s. The mortality rates then peaked and for the last few years have decreased slightly, currently reaching 6.5 per 100,000 males and 4.1 per 100,000 females in 2007.[23]

Low-grade lymphomas account for around 30% to 40% of NHL subtypes. Follicular lymphoma is the most common low-grade NHL.[24]

The Follicular Lymphoma International Prognostic Index (FLIPI) identified five factors that are useful for predicting survival (prognosis):[24, 25]

- Being older than 60 years.
- Having stage 3 or 4 follicular lymphoma.
- Being anaemic.
- More than four involved lymph node areas.
- Serum lactate dehydrogenase level greater than the upper limit of normal.

Using this system, four risk groups with predicted 5-year survival rates of 73%, 51%, 43% and 26% were identified.[25] Survival rates for NHL vary significantly by age: the five-year survival rate for those diagnosed aged 15 – 44 is 65%, whereas for those aged 65 – 74 it is 37%, and for those aged 85+ it is 13%.[26]

Levact i.v. is effective in rituximab-refractory indolent NHL. The two studies included in this section (both single arm Phase II studies) formed the basis of the licensed indication for ***Levact*** i.v. in the UK.

Summary

- This was a Phase II study to investigate the safety and activity of bendamustine in patients with indolent NHL who are refractory to rituximab.
- The total number of patients treated in this trial was 76.
- The median number of bendamustine cycles per patient was 5.
- Bendamustine produced a high rate of durable responses, even in rituximab-refractory indolent NHL patients.
- The ORR in all assessable patients was 77% (88% of whom had stage III/IV disease) – this included 34% CRs/CRus and 43% PRs.
- An ORR of 75% was seen in patients with >2 prior chemotherapy regimens.
- The median PFS was 7.1 months.

A multicentre, Phase II study to investigate the safety and activity of bendamustine in patients with indolent non-Hodgkin's lymphoma (NHL) who are refractory to rituximab[27, 28]

Trial methodology

Trial design

This was a Phase II, non-randomised, single agent, open-label study conducted at 12 centres in the US and two centres in Canada.

A control group was not used because at the time the study was conducted, there was no widely available effective treatment for this subgroup of refractory patients with NHL. Figure 14 shows the design of this study.

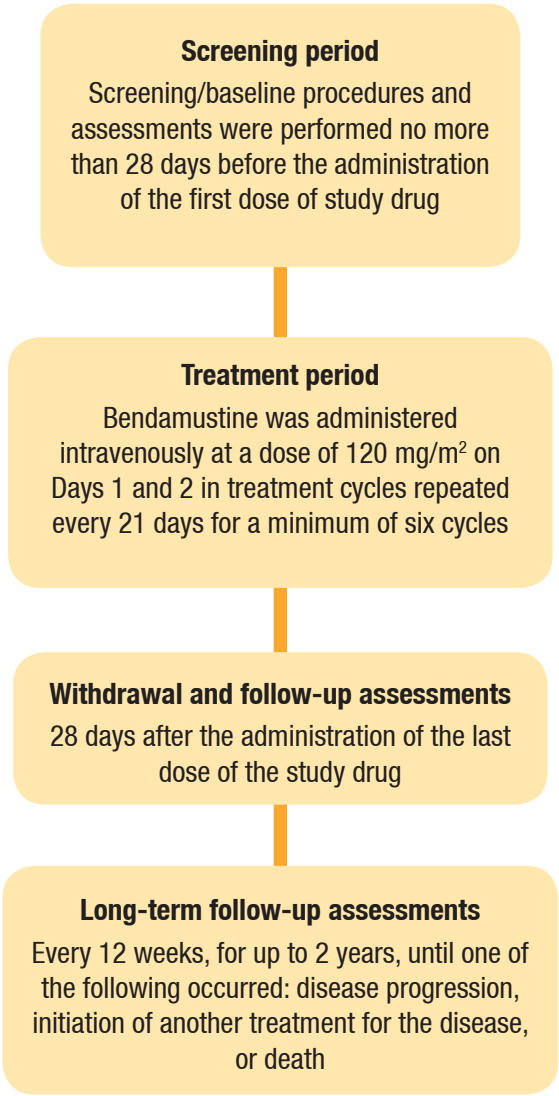

Figure 14: The overall study schema.

Inclusion criteria

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

- The patient was at least 18 years old at the screening visit, had documented low grade or transformed B-cell NHL, had bi-dimensionally measurable disease with at least one lesion measuring 2.0 cm or more in a single dimension, and had an estimated life expectancy of at least 3 months.
- The patient had received treatment with no more than three prior chemotherapy regimens.
- The patient had received prior treatment with rituximab, but further rituximab treatment was considered inappropriate due to documented disease refractory to rituximab treatment or an untoward reaction to prior rituximab treatment.
- The patient had a World Health Organization (WHO) performance status of 0 to 2, an absolute neutrophil count (ANC) of 1,000 cells/mm^3 or more and a platelet count of 100,000 cells/mm^3 more, or a creatinine clearance of more than 30 mL/min, and adequate hepatic function.

Exclusion criteria

Patients were excluded from participating in this study if one or more of the following main criteria were met (not all inclusive):

- The patient had received previous chemotherapy or immunotherapy within 3 weeks before entering the study (for prior treatment with nitrosoureas or mitomycin, within 6 weeks before entering the study), had received treatment with investigational agents within 28 days before entering the study, or had not recovered from adverse events due to any chemotherapy or immunotherapy agents administered previously.
- The patient had a history of prior high-dose chemotherapy with allogeneic stem cell support, was receiving concurrent treatment with therapeutic doses of systemic steroids, had received haematopoietic growth factors within 14 days of entering the study (chronic erythropoietin treatment was allowed), or had a known hypersensitivity to mannitol.
- The patient had a concurrent, active malignancy other than the target cancer (exceptions were completely excised non-melanoma skin cancer or *in situ* cervical or bladder cancer), had primary or active central nervous system (CNS) lymphoma, or had a serious infection, medical condition, or psychiatric condition.

Study drugs

Patients were given bendamustine hydrochloride intravenously over 30 – 60 minutes at a dose of 120 mg/m^2 on Days 1 and Day 2 in treatment cycles that were repeated every 3 weeks.

Dose adjustments

Patients who experienced grade 3 or 4 non-haematologic or grade 4 haematologic toxicity at a dose of 120 mg/m^2 had their dose decreased to 90 mg/m^2 for the next cycle, providing the patient had recovered and the toxicities were at baseline values or of grade 1 or less.

If grade 3 or 4 non-haematologic or grade 4 haematologic toxicity appeared at this reduced dose level, the dose was further decreased to 60 mg/m^2 for the next cycle.

Patients who continued to experience toxicities at the 60 mg/m^2 dose were withdrawn from the study.

Allowed and disallowed concomitant therapy

The investigators were permitted to prescribe supportive treatment for adverse events, including antiemetics, antidiarrhoeals, antipyretics, antiallergic agents, antihypotensives, analgesics, antibiotic medications, and other therapies such as blood products.

Chronic erythropoietin therapy was permitted, but bone marrow growth factors were not permitted during the first cycle of treatment.

Prophylactic use of cytokines, such as granulocyte-colony stimulating factor (G-CSF) to stimulate white blood cells (WBCs), was discouraged.

Endpoints

The primary efficacy measure for this study was the ORR; this was defined as the proportion of patients who achieved a best response of CR, CRu (complete response unconfirmed), or PR during the study.

The secondary efficacy measures were DoR and PFS.

(i) Duration of response

DoR was determined for patients with a response of CR, CRu or PR and was defined as the time interval from the date of first documentation of the response for a patient to the first documentation of disease progression, death (regardless of cause), or change of therapy due to disease progression, whichever occurred first.

(ii) Progression-free survival

PFS was determined for all patients and was defined as the time interval from the date of the first bendamustine dose to the first documentation of disease progression, death (regardless of cause), or change of therapy due to disease progression, whichever occurred first.

Populations included

The primary analysis set included all enrolled patients who were treated with at least one dose of study drug.

The evaluable set included all patients who met the following criteria:

- Treated with at least one dose of study drug.
- Met inclusion criteria and did not violate exclusion criteria.
- Baseline absolute lymphocyte count less than 5 x 10^9/L.
- At least one post baseline response assessment or withdrew before having a post baseline response assessment due to rapid disease progression or death.

Trial results

Patient disposition

Between September 2003 and February 2005, 77 patients were enrolled at 14 institutions. One patient did not receive treatment and was excluded from the analyses.

Patients received a median of 5.0 cycles of bendamustine (range one to nine cycles). Thirty-four patients received at least six cycles, and four patients received nine cycles of bendamustine. Forty-three patients discontinued bendamustine treatment before completing six cycles because of adverse events (n = 23), disease progression (n = 14), or patient or investigator decision (n = 6). Thrombocytopenia was the most common reason for early study termination.

Baseline demographics

Table 11 shows the baseline demographics. The age range was 38 – 84 years (median age of 63 years). Sixty-one patients had low grade B-cell NHL [46 follicular, 12 small lymphocytic lymphoma (SLL), one lymphoplasmacytoid, two marginal zone], and 15 had transformed disease.*

*NB ***Levact*** i.v. is licensed only for patients with indolent NHL who are refractory to rituximab.

Characteristics	Number	
Sex (number of patients)		
Male	41	
Female	35	
Median age (range) in years	63	(38 – 84)
Disease stage [number (%) of patients]		
II	9	(12)
III	23	(30)
IV	44	(58)
Mean number of unique prior therapies (range)	2	(1 – 5)
Prior therapy [number (%) of patients]		
Single agent rituximab	58	(76)
CHOP-like chemotherapy + rituximab	41	(54)
CVP + rituximab	21	(28)

Table 11: Baseline demographics

Primary outcome analysis

A 77% ORR was observed among 74 assessable patients, which included 11 CRs, 14 CRus (34% CR/CRu), and 32 PRs (43%) (see Table 12). Among the 45 patients with follicular lymphoma, including almost half with a high-risk FLIPI score, an 82% ORR was documented, including seven CRs, 10 CRus, and 20 PRs. An ORR of 75% was seen in patients with >2 prior chemotherapy regimens.

Secondary analyses

The median DoR for responders in the treated population was 6.7 months (95% CI, range 5.1 to 9.9); for patients with low grade lymphoma, it was 9.0 months (95% CI, range 5.8 to 16.7 - see Figure 15).

		% of patients				
Response	**No of patients**	**CR/CRu**	**PR**	**SD**	**PD**	**Unknown**
Total	74	34	43	4	17	3
Follicular	45	37	44	4	11	2
Small lymphocytic	11	36	27	0	36	0
Lymphoplasmacytic	1	100	0	0	0	0
Marginal zone	2	50	50	0	0	0
Transformed	15	13	53	7	27	0

Table 12: Treatment response

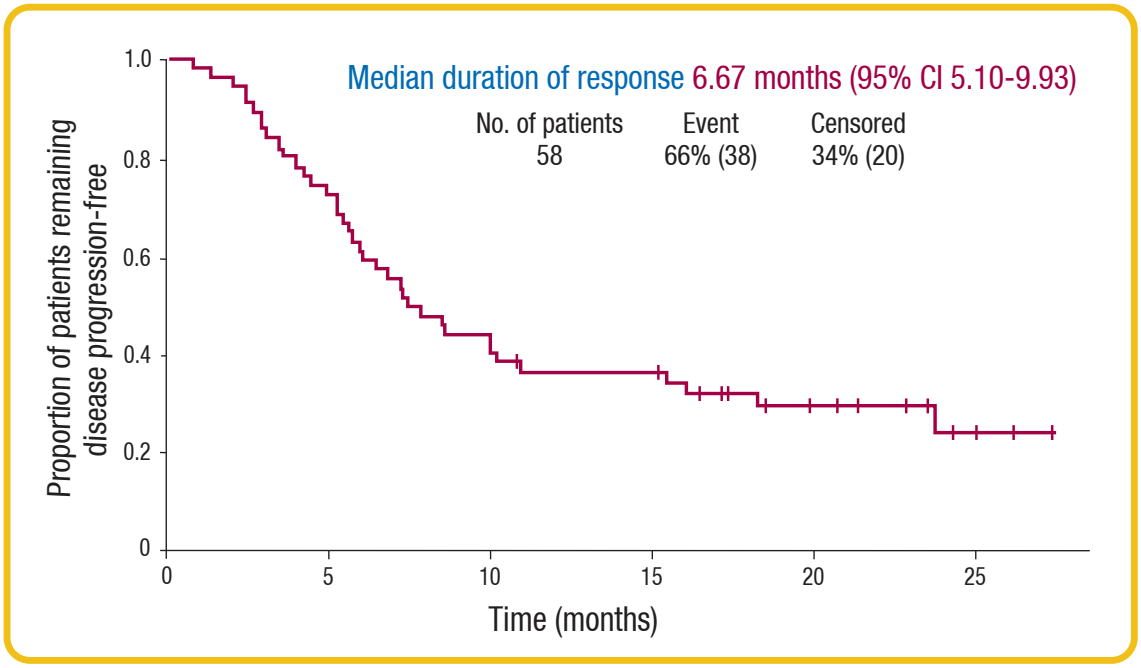

Figure 15: Duration of response

Based on a median follow-up period of 26 months, median PFS was 7.1 months for all patients, and 8.3 months (95% CI, 6.6 to 10.9) for patients with low-grade disease (see Figure 16).

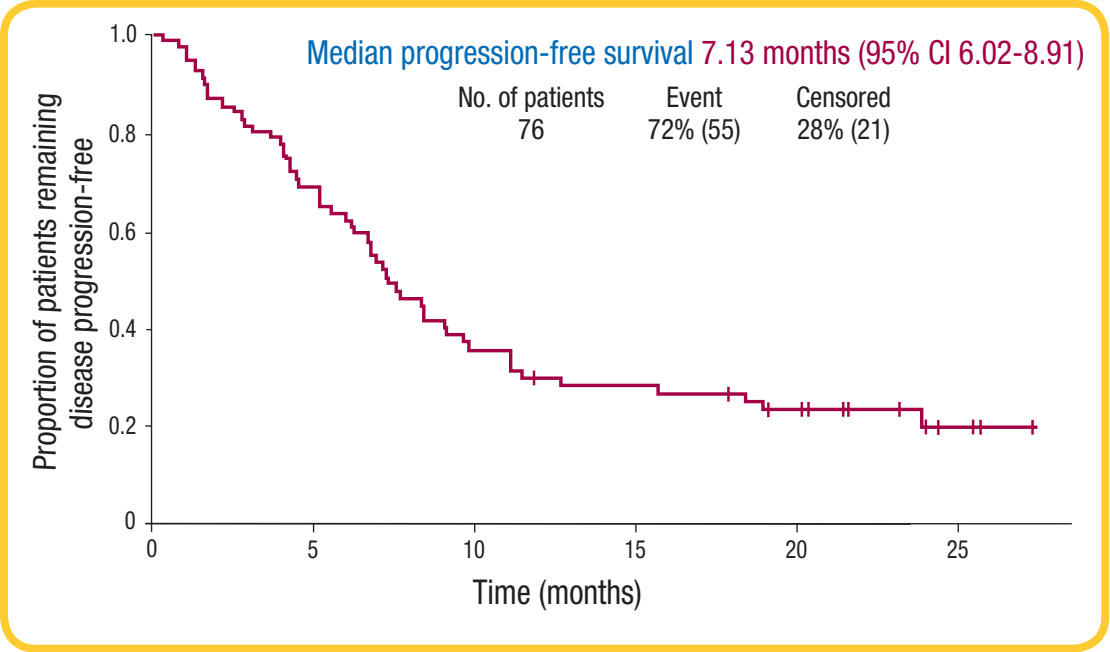

Figure 16: Progression-free survival

Adverse events/toxicity

All 76 patients receiving bendamustine treatment reported at least one adverse event during the treatment period. Three patients had adverse events leading to death. One patient had PD that was reported as an adverse event with an outcome of death. In addition, four other patients died due to disease progression.

The most frequent reasons for discontinuation of study drug treatment due to adverse events were thrombocytopenia [11(14%) patients] and neutropenia [2 (3%) patients].[27]

Table 13 shows the adverse events that occurred in this trial listed by severity grade.

All 76 treated patients received between one and nine cycles of bendamustine treatment, with a mean of 4.8 and median of 5.0 treatment cycles.[27]

Twenty-five percent of the patients had dose reductions as allowed according to the protocol: 20% of the patients had dose reductions from 120 mg/m^2 to 90 mg/m^2, and 5% had dose reductions from 120 mg/m^2 to 90 mg/m^2 to 60 mg/m^2.

	Number (%) of patients									
Adverse event	**Grade 1**		**Grade 2**		**Grade 3**		**Grade 4**		**Total**	
Haematologic*										
Neutropenia	7	(9)	17	(22)	23†	(30)	18	(24)	65	(85)
Anaemia	27	(36)	35	(46)	9	(12)	0	–	71	(94)
Thrombocytopenia	27	(36)	18	(24)	12	(16)	7	(9)	64	(85)
Non-haematologic¥										
Nausea	30	(39)	22	(29)	3	(4)	0	–	55	(72)
Fatigue	17	(22)	15	(20)	5	(7)	0	–	55	(72)
Vomiting	16	(21)	12	(16)	3	(4)	0	–	31	(41)
Anorexia/decreased appetite	18	(24)	8	(10)	0	–	0	–	26	(34)
Diarrhoea	14	(18)	8	(11)	1	(1)	0	–	23	(30)
Cough	17	(22)	5	(7)	0	–	0	–	22	(29)
Constipation	15	(20)	4	(5)	1	(1)	0	–	20	(26)
Pyrexia without documented neutropenia	13	(17)	4	(5)	2	(3)	0	–	19	(25)
Headache	13	(17)	2	(3)	0	(0)	0	–	15	(20)
Back pain	5	(7)	5	(7)	2	(3)	0	–	12	(16)
Dehydration	3	(4)	4	(5)	2	(3)	0	–	9	(12)
Candida infection	3	(4)	1	(1)	2	(3)	0	–	6	(8)
Hypokalemia	0	–	1	(1)	3	(4)	0	–	4	(5)
Pneumonia	0	–	0	–	4	(5)	0	–	4	(5)

Table 13: Adverse events during the study. *Severity was determined using the National Cancer Institute common toxicity criteria for adverse events. †Includes five patients with febrile neutropenia. ¥Commonly-occurring non-haematologic adverse events (occurring >20% of patients) and all grade 3/4 non-haematologic adverse events occurring in >1 patient.

A multicentre Phase II study to investigate the safety and efficacy of bendamustine in patients with indolent non-Hodgkin's lymphoma (NHL) who are refractory to rituximab[29, 30]

Trial methodology

Trial design

This was a multicentre, non-randomised, open-label, single-agent clinical study conducted at 24 study centres in the US and four centres in Canada by 28 investigators. The study design is shown in Figure 17.

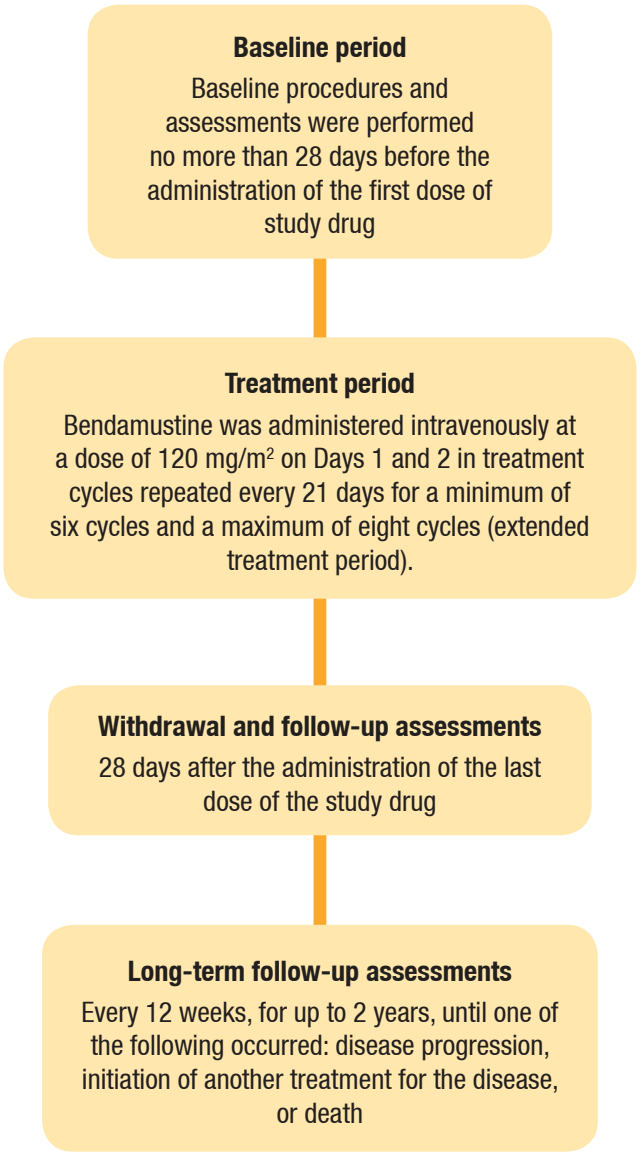

Figure 17: Study schema

Summary

- This was a Phase II study to investigate the safety and activity of bendamustine in patients with indolent NHL who are refractory to rituximab.
- The total number of patients treated in this trial was 100.
- The ORR was 75% with 14% patients having a CR, 3% patients having CRu, and 58% patients having PR (P <0.0001).
- Patients who responded to bendamustine had durable responses and a median DoR of 9.2 months.
- Based on a median follow up of 11.8 months, the median PFS for the overall study population was 9.3 months.
- The median PFS for patients who were sensitive or refractory to their last chemotherapy regimen was 11.8 months and 7.5 months, respectively.

Inclusion criteria

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

- The patient had documented relapsed low-grade B-cell NHL.
- The patient had disease documented to be refractory to rituximab treatment. Rituximab-refractory disease was defined as no objective response or documented progression within 6 months of:

1. receiving the first dose of a full course of single agent rituximab (≥4 doses of 375 mg/m^2 weekly);
2. completion of rituximab maintenance therapy or progression before the next scheduled rituximab dose;
3. completion of a full course of rituximab in combination with chemotherapy.

- Patients could receive additional systemic treatment after the qualifying rituximab regimen and had received treatment with at least one previous chemotherapy regimen with a maximum of three previous chemotherapy regimens.
- The patient was at least 18 years old at the time of informed consent, had a bidimensionally measurable disease with at least one lesion measuring 2.0 cm or more in a single dimension, had a bone marrow biopsy within 28 days of the first dose of study treatment, had a WHO performance status of 0 to 2, and had an estimated life expectancy of at least 3 months.
- In patients with thrombocytopenia attributable to bone marrow involvement with NHL, the patient had an absolute neutrophil count (ANC) of 1,000 cells/mm^3 or more and a platelet count of 100,000 cells/mm^3 or more (or platelet count 75,000 cells/mm^3 or more) a creatinine clearance of more than 30 mL/min as determined by Cockroft-Gault calculation, adequate hepatic function [no more than 2.5 times the upper limit of the normal (ULN) laboratory range for aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase, and no more than 1.5 times the ULN for total bilirubin].

Exclusion criteria

Patients were excluded from participating in this study if one or more of the following main criteria were met (not all-inclusive):

- The patient had received previous radiotherapy, radioimmunotherapy, chemotherapy or immunotherapy within 28 days before Cycle 1, Day 1. For treatment with nitrosoureas or mitomycin, the time limit was 6 weeks before entering the study.
- The patient had received treatment with investigational agents within 28 days of Cycle 1, Day 1, had received haematopoietic growth factors or was receiving concurrent treatment with therapeutic doses of systemic steroids within 14 days of Cycle 1, Day 1, had a history of previous high-dose chemotherapy with allogeneic stem cell support, had a known hypersensitivity to mannitol, or had used bendamustine previously.
- The patient had transformed disease, had any history of CNS or leptomeningeal lymphoma, had an active malignancy within the past five years other than the target cancer, had a serious infection, medical condition, or psychiatric condition, and was known to be positive for human immunodeficiency virus (HIV).

Study drugs

Patients were given i.v. bendamustine at a dose of 120 mg/m^2 on Day 1 and Day 2 in treatment cycles that were repeated every 21 days for a minimum of six cycles. Bendamustine was administered as an i.v. infusion over 60 minutes.

Dose adjustment

Patients who experienced grade 3 or 4 non-haematological or grade 4 haematological toxicity at a dose of 120 mg/m^2 had their dose decreased to 90 mg/m^2 for the next cycle, provided the patient had recovered and the toxicities were at baseline values or of grade 1 or less.

If grade 3 or 4 non-haematologic or grade 4 haematologic toxicity appeared at this reduced dose, the dose was further decreased to 60 mg/m^2 for the next cycle. Patients who continued to experience toxicities at the 60 mg/m^2 dose were withdrawn from the study.

Allowed and disallowed therapy

Investigators were permitted to prescribe supportive treatment for patients with adverse events including antiemetics, antidiarrhoeals, antipyretics, antiallergic agents, antihypotensives, analgesics, antibiotics, and other therapies such as blood products. Chronic erythropoietin therapy was permitted.

The prophylactic use of cytokines to stimulate WBCs, such as G-CSF, was discouraged during the first cycle.

Treatment with low doses of chronic steroids (up to 10 mg/day of prednisone or equivalent) was permitted for non-neoplastic disorders. However, other on-study treatment with corticosteroids was not allowed, with the exception of single doses of steroids used as antiemetics (two doses per cycle).

Treatment with radiation was not allowed during the study.

Endpoints

The primary efficacy variables for this study were the ORR (defined as the proportion of patients who achieved a best response of CR, CRu, or PR during the study) and the DoR.

The secondary efficacy variable was PFS. This was determined for all patients and was defined as the time interval from the date of the first bendamustine dose to the first documentation of disease progression, death (regardless of cause), or change of therapy due to disease progression, whichever occurred first.

Population included

The primary analysis set included all enrolled patients who were treated with study drug.

The evaluable set included all patients who met the following criteria:

- Treated with study drug.
- Had none of the following major eligibility violations:
    - Missing CT scans at baseline.
    - Missing bone marrow biopsy at baseline.
    - Baseline CT scans that were deemed to be inadequate as determined by a third-party radiology review Image Quality Assessment (IQA) process.
    - Disease that did not meet criteria to be a low-grade lymphoma.
    - Disease was not refractory to rituximab.
    - No history of chemotherapy or more than three previous unique courses.
    - No measurable disease lesion (2 cm or more).
    - Use of systemic steroids within 14 days of study treatment, other than low doses of chronic steroids.
    - History of transformed disease.
    - History of CNS or leptomeningeal lymphoma.
    - Had a baseline ALC less than 5×10^9/L.
    - Had at least one post baseline response assessment or withdrew before having a post baseline response assessment due to rapid disease progression or death.

Trial results

Patient disposition

A total of 102 patients at 24 centres in the US and four centres in Canada were enrolled into the study. One hundred patients received at least one dose of bendamustine. Two enrolled patients did not receive any treatment because they were subsequently considered ineligible for the study.

Of the 100 patients treated with bendamustine, 60 (60%) received treatment for six or more cycles. Patients were discontinued from study drug treatment due to adverse events (n = 27), disease progression (n = 10), patient decision (n = 1) and an excessive treatment delay (n = 1).

Baseline demographics

The median age of the patients was 60 years (range 31 to 84 years). Of the 100 patients treated, 62 had follicular lymphoma, 21 had B-cell CLL/SLL, 16 had marginal zone B-cell lymphoma, and one had lymphoplasmacytic lymphoma. Most patients with follicular lymphoma had either grade 1 or grade 2 disease.

The average age at onset of disease was 54.7 years. The average number of months since the original primary diagnosis was 56.9. The median number of prior chemotherapy regimens was 2 (range 0 – 6).

Primary outcome analysis

The ORR by independent review committee (IRC) in the 100 patients in the primary analysis set was 75% (95% CI 65.3, 83.1, $P<0.0001$) with 14 (14%) patients having CR, three (3%) patients having CRu, and 58 (58%) patients having PR. This result was statistically significant against the null hypothesis of a response rate of 40% ($P<0.0001$).

Secondary analyses

Duration of response

Median DoR in patients who achieved an objective response (n = 75) was 9.2 months (range 7.1 – 10.8) (see Figure 18).

Progression-free survival

PFS was comparable across all patient groups defined by baseline characteristics. Based on a median follow-up of 11.8 months, median PFS for the overall study population was 9.3 months (95% CI 8.1 – 11.9; see Figure 19). Median PFS for patients who were sensitive (n = 51) and refractory (n = 36) to their last chemotherapy regimen were 11.8 months (95% CI 9.0 – 13.0) and 7.5 months (95% CI 4.4 – 12.0), respectively.

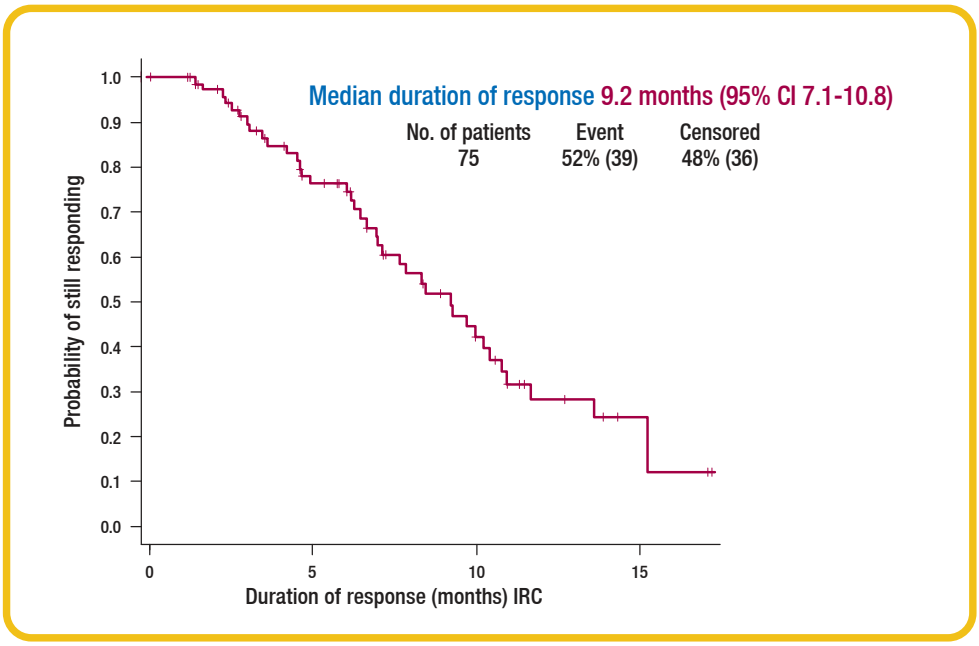

Figure 18: Duration of response[31]

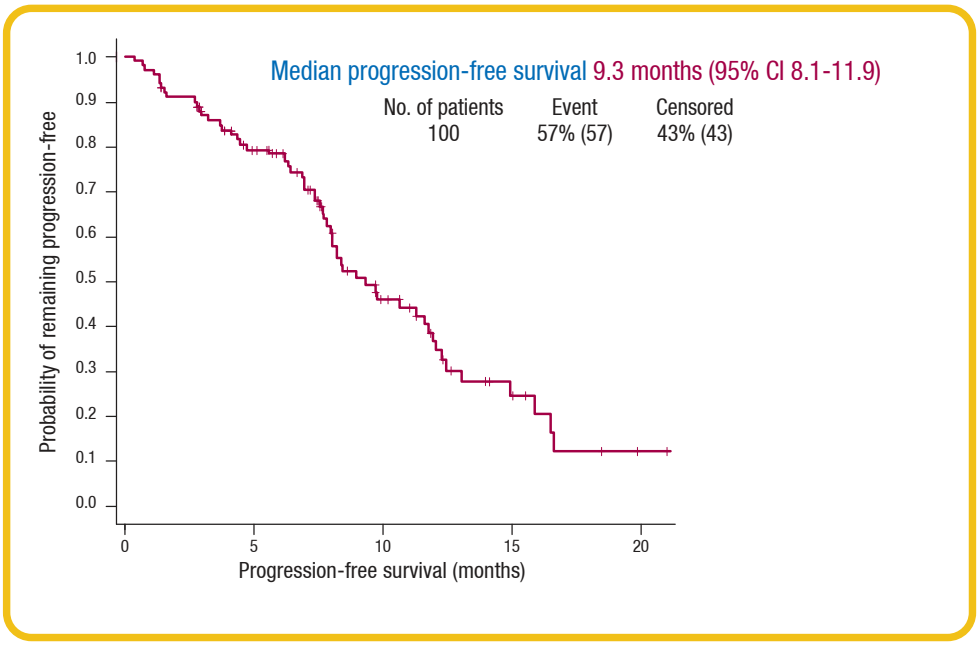

Figure 19: Progression-free survival

Tolerability and toxicity

All 100 patients treated with bendamustine reported at least one adverse event during the treatment period. Table 14 shows the rates of grade 3 and 4 haematological adverse events occurring in this study

During the study, 24% of the patients had dose reductions: 20% of the patients had dose reductions from 120 mg/m^2 to 90 mg/m^2, and 4% had dose reductions from 120 mg/m^2 to 90 mg/m^2 to 60 mg/m^2. Patients with dose reductions due to thrombocytopenia or neutropenia generally continued the study drug treatment, and most received at least six cycles of treatment. The mean relative dose intensity was 88%.

A total of 27 patients (27%) discontinued treatment early due to adverse events. Failure to recover platelet counts was the most common reason for premature treatment discontinuation (9%). Grade 3/4 thrombocytopenia occurred in 25% of patients.

Infections (any grade) occurred in 69% of patients. Eight grade 4 infections occurred in six patients, including pneumonia and sepsis. Five episodes of cytomegalovirus were reported.

Secondary malignancies occurred in two patients (2%) – myelodysplastic syndrome and squamous cell carcinoma.

There were two episodes of tumour lysis syndrome which resolved with supportive care.

A total of 11 deaths occurred: seven were due to serious adverse events (including thrombocytopenia, sepsis and respiratory failure) and four were due to disease progression.

	Grade 3 (%)	Grade 4 (%)
Lymphocytopenia	21	73
Neutropenia	38	23
Febrile neutropenia	5	1
Thrombocytopenia	19	6
Anaemia	7	3

Table 14: Adverse events during the study

Combination therapy in indolent NHL

Levact i.v. is licensed as monotherapy in patients refractory to rituximab. It has been used in combination with other agents in various studies - however it is important to note that dosing of ***Levact*** i.v. needs to be reduced in these settings.

Advice on combination data and dosing can be obtained from the Medical Information Department at Napp Pharmaceuticals Limited on oncologymedinfo@napp.co.uk or on 01223 424444.

Chapter four: Advanced multiple myeloma

Introduction

In 2006, almost 4,000 cases of MM were diagnosed in the UK, equivalent to approximately 1% of all cancers.[32] Men are more likely to develop MM than women: the age standardised rates in Europe for 2006 were 6.0 and 4.0 per 100,000, respectively.[33] It has been estimated that the lifetime risk of developing MM is 1 in 148 for men and 1 in 186 for women in the UK (based on mortality and incidence data for 2001 – 2005).[33]

The risk of developing myeloma increases with advancing age.[33] The rate per 100,000 of the population aged between 40 – 44 years is 1.0 in men and 1.1 in women. The rate increases to 52.5 in men and 33.1 in women aged between 80 and 84 years.[33]

MM caused approximately 2,700 deaths in the UK in 2007.[34] Survival depends on age and has improved incrementally since the 1960s as new treatments entered clinical practice.[35, 36] Median survival was less than one year before the introduction of alkylating agents, and the introduction of melphalan in the 1960s resulted in improved survival.[36] Five-year survival rates (patients diagnosed between 1986 and 1990 in England and Wales) in men aged 15 to 39 years is 51%, falling to 7% in those aged 80 to 99 years. In women, the respective figures are 55% and 9%.[35]

The armamentarium against MM expanded further in recent years to include thalidomide, lenalidomide and bortezomib. MM patients treated with one or more of these drugs (thalidomide, lenalidomide or bortezomib) show longer survival following relapse after first-line therapies compared with those people not treated: 30.9 and 14.8 months, respectively ($P<0.001$).[36] Improvements in supportive care, such as growth factors, bisphosphonates and management of renal failure, also contributed to the improved survival.[36] Nevertheless, as the survival data suggest, there is still a need for innovations in disease management.

Studies performed in the 1960s suggested that bendamustine should offer an effective treatment for MM. Anger *et al* (1969)[37] reported that 16 of 18 MM patients treated with bendamustine remained alive nine months after treatment started. This compared with four of 16 historical controls.[37] Since then, the evidence suggesting that bendamustine offers an effective treatment for MM has continued to emerge.

Summary

- This was a randomised, Phase III study to compare bendamustine and prednisone (BP) with melphalan and prednisone (MP).
- The number of patients treated in this trial was 131.
- The ORRs were 75% and 70% with BP and MP, respectively.
- The time to treatment failure (TTF) was significantly longer in the BP group compared with the MP group (14 months *vs.* 10 months; $P<0.02$). The benefits of BP over MP in terms of TTF were maintained beyond 30 months.
- A significantly higher number of patients treated with BP achieved a CR compared with patients receiving MP (32% *vs.* 13%, respectively; $P = 0.007$).
- Five-year survival rates in the BP and MP arms were 29% and 19%, respectively.
- No significant differences in toxicity were seen between the two study groups, except for grade 3 nausea and vomiting, which was higher in the BP arm.
- No treatment-related toxicities resulted in discontinuation of therapy and most treatment cycles were completed without the need for dose reduction (80% for BP *vs.* 92% for MP).

Bendamustine and prednisone (BP) *vs.* melphalan and prednisone (MP): a Phase III, multicentre, randomised, open-label trial[38, 39]

Bendamustine demonstrates superiority to melphalan

Until relatively recently, the combination of melphalan and prednisone (MP) had remained the mainstay of treatment of MM for approximately 30 years. Approximately 40 – 50% of MM patients show a clinical response to MP and median survival is approximately 24 – 30 months.[40, 41] However, melphalan is associated with cytopenia and myelodysplasia.[42] Therefore, there is a need for better tolerated alternatives. Bendamustine has been shown to offer superior response rates to melphalan in the first-line treatment of MM.[42]

N.B. The following trial formed the basis of the licence for ***Levact*** i.v. in the UK. However, it should be noted that ***Levact*** i.v. is only licensed for ***front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib-containing treatment.***

Trial methodology

Trial design

A prospective, open-label, randomised, multicentre, Phase III trial of BP compared with MP as a first-line treatment for patients with advanced MM (Durie Salmon stage II with progression or stage III).

Randomisation was stratified according to stage of disease.

Inclusion criteria:

- Age 18-80 years.
- Advanced MM (Durie Salmon stage II with progression or stage III).
- Quantitatively measurable myeloma proteins in serum and/or urine by protein electrophoresis.
- Leukocyte count ≥2,000/µl.
- Platelet count ≥50,000/µl.
- Karnofsky performance status ≥60%.
- Life expectancy ≥3 months.
- No prior chemotherapy or radiotherapy.

Exclusion criteria:

- Non-secretory and local plasmacytoma.
- HIV or Hbs-AG positivity or active hepatitis.
- Secondary malignancy.
- Pregnancy or lactation.
- Participation in a clinical trial within the last 28 days.
- Serious concomitant diseases.

Study drugs

Bendamustine 150 mg/m^2 in 500 ml 0.9% saline on Days 1 and 2 of each 28-day cycle. Melphalan 15 mg/m^2 in 100 ml 0.9% saline on Day 1 of each 28-day cycle.

All patients received prednisone (60 mg/m^2 intravenously or orally on Days 1 – 4) in addition to either bendamustine or melphalan.

Toxicity	Dose adjustment
Leukocyte count ≥3,000/µl and/or platelet count ≥75,000/µl and/or non-haematological toxicity grade 1	No dose adjustment
Leukocyte count ≥2,000/µl - <3,000/µl and/or platelet count ≥50,000/µl – 75,000/µl and/or non-haematological toxicity grade 2	Dose reduced by 25%
Leukocyte count <2,000/µl and/or platelet count <50,000/µl and or non-haematological toxicity grade 3	Dose reduced by 50%

Table 15: Dose adjustments. The dose was also reduced by 50% in the case of renal failure with an increase in creatinine to ≥500 µmol/l.

Dose adjustments

The next cycle of BP or MP was delayed by one week if leukocyte counts were <3000/µl and or platelet counts were <75,000/µl.

Dosage of melphalan and bendamustine was modified in subsequent cycles according to WHO criteria (see Table 15). Prednisone doses were not adjusted.

Permitted and disallowed concomitant therapy

Patients could receive supportive therapy as indicated, including treatment of bone lesions, platelet or erythrocyte transfusions and growth factors. Prophylactic antibiotics and antimycotics were permitted. Hypercalcaemia was treated with bisphosphonates and hydration.

Endpoints

The primary endpoint was TTF defined as the time from randomisation to the occurrence of PD during the first cycle or any time thereafter, therapy switch, discontinuation of therapy or death.

Secondary endpoints were overall survival, remission rate, duration of remission, toxicity and quality of life.

Complete response

- Decline in serum myeloma protein by ≥75% to ≤25 g/l.
- Reduction in 24 hour urinary protein by ≥90% to ≤200 mg/24 hour.
- No increase in skeletal destruction.
- Serum Ca within normal range.
- No blood transfusion required in the previous three months.

Partial response

- Decline in serum myeloma protein of 25 – 74%.
- Reduction in 24 hour urinary protein of 25 – 89%.
- No increase in skeletal destruction.
- Serum Ca within normal range.

No change

- Minor variations (<±25%) in serum myeloma protein and/or 24 hour urinary protein.

Progressive disease

- Increase in serum myeloma protein and/or 24 hour urinary protein by at least 25%.
- New osteolytic lesions or hypercalcaemia.
- Progressive worsening of anaemia with increased infiltration of plasma cells into the bone marrow.

Maximal remission was achieved if three additional courses of therapy did not further reduce the myeloma protein by >10% in the serum and/or urine (24 hour urine protein), and if no disease progression was observed.

Population included

A total of 136 patients were enrolled between June 1994 and July 1999. Five patients had not received the assigned treatment and thus were not evaluable.

Trial results

Patient demographics

Table 16 shows patient characteristics at diagnosis. There were no significant differences between the two groups.

	Treatment regimen		
	BP (n = 68)	**MP (n = 63)**	***P* value**
Age: median (range) in years	62 (38 - 76)	62 (42 - 80)	0.64
Sex (male/female)	38/30	35/28	0.97
Haemoglobin [median (range) g/dl]	11.1 (6.7 - 5.5)	11.0 (6.1 - 15.5)	0.34
Serum creatinine [median (range) µmol/l]	91 (58 - 327)	99 (65 - 272)	0.38
Serum B2 microglobulin [median (range) mg/l]	3.4 (1.1 - 7.5)	3.3 (1.1 - 16.4)	0.75
Serum calcium [median (range) mmol/l]	2.3 (2.0 - 4.2)	2.4 (1.2 - 3.5)	0.80
Advanced bone destruction	50 (74%)	48 (76%)	0.84
Spontaneous fractures	17 (25%)	14 (22%)	0.84
Immunoglobulin type			
IgG	47 (69%)	45 (71%)	0.85
IgA	17 (25%)	14 (22%)	0.84
IgE	0 (0%)	1 (2%)	0.48
Bence-Jones protein	4 (6%)	3 (5%)	1.00
Durie-Salmon stage			
Stage II (with progression)	7 (10%)	4 (6%)	0.53
Stage III	61 (90%)	59 (94%)	0.53

Table 16: Patient demographics

Primary outcome analysis

TTF was significantly longer in BP-treated patients compared with MP-treated patients (14 months *vs.* 10 months, $P<0.02$ (see Figure 20). Remission duration in patients achieving a CR or PR was 18 months *vs.* 12 months, $P<0.02$. The benefits of BP over MP in terms of TTF were maintained beyond 30 months.

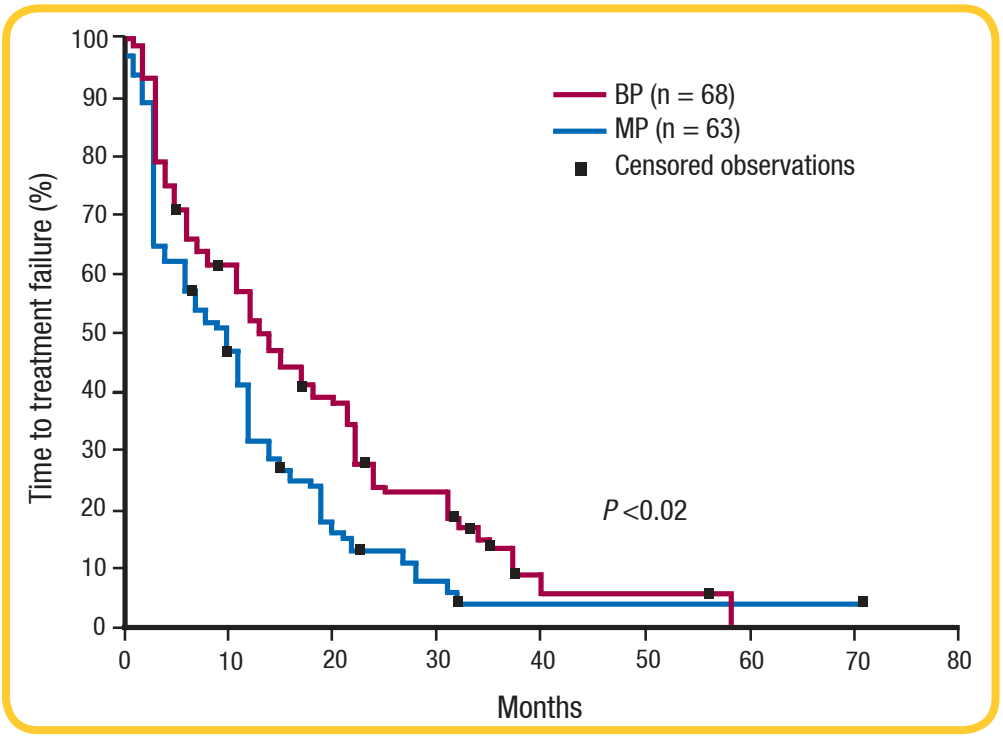

Figure 20: Time to treatment failure

Secondary analyses

The ORRs (CR + PR) were 75% and 70% with BP and MP, respectively; see Table 17). A significantly higher number of patients treated with BP achieved a CR, compared with patients receiving MP (32% *vs.* 13%, $P = 0.007$). Furthermore, patients who responded did so after a median of 6.8 cycles in the BP arm. This compared with 8.7 cycles among those who responded to MP.

Median overall survival rates were not significantly different between patients receiving BP or MP (32 months *vs.* 33 months, respectively; see Figure 21). Five-year survival rates in the BP and MP arms were 29% and 19%, respectively.

Quality of life improved to a greater extent in the BP arm than with MP (see Figure 22):

- Four months after the start of treatment, global health status and emotional functioning were better in BP-treated patients than those who received MP.
- The greater improvement in these markers of quality of life associated with BP treatment persisted beyond six months.
- Four months after the start of treatment, the BP group experienced pain (usually in bone) less frequently than those receiving MP.

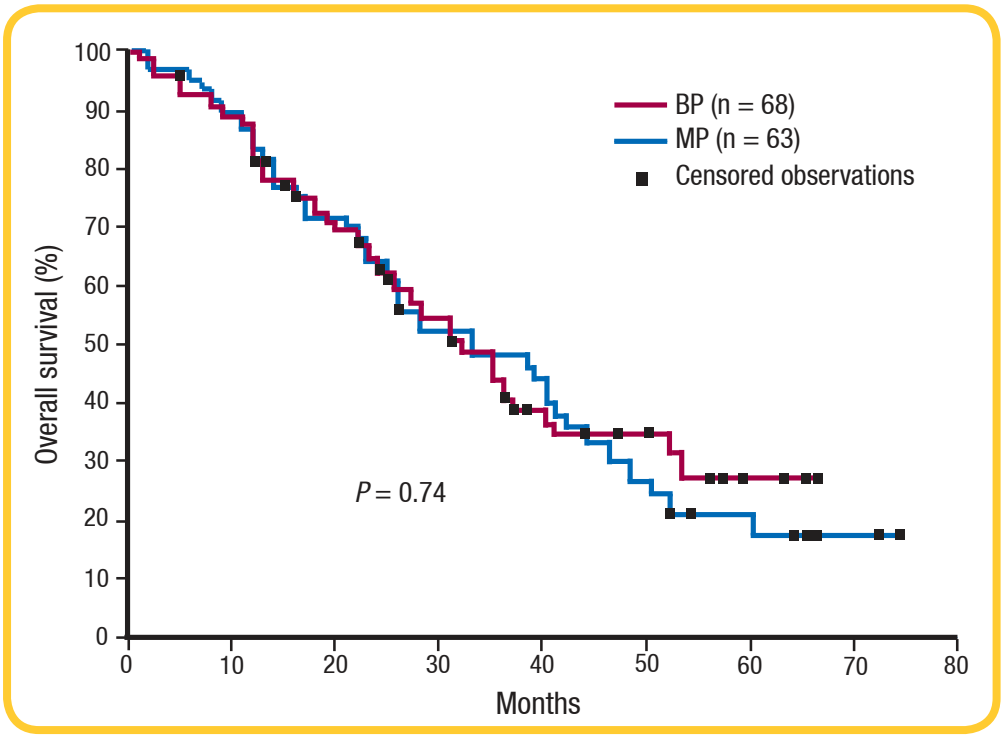

Figure 21: Overall survival

	Treatment regimen				
Response	**BP (n = 68)**	**% patients**	**MP (n = 63)**	**% patients**	***P* value***
ORR	51	75	44	70	NS
CR	22	32	8	13	$P = 0.007$
PR	29	43	36	57	NS
SD	16	23	17	27	NS
PD	1	2	2	3	NS

Table 17: Response rates. NS = non significant. *Fisher's exact test

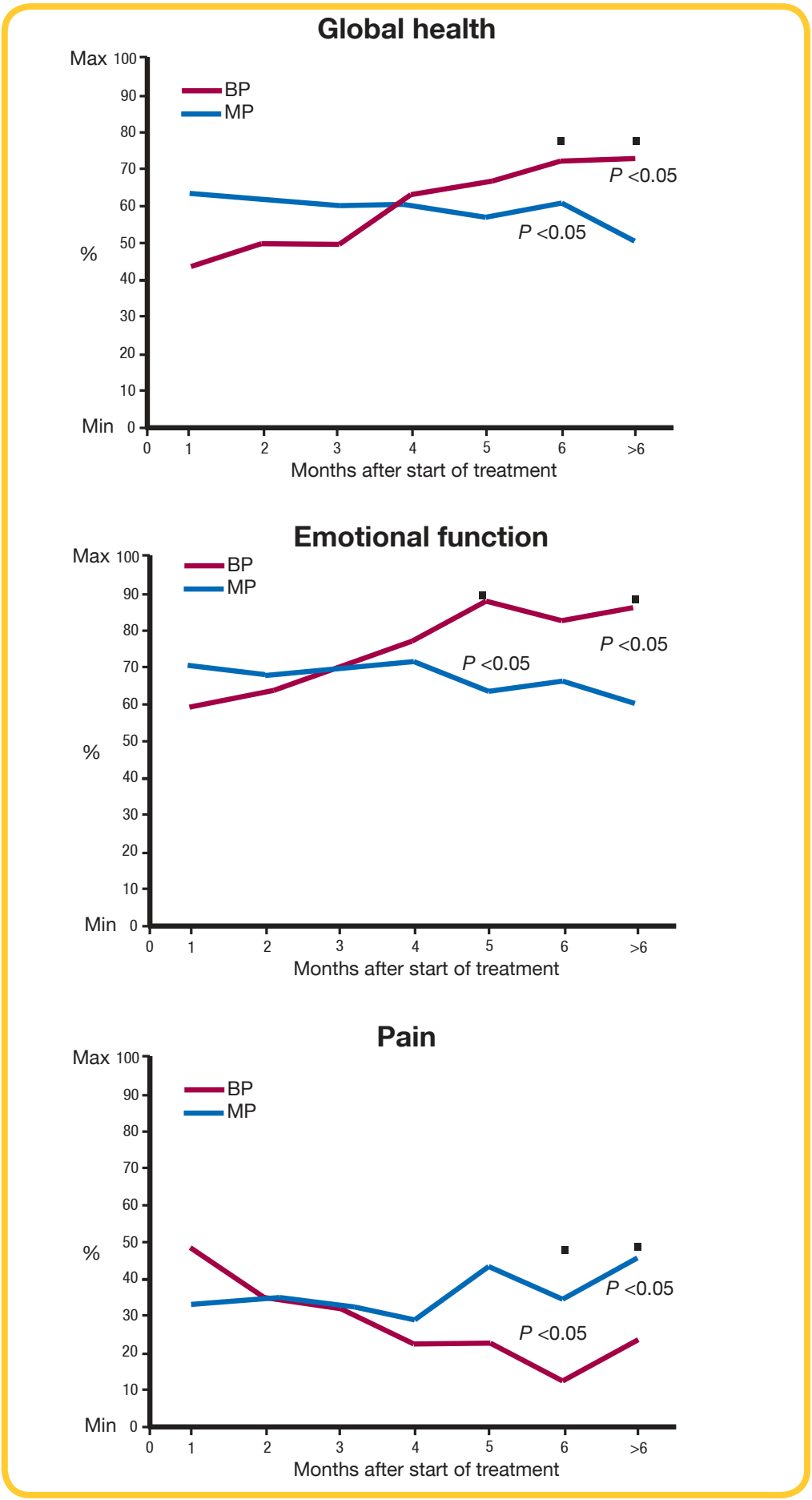

Figure 22: The effect of BP and MP on several measures of health-related quality of life

Patients >65 years

A post-hoc sub-analysis of time to treatment failure (TTF) was performed for regulatory purposes. In patients >65 years of age, TTF was significantly better in the BP group *vs*. the MP arm (median = 13 *vs*. 9 months, respectively; P = 0.011) despite the low numbers in each subgroup (n = 29 in BP arm *vs*. n = 25 in the MP arm; see Figure 23).[39]

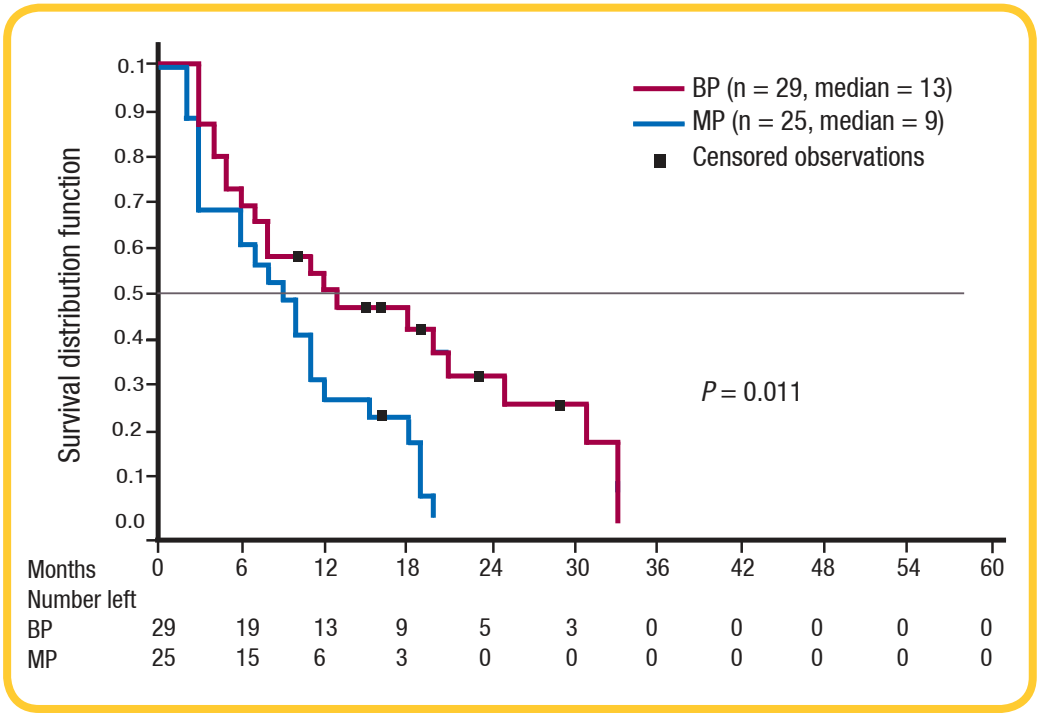

Figure 23: Time to treatment failure in >65 year old patients

PFS was also analysed for patients >65 years of age. PFS was significantly longer after treatment with BP than after treatment with MP (18 months *vs*. 11 months; *P* = 0.017).

Adverse events and toxicity

No significant differences in toxicity were observed between groups (see Table 18), except for grade 3 nausea and vomiting, which was higher in the bendamustine arm. No treatment-related toxicities resulted in discontinuation of therapy. Most treatment cycles were completed without the need for dose reduction (80% BP *vs.* 92% MP).

The percentage of patients receiving BP who required a dose reduction for leukocytopenia (8.6 *vs.* 4.1%) or thrombocytopenia (1.8 *vs.* 0.9%) was twice that of patients receiving MP.

		WHO grade				
		1	**2**	**3**	**4**	***P* value**
Anaemia	BP	25%	16%	21%	3%	0.1878
	MP	19%	35%	21%	3%	
Leukocytopenia	BP	10%	25%	28%	12%	0.2808
	MP	14%	27%	25%	6%	
Thrombocytopenia	BP	10%	4%	6%	4%	0.3392
	MP	11%	18%	10%	5%	
Fever	BP	12%	27%	2%	0%	0.4267
	MP	10%	18%	0%	0%	
Infection	BP	18%	15%	10%	2%	0.8270
	MP	18%	5%	10%	2%	
Mucositis	BP	13%	0%	4%	0%	0.0135
	MP	3%	0%	2%	0%	
Nausea/vomiting	BP	19%	21%	12%	0%	0.0009
	MP	18%	10%	0%	0%	

Table 18: Adverse events during the study

Chapter five: Toxicity and tolerability

Adverse events in clinical trials

Table 19 shows the adverse events seen in clinical trials with ***Levact*** i.v.[1] The most common adverse reactions are haematological (leukopenia, thrombocytopenia), dermatological toxicities (allergic reactions), constitutional symptoms (fever), and gastrointestinal symptoms (nausea, vomiting).

Contra-indications

- Hypersensitivity to the active substance or to any of the excipients.
- During breast-feeding.
- Severe hepatic impairment (serum bilirubin >3.0 mg/dl).
- Jaundice.
- Severe bone marrow suppression and severe blood count alterations (leukocyte and/or platelet values dropped to <3,000/µl or <75,000/µl, respectively).
- Major surgery less than 30 days before start of treatment.
- Infections, especially involving leukocytopenia.
- Yellow fever vaccination.

Myelosuppression

Patients treated with ***Levact*** i.v. may experience myelosuppression. The leukocyte and platelet Nadir is reached after 14 – 20 days with regeneration after 3 – 5 weeks. In the event of treatment-related myelosuppression, leukocytes, platelets, haemoglobin, and neutrophils must be monitored at least weekly. Prior to the initiation of the next cycle of therapy, the following parameters are recommended: leukocyte and/or platelet values >4,000/µl or >100,000/µl, respectively.[1]

When ***Levact*** i.v. is combined with myelosuppressive agents, the effect of ***Levact*** i.v. and/or the co-administered medicinal products on the bone marrow may be potentiated. Any treatment reducing the patient's performance status or impairing bone marrow function can increase the toxicity of ***Levact*** i.v.

Infections

Infection, including pneumonia and sepsis, has been reported. In rare cases, infection has been associated with hospitalisation, septic shock and death. Patients with neutropenia and/or lymphocytopenia following treatment with ***Levact*** i.v. are more susceptible to infections.

Patients with myelosuppression following treatment with ***Levact*** i.v. should be advised to contact a physician if they have symptoms or signs of infection, including fever or respiratory symptoms.[1]

The CD4/CD8 ratio may be reduced. In immuno-suppressed patients, the risk of infection (e.g. with herpes zoster) may be increased.

Table 20 shows the infections occurring in the pivotal CLL trial[15] (***Levact*** i.v. *vs.* chlorambucil first-line). Opportunistic infections in this group were uncommon. In NHL patients refractory to rituximab, infection rates in the single arm Phase II trials[43] are outlined in Table 21.

Infusion reactions and anaphylaxis

Infusion reactions to ***Levact*** i.v. have occurred commonly in clinical trials. Symptoms are generally mild and include fever, chills, pruritus and rash. In rare instances, severe anaphylactic and anaphylactoid reactions have occurred. Patients must be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Measures to prevent severe reactions, including antihistamines, antipyretics and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion reactions. Patients who experienced grade 3 or worse allergic-type reactions were typically not rechallenged.[1]

MedDRA system organ class	Very common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1000, <1/100	Rare ≥1/10,000 to <1/1000	Very rare < 1/10,000
Infections and infestations	Infection NOS*			Sepsis	Pneumonia primary atypical
Neoplasm benign, malignant		Tumour lysis syndrome			
Blood and lymphatic system disorders	Leukopenia NOS*, thrombocytopenia	Haemorrhage anaemia, neutropenia			Haemolysis
Immune system disorders		Hypersensitivity NOS*		Anaphylactic reaction, anaphylactoid reaction	Anaphylactic shock
Nervous system disorders		Insomnia		Somnolence, aphonia	Dysgeusia, paraesthesia, peripheral sensory neuropathy, anticholinergic syndrome, neurological disorders, ataxia, encephalitis
Cardiac disorders		Cardiac dysfunction, such as palpitations, angina pectoris arrhythmia	Pericardial effusion		Tachycardia, myocardial infarction, cardiac failure
Vascular disorders		Hypotension, hypertension		Acute circulatory failure	Phlebitis
Respiratory, thoracic and mediastinal disorders		Pulmonary dysfunction			Pulmonary fibrosis
Gastrointestinal disorders	Nausea, vomiting	Diarrhoea, constipation, stomatitis			Haemorrhagic oesophagitis, gastrointestinal haemorrhage
Skin and subcutaneous tissue disorders		Alopecia, skin disorders NOS*		Erythema, dermatitis, pruritus, maculo-papulo rash, hyperhidrosis	
Reproductive system and breast disorders		Amenorrhea			Infertility
General disorders and administration site conditions	Mucosal inflammation, fatigue, pyrexia	Pain, chills, dehydration, anorexia			Multi-organ failure
Investigations	Haemoglobin decrease, creatinine increase, urea increase	AST increase, ALT increase, alkaline phosphatase increase, bilirubin increase, hypokalaemia			

Table 19: Adverse events seen in clinical trials with ***Levact*** i.v. *Not otherwise specified

	Number (%) of patients*					
	Bendamustine (n = 153)			Chlorambucil (n = 143)		
System organ class	Grade					
Preferred term	3	4	3 or 4	3	4	3 or 4
Infections and infestations	10 (7)	0	10 (7)	4 (3)	1 (<1)	5 (3)
Pneumonia	4 (3)	0	4 (3)	0	0	0
Infection	3 (2)	0	3 (2)	1 (<1)	0	1 (<1)
Pseudomonal sepsis	1 (<1)	0	1 (<1)	0	0	0
Sepsis	1 (<1)	0	1 (<1)	0	0	0
Tracheobronchitis	1 (<1)	0	1 (<1)	0	0	0
Upper respiratory tract infection	1 (<1)	0	1 (<1)	0	0	0
Viral infection	1 (<1)	0	1 (<1)	0	0	0
Hepatitis B	0	0	0	1 (<1)	0	1 (<1)
Herpes zoster	0	0	0	1 (<1)	0	1 (<1)
Pneumonia bacterial	0	0	0	0	1 (<1)	1 (<1)
Respiratory tract infection	0	0	0	1 (<1)	0	1 (<1)

Table 20: Infection rates in pivotal CLL trial. *If a patient reported an adverse event more than once, the greatest severity is presented for that adverse event.

Skin reactions

A number of skin reactions have been reported. These events have included rash, toxic skin reactions and bullous exanthema. Some events occurred when ***Levact*** i.v. was given in combination with other anticancer agents, so the precise relationship is uncertain. Where skin reactions occur, they may be progressive and increase in severity with further treatment. If skin reactions are progressive, ***Levact*** i.v. should be withheld or discontinued. For severe skin reactions where a relationship to ***Levact*** i.v. is suspected, treatment should be discontinued.[1]

Tumour lysis syndrome

Tumour lysis syndrome associated with ***Levact*** i.v. treatment has been reported in patients in clinical trials. The onset tends to be within 48 hours of the first dose of ***Levact*** i.v. and, without intervention, may lead to acute renal failure and death. Preventive measures include adequate volume status and close monitoring of blood chemistry, particularly potassium and uric acid levels. The use of allopurinol during the first one to two weeks of ***Levact*** i.v. therapy can be considered but not necessarily as standard. However, there have been a few cases of Stevens-Johnson Syndrome and toxic epidermal necrolysis reported when bendamustine and allopurinol are administered concomitantly.[1]

	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infection	108 (61)	26 (15)	7 (4)
Pneumonia	14 (8)	7 (4)	2 (1)
Sepsis	4 (2)	1 (<1)	3 (2)
Urinary tract infection	17 (10)	4 (2)	0 (0)
Clostridial infection	3 (<2)	0 (0)	1 (<1)
Opportunistic infection			
Atypical mycobacterial	1 (<1)	0 (0)	1 (<1)
Candidiasis	15 (9)	3 (2)	0 (0)
Cytomegalovirus	5 (3)	3 (2)	0 (0)
Herpes simplex	7 (4)	0 (0)	0 (0)
Herpes zoster	18 (10)	5 (3)	0 (0)
P. jiroveci pneumonia	2 (1)	1 (<1)	0 (0)
Tuberculosis	1 (<1)	0 (0)	1 (<1)

Table 21: Infection rates and opportunistic infections in relapsed/refractory indolent NHL (n = 176). Cytostatics can reduce antibody formation following live-virus vaccination and increase the risk of infection.

Secondary malignancy

There are reports of secondary tumours, including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukaemia and bronchial carcinoma. The association with ***Levact*** i.v. therapy has not been determined.[1]

Special populations

Pregnancy, lactation and contraception

There are insufficient data from the use of ***Levact*** i.v. in pregnant women. In non-clinical studies ***Levact*** i.v. was embryo-/feto-lethal, teratogenic and genotoxic. During pregnancy, ***Levact*** i.v. should not be used unless clearly necessary. The mother should be informed about the risk to the foetus. If treatment with ***Levact*** i.v. is absolutely necessary during pregnancy or if pregnancy occurs during treatment, the patient should be informed about the risks for the unborn child and be monitored carefully. Genetic counselling should be considered.

It is not known whether bendamustine passes into the breast milk, therefore, ***Levact*** i.v. is contra-indicated during breast-feeding. Breast-feeding must be discontinued during treatment with ***Levact*** i.v.

Women of childbearing potential must use effective methods of contraception both before and during ***Levact*** i.v. therapy.

Men being treated with ***Levact*** i.v. are advised not to father a child during and for up to six months following cessation of treatment. Advice on conservation of sperm should be sought prior to treatment because of the possibility of irreversible infertility due to therapy with ***Levact*** i.v.

Hepatic impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with mild hepatic impairment (serum bilirubin <1.2 mg/dl). A 30% dose reduction is recommended in patients with moderate hepatic impairment (serum bilirubin 1.2 - 3.0 mg/dl).

No data are available in patients with severe hepatic impairment (serum bilirubin values of >3.0 mg/dl).[1]

Renal impairment

On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with a creatinine clearance of >10 ml/min. Experience in patients with severe renal impairment is limited. ***Levact*** i.v. and its metabolites are dialysable to a small extent.[1]

Paediatric patients

There is no experience with ***Levact*** i.v. in children and adolescents.

Elderly patients

There is no evidence that dose adjustments are necessary in elderly patients.

Overdose and countermeasures

After application of a 30 min infusion of ***Levact*** i.v. once every three weeks, the maximum tolerated dose (MTD) was 280 mg/m^2. Cardiac events of CTC grade 2, which were compatible with ischaemic ECG changes, occurred, which were regarded as dose limiting.

In a subsequent study with a 30 min infusion of ***Levact*** i.v. at Day 1 and 2 every three weeks, the MTD was found to be 180 mg/m^2. The dose limiting toxicity was grade 4 thrombocytopenia. Cardiac toxicity was not dose limiting with this schedule.

There is no specific antidote. Bone marrow transplantation and transfusions (platelets, concentrated erythrocytes) may be performed or haematological growth factors may be given as effective countermeasures to control haematological side-effects.

Extravasation

An extravasal injection should be stopped immediately. The needle should be removed after a short aspiration. Thereafter, the affected area of tissue should be cooled. The arm should be elevated. Additional treatments like the use of corticosteroids are not of clear benefit.

Potassium levels

Bendamustine has a diuretic effect which can result in loss of potassium. It is therefore important to check electrolytes before administering ***Levact*** i.v. and to instigate replacement therapy if potassium levels are below 3.5mEq/l to reduce any risk of cardiac arrhythmias. This is especially important in patients with pre-existing cardiac disorders.

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Levact®▼ 2.5 mg/ml, powder for concentrate for solution for infusion

Prescribing Information United Kingdom Please read the Summary of Product Characteristics before prescribing.

Presentation Powder for concentrate for solution for infusion. White, microcrystalline powder. One 26 ml vial of powder contains 25 mg bendamustine hydrochloride. One 60 ml vial of powder contains 100 mg bendamustine hydrochloride.

Indications First-line treatment of chronic lymphocytic leukaemia (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. Indolent non-Hodgkin's lymphomas as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen. Front line treatment of multiple myeloma (Durie-Salmon stage II with progress or stage III) in combination with prednisone for patients older than 65 years who are not eligible for autologous stem cell transplantation and who have clinical neuropathy at time of diagnosis precluding the use of thalidomide or bortezomib-containing treatment.

Dosage and administration For i.v. infusion over 30 – 60 minutes. Monotherapy for CLL, 100 mg/m^2 on Days 1 & 2, every 4 weeks. Monotherapy for indolent NHL, 120mg/m^2 on Days 1 & 2, every 3 weeks. MM, 120 – 150mg/m^2 on Days 1 & 2, 60 mg/m^2 prednisone i.v. or per os on Day 1 to 4, every 4 weeks. For further details please refer to the SmPC.

Contra-indications Hypersensitivity to the active substance or excipients, during breast feeding, severe hepatic impairment, jaundice, severe bone marrow suppression and severe blood count alterations, major surgery (less than 30 days prior to start of treatment), infections, yellow fever vaccinations.

Precautions and warnings Myelosuppression, infections, skin reactions, patients with cardiac disorders, nausea, vomiting, tumour lysis syndrome, anaphylaxis, contraception, extravasation.

Interactions No *in vivo* interaction studies have been performed. Combined use with myelosuppressive agents may potentiate effects on bone marrow. Combination with cyclosporine or tacrolimus may result in excessive immunosuppression. Risk of infection following live virus vaccination which may be fatal. Potential for interaction with CYP1A2 inhibitors exists. *Pregnancy and lactation* Not recommended.

Side-effects The most common adverse drug reactions are haematological reactions (leukopenia, neutropenia, thrombocytopenia), dermatologic toxicities (allergic reactions), constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting), infection, tumour lysis syndrome, haemorrhage, anaemia, hypersensitivity, insomnia, cardiac dysfunction (such as palpitations, angina pectoris, arrhythmia), hypotension, hypertension, pulmonary dysfunction, diarrhoea, constipation, stomatitis, alopecia, skin disorders, amenorrhea, mucosal inflammation, fatigue, pyrexia, pain, chills, dehydration, anorexia, haemoglobin decrease, creatinine increase, urea increase, AST increase, ALT increase, alkaline phosphatase increase, bilirubin increase, and hypokalemia. Other side effects that could be serious are sepsis, pneumonia primary atypical, haemolysis, anaphylaxis, somnolence, aphonia, paraesthesia, peripheral sensory neuropathy, anticholinergic syndrome, ataxia, encephalitis, pericardial effusion, tachycardia, myocardial infarction, cardiac failure, acute circulatory failure, pulmonary fibrosis, GI haemorrhage, hyperhidrosis, infertility, multi-organ failure, Stevens-Johnson syndrome, toxic epidermal necrolysis and encephalitis. Please refer to the SmPC for further details of other uncommon side-effects.

Legal category POM

Package quantities and price 26 ml vials containing 25 mg bendamustine are supplied in packs of:
5 vials £347.26
20 vials £1379.04
60 ml vials containing 100 mg bendamustine are supplied in packs of:
5 vials £1379.04

Marketing Authorisation numbers
PL 14427/0026

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Adverse events should be reported. Reporting forms and information can be found at www.yellowcard.gov.uk. Adverse events should also be reported to Napp Pharmaceuticals Limited on 01223 424444.

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