EXHIBIT 2009

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Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial

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Summary

The efficacy of bendamustine *versus* chlorambucil in a phase III trial of previously untreated patients with Binet stage B/C chronic lymphocytic leukaemia (CLL) was re-evaluated after a median observation time of 54 months in May 2010. Overall survival (OS) was analysed for the first time. At follow-up, investigator-assessed complete response (CR) rate (21·0% vs 10·8%), median progression-free survival (21·2 vs 8·8 months; $P < 0·0001$; hazard ratio 2·83) and time to next treatment (31·7 vs 10·1 months; $P < 0·0001$) were improved for bendamustine over chlorambucil. OS was not different between groups for all patients or those ≤ 65 years, >65 years, responders and non-responders. However, patients with objective response or a CR experienced a significantly longer OS than non-responders or those without a CR. Significantly more patients on chlorambucil progressed to second/further lines of treatment compared with those on bendamustine (78·3% vs 63·6%; $P = 0·004$). The benefits of bendamustine over chlorambucil were achieved without reducing quality of life. In conclusion, bendamustine is significantly more effective than chlorambucil in previously untreated CLL patients, with the achievement of a CR or objective response appearing to prolong OS. Bendamustine should be considered as a preferred first-line option over chlorambucil for CLL patients ineligible for fludarabine, cyclophosphamide and rituximab.

Keywords: bendamustine, chlorambucil, chronic lymphocytic leukaemia, complete response, overall survival.

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Chronic lymphocytic leukaemia (CLL) is the most prevalent adult leukaemia in the Western hemisphere. It is predominantly a disease of the elderly with a median age at diagnosis of 72 years according to Surveillance Epidemiology and End Results (SEER) cancer statistics for 2004–2008 (NCI, 2011). Approximately 70% of individuals newly diagnosed with CLL are $\geq$65 years of age, with 42·5% being 75 years or older. Consistent with their advanced age, the majority of individuals with CLL have comorbidities. In a study of 1,195 individuals with newly diagnosed CLL, 89% had $\geq$1 comorbidity and 46% had $\geq$1 major comorbidity (Thurmes *et al*, 2008).

The combination of fludarabine with cyclophosphamide and rituximab (FCR) is the current recommended standard first-line regimen for the treatment of CLL (Eichhorst *et al*, 2010). In a phase III trial (CLL8) conducted by the German CLL Study Group (GCLLSG), FCR was associated with a significantly higher complete response (CR) rate, median progression-free survival (PFS) and overall survival (OS) rate than fludarabine plus cyclophosphamide (FC) (Hallek *et al*, 2010). However, due to its toxicity, FCR is only considered suitable for a minority of 'fit' CLL patients without significant comorbidities (Eichhorst *et al*, 2010; NCCN, 2011). In the CLL8 trial, these eligible patients were defined as having a Cumulative Illness Rating Scale (CIRS) score $\leq$ 6 (Fortin *et al*, 2005; Hallek *et al*, 2010).

Improved first-line treatment options are required for the majority of patients with CLL who are ineligible for FCR. The alkylating agent chlorambucil has traditionally been the first-line treatment of choice for elderly, comorbid or frail patients with CLL (Eichhorst *et al*, 2010). Chlorambucil demonstrated similar efficacy in terms of PFS and OS, and significantly reduced haematological toxicity by comparison with fludarabine alone in a recent phase III trial in treatment-naive CLL patients aged 65–80 years (Eichhorst *et al*, 2009). On the basis of this trial, chlorambucil has become a standard of care for patients not fit enough for fludarabine-based regimens. However, chlorambucil treatment is also associated with a low CR rate in first-line CLL – 0% in this trial *versus* 7% with fludarabine (Eichhorst *et al*, 2009). This is important because higher CR rates may be associated with prolonged PFS (and perhaps OS).

Bendamustine is a chemotherapeutic agent with structural similarities to alkylating agents and purine analogues. However, bendamustine has a distinct mechanism of action, which includes the induction of TP53-dependent apoptosis, the base excision DNA-repair pathway, and TP53/apoptosis-independent mitotic catastrophe (Leoni *et al*, 2008; Dennie & Kolesar, 2009). In addition, bendamustine is effective against lymphoma cells that are resistant to structurally similar chemotherapies like cyclophosphamide, at therapeutically relevant concentrations (Leoni *et al*, 2008).

Bendamustine has been approved by the European Medicines Agency (EMA) for the first-line treatment of patients with CLL (Binet stage B/C) for whom fludarabine combination chemotherapy is not appropriate, and is currently licensed in a number of European countries, including Germany and the UK. The approval of bendamustine was based on the results of a randomized phase III trial in comparison with chlorambucil in previously untreated patients with CLL (Binet stage B or C) (Knauf *et al*, 2009a). Bendamustine induced significantly higher objective response rates (ORR; 68% vs 31%; $P < 0{\cdot}0001$) and CR rates (31% vs 2%) than chlorambucil (Knauf *et al*, 2009a, 2010). Also, bendamustine demonstrated a significant median PFS benefit over chlorambucil (21·6 vs 8·3 months; $P < 0{\cdot}0001$) that was sustained in patients <65 or $\geq$65 years (Knauf *et al*, 2009a,b). Guidance issued by the UK's National Institute for Health and Clinical Excellence (NICE) in February 2011 recommended bendamustine for use within the National Health Service (NHS) in England and Wales (NICE, 2011). The NICE evidence review group reported that overall, the economic model was of high quality and contained no logical errors. Bendamustine had more quality-adjusted life years (QALYs) than chlorambucil (4·82 QALYs vs 3·55 QALYs). The estimated cost per QALY gained for bendamustine according to a *de novo* Markov model was estimated to be GBP 11 960 per QALY gained, but was favourably revised following the NICE appraisal and was reported to be GBP 9 400 (NICE, 2011).

Bendamustine, either alone or as combination therapy, is a recommended treatment option in European and American guidelines for CLL patients, including those eligible (<70 years and/or without significant comorbidities) and ineligible for FCR (comorbid, unfit, and/or $\geq$70 years) (Eichhorst *et al*, 2010; NCCN, 2011). Furthermore, bendamustine-based regimens are the most commonly used first-line treatments for CLL in Germany, according to results from a community centre based patient registry of lymphatic neoplasias (Wolfgang U. Knauf, unpublished observations).

The objective of this report, in fulfilment of an EMA post-licensing commitment, is to convey updated efficacy results from a randomized phase III trial of bendamustine *versus* chlorambucil in patients with previously untreated CLL (Knauf *et al*, 2009a), based on an updated 2009 analysis and a final follow-up in May 2010. We also report OS results for the first time, including comparisons in subsets of patients stratified by ORR and CR as well as evaluating the impact of treatment on quality of life (QoL).

Methods

As previously reported in the original published results of this phase III, multicentre, randomized, open-label parallel group trial, the study protocol was approved by the local ethics committees at each of the 45 participating centres in eight European countries (Knauf *et al*, 2009a). The study was also conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.

Patients

As described before, eligible patients were previously untreated, aged $\leq$ 75 years with a confirmed diagnosis of Binet stage B/C CLL, and requiring treatment (Knauf *et al*, 2009a). Eligible patients also had a World Health Organization performance status of 0–2 and a life expectancy of at least 3 months. Written and informed consent was obtained from all patients prior to study inclusion.

Study design

Treatments. The full study design details have been previously described (Knauf *et al*, 2009a). Briefly, patients were randomly assigned 1:1 to receive bendamustine or chlorambucil, and stratified by centre and Binet stage. Bendamustine (Ribosepharm, Munich, Germany) was administered intravenously over 30 min at a dose of 100 mg/m^2/day on days 1–2, every 4 weeks. Chlorambucil (GlaxoSmithKline, Uxbridge, UK) was administered orally at a dose of 0·8 mg/kg (Broca's normal weight in kg: the body weight for the dose being the height of the patient in cm minus 100) on days 1 and 15 (or as divided doses on days 1–2 and 15–16 for patient comfort in some individual cases) every 4 weeks.

Endpoints. The primary study endpoints were ORR and PFS. Secondary endpoints included OS (Knauf *et al*, 2009a).

Follow-up analyses and statistics

A follow-up analysis of this pivotal phase III trial was conducted in May 2010 on the intention-to-treat (ITT) population, which included all randomized patients. Each endpoint listed below was analysed at the 2010 follow-up. However, PFS data from an earlier updated analysis in 2009 (conducted 12 months after the originally published results) will also be reported. In contrast to the original trial results, the updated and follow-up analyses were investigator assessed and were not reviewed by a blinded independent committee for response assessment. All statistical analyses and summaries were generated using SAS version 9.2 software. *P* values $< 0{\cdot}05$ were considered statistically significant.

Progression-free survival. PFS was defined as the time from randomization until the day of progression/death. Median PFS was determined in an update 12 months after the originally published trial results in 2009 and at the 2010 follow-up. In the 2010 follow up PFS was updated for patients without progressive disease in the 2009 assessment if progression was documented at follow-up and no second-line treatment was given prior to the date of progression. Differences in median PFS between the two treatment groups were analysed by log-rank test, stratified by Binet stage B or C. Hazard ratios (HRs) for treatment differences and associated 95% confidence intervals (CIs) were adjusted for Binet stage B/C and based on a Cox regression (proportional hazard) model. Results were plotted as Kaplan–Meier curves.

Last known disease status. All response assessments were conducted in accordance with National Cancer Institute Working Group (NCIWG) criteria (Cheson *et al*, 1996). Response categories included CR, partial response (PR), PR with nodular involvement (nPR), stable disease (SD), or progressive disease (PD). The ORR was defined as the sum of the PR+nPR+CR rates. The last known status of disease after first-line therapy was compared between groups using the Cochrane-Mantel-Haenszel (CMH) test adjusting for Binet stage B/C.

Overall survival. This was calculated from the time interval from the date of randomization to death, regardless of cause, for each patient for which data were available at the 2010 follow-up. Differences in median OS between the bendamustine and chlorambucil treatment groups were compared by a log-rank test adjusted for Binet stage. HRs for treatment differences and associated 95% CIs were adjusted for Binet stage and based on a Cox regression (proportional hazard) model. Results were plotted as Kaplan–Meier curves. The median OS was compared between treatment groups in several patient subsets, including those with Binet stage B, Binet stage C disease, aged $>$ 65 years, $\leq$65 years, those with a response, and those without a response. In addition, the median OS was compared for all patients with a response (regardless of treatment) *versus* all patients without a response, and for all patients with a CR *versus* those without a CR.

Time to next treatment. The time to next treatment (TTNT) was defined as the time from the date of termination of first-line treatment until the start date of a second-line treatment. Differences in the calculated median TTNT between first-line treatment groups were analysed using an extended Mantel-Haenszel test stratified by Binet stage B/C. HRs for treatment differences and associated 95% CIs were adjusted for Binet stage B/C and based on a Cox regression (proportional hazard) model. Results were plotted as Kaplan–Meier curves.

Best response after second-line therapy. The best response after second-line therapy (CR, PR, SD or PD) was also determined. Differences between treatment groups were analysed by the Mantel-Haenszel test (for best response) and Fisher's exact test (for ORR).

Quality of life. The QoL was analysed using the EORTC questionnaires QLQ C30 and QLQ-CLL25.

Second or further lines of treatment. The types of second or further lines of treatment received by patients after first-line bendamustine or chlorambucil were recorded. Differences in the overall proportion of patients who received a second or

further line of treatment were analysed by the CMH test, adjusted for Binet stage B/C.

Results

The original results of this randomized, phase III multicentre trial in previously untreated patients with Binet stage B/C CLL who received bendamustine (n = 162) or chlorambucil (n = 157) were first published in 2009 after a median observation time of 35 months (Knauf *et al*, 2009a).

This follow-up efficacy analysis was conducted in May 2010 on the final ITT population (N = 319) after a median observation time of 54 months (range: 0–90 months). Follow-up results for the primary endpoints (PFS and ORR) are provided, and OS results for the ITT population and defined patient subgroups are reported for the first time.

Patient characteristics

In total, 247 patients (bendamustine n = 131; chlorambucil n = 116) were alive at the end of the study and follow-up documentation was available for 244 of them (bendamustine n = 129; chlorambucil n = 115). It was previously reported that the baseline demographic characteristics of the bendamustine and chlorambucil treatment groups were similar (Knauf *et al*, 2009a). The majority of patients were male (bendamustine 63%; chlorambucil 60·5%) and the mean age was 63·0 years in the bendamustine group and 63·6 years in the chlorambucil group. The majority of patients had Binet stage B CLL (bendamustine 71·6%; chlorambucil 70·7%), with the remainder having Binet stage C disease (Knauf *et al*, 2009a).

Progression-free survival

Median PFS was re-assessed by the investigators in 2009 and at the 2010 follow-up (Fig 1). According to the 2009 assessment, the median PFS was significantly longer in the bendamustine group than in the chlorambucil group (21·2 vs 8·9 months; $P < 0·0001$). The chlorambucil/bendamustine HR, adjusted for Binet stage, was 3·30 (95% CI: 2·48, 4·41). The median PFS at the 2010 follow-up was also significantly longer in the bendamustine group by comparison with the chlorambucil group (21·2 vs 8·8 months; $P < 0·0001$). The chlorambucil/bendamustine HR, adjusted for Binet stage, was 2·83 (95% CI: 2·16, 3·71).

Last known status of disease after first-line therapy

The last known status of disease after first-line therapy, including any further therapies, was assessed by the study investigators at the 2010 follow-up. It was reported for 236 of 319 patients (74%; Table I). The CR rate was 21·0% with first-line bendamustine and 10·8% with first-line chlorambucil, respectively. The PR rate was 13·6% with first-line bendamustine and 19·1% with first-line chlorambucil. Overall best response (CR,PR, SD, PD) was statistically not significant between groups.

Overall survival

A total of 132 patients had died at the time of the 2010 follow-up. However, the date of death was unknown for 26 patients (n = 15 bendamustine group; n = 11 chlorambucil group). These 26 patients were censored with the time from date of randomization until the date of the last contact upon which the patient was still documented to be alive. The median OS had not yet been reached in the bendamustine group and was 78·8 months for patients in the chlorambucil group (Table II, Fig 2). Although the chlorambucil/bendamustine HR of 1·30 (95% CI: 0·89, 1·91) slightly favoured bendamustine, there was no statistically significant difference in median OS adjusted for Binet stage between groups in this trial at this stage (P = 0·1801).

Overall survival in patients with Binet stage B or C. Median OS was similar between the two treatment groups when observing the entire treated population irrespective of Binet stage of disease. In both Binet stage subgroups of patients there was a numerical advantage for both Binet B (HR 1·28 with 95% CI: 0·80, 2·04) and Binet stage C (HR 1·35 with 95% CI: 0·68, 2·65) patients treated with Bendamustine compared to those treated with chlorambucil. There was not, however, a statistically significant difference between the bendamustine and chlorambucil groups at the 2010 follow-up (Table II, Fig 2).

Overall survival in patients aged > 65 years. There was also no statistically significant difference between the bendamustine and chlorambucil groups in terms of median OS adjusted for Binet stage for the subset of patients aged > 65 years at the 2010 follow-up (Table II, Fig 2).

Overall survival in patients aged ≤ 65 years. Similarly, there was no statistically significant difference in median OS adjusted for Binet stage between the two treatment groups for patients aged ≤ 65 years (Table II). However, according to the HR, patients aged ≤ 65 years who received bendamustine had a 1·66-times greater probability of survival compared with those who received chlorambucil.

Overall survival in patients with an objective response. Patients who achieved a response (i.e. CR or PR) with bendamustine were 1·63 times more likely to survive than those who had achieved a response with chlorambucil (Table II). There was no statistically significant difference in OS between the two treatment groups (P = 0·1642). Median OS had not been reached in either group at the time of the 2010 follow-up.

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