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Idelalisib or Placebo in Combination with Bendamustine and Rituximab in Patients with Relapsed/Refractory CLL - Interim Results of a Phase 3 Randomized, Double-blind Placebo-Controlled Trial

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Contributors

ADZ and AHA wrote the initial draft of the manuscript and ET and SS performed the genetic analyses. Employees of Gilead Sciences, Inc., contributed to the study design, implementation, and data analyses. All authors critically reviewed each draft and provided feedback and intellectual content, contributed to the data, reviewed the data analyses, and provided final approval to submit the manuscript for publication.

Declaration of Interests

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Summary

Background—Bendamustine and rituximab (BR) has been a standard of care for the management of patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL). We evaluated the efficacy and safety of adding idelalisib, a first-in-class targeted PI3Kδ inhibitor, to BR in patients with R/R CLL

Methods—This trial was a global, multicenter, double-blind, placebo -controlled trial in adult patients (≥18 years) with R/R CLL requiring treatment for their disease. Patients had to have measurable lymphadenopathy (≥1 nodal lesion ≥2.0 cm in the longest diameter and ≥1.0 cm in the longest perpendicular diameter) by computer tomography or magnetic resonance imaging, disease progression within <36 months since last prior therapy, a Karnofsky Performance Status score ≥60 and adequate bone marrow, liver and kidney function. Key exclusion criteria included histological transformation to an aggressive lymphoma (eg, Richter transformation) or disease refractory to bendamustine. Patients were randomised 1:1 using a central interactive web response system that assigned a unique treatment code for each patient, to receive intravenous BR infusions for a maximum of 6 cycles in addition to blinded study drug matching the assigned treatment of either twice-daily oral idelalisib 150 mg or placebo administered continuously until disease progression or intolerable study drug-related toxicity. Randomisation was stratified based on high-risk features (*IGHV*, del(17p)/*TP53* mutation) and refractory vs relapsed disease. The primary endpoint was progression-free survival (PFS) assessed by an independent review committee in the intent-to-treat population. Overall survival was a key secondary endpoint. Crossover was not permitted to the idelalisib arm at progression. The trial is ongoing (ClinicalTrials.gov # NCT01569295).

Findings—Between 26 June 2012 and 21 August 2014, 416 patients with R/R CLL were enrolled; 207 patients were randomised to the idelalisib and 209 to the placebo arm. After the prespecified interim analysis, the Independent Data Monitoring Committee (IDMC) recommended discontinuation and unblinding of the trial due to efficacy. Updated data are presented in this manuscript with a cutoff date of 07 October 2015. Median (95% CI) PFS was 20·8 (16·6, 26·4) and 11·1 (8·9, 11·1) months in the idelalisib and placebo arms, respectively (hazard ratio [HR], 0·33; 95% CI, 0·25, 0·44; P<0·0001) at a median (Q1, Q3) follow-up of 14 (7, 18) months. The most frequent grade 3 or greater AEs were neutropenia (124/207 [60%]) and febrile neutropenia (48/207 [23%]) in the idelalisib arm and neutropenia (99/209 [47%]) and thrombocytopenia (27/209 [13%]) in the placebo arm. Serious AEs included febrile neutropenia, pneumonia and pyrexia and were common in both treatment arms. An increased risk of infection was observed in the idelalisib vs placebo arm.

Interpretation—Idelalisib plus BR is superior to BR alone, improving PFS and OS. This regimen represents an important new treatment option for patients with R/R CLL.

Introduction

Most patients with chronic lymphocytic leukemia (CLL) will suffer disease relapse following standard frontline chemoimmunotherapy.[1] Relapse risk is increased in patients with high-risk features (eg, unmutated immunoglobulin heavy chain variable region [*IGHV*] genes, *TP53* mutation [*TP53mut*], deletions of the short arm of chromosome 17 [del(17p)]) or disease refractory to therapy.[1–4] Treatment choice at relapse is dependent on the interval since completion of last therapy, presence of high-risk features, previously administered agents, and patient fitness.[1,5] For most patients, the goals of therapy are to maximize durable disease control and relief of symptoms; however, disease control becomes increasingly difficult at relapse due to toxicities from pre-existing therapies and clonal evolution resulting in resistance to therapy.

Phosphoinositide 3-kinase (PI3K) cellular signaling pathways mediate key cellular functions including cell growth, proliferation, differentiation, motility, and survival.[6] Expression of the PI3K delta isoform (PI3Kδ) is largely restricted to leucocytes. In CLL, cellular trafficking via chemokine receptor type 4/5 and B-cell receptor responses involve PI3Kδ signaling, making it an attractive target for therapy.[6] Idelalisib, a first-in-class PI3Kδ inhibitor, is approved for use in combination with rituximab for patients with relapsed CLL who are not candidates for chemotherapy.[7,8] We hypothesized that idelalisib in combination with bendamustine and rituximab (BR) would improve efficacy as defined by progression-free survival (PFS) with tolerable toxicity in patients with relapsed/refractory (R/R) CLL.

Methods

Study design and participants

In this phase 3, randomized, multicenter, double-blind, placebo-controlled study, patients were enrolled at total of 110 sites in the following 19 countries: Australia, Belgium, Canada, Croatia, Czech Republic, France, Greece, Hungary, Ireland, Italy, New Zealand, Poland, Portugal, Romania, Russia, Spain, Turkey, United Kingdom, and United States (Appendix

page 3). The trial was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki. Institutional review boards at each study site approved the protocols. All patients provided written informed consent.

Eligible were male and female patients ≥18 years of age who had a diagnosis of CLL requiring treatment according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria,[9] measurable lymphadenopathy (≥1 nodal lesion that measures ≥2.0 cm in the longest diameter and ≥1.0 cm in the longest perpendicular diameter) by computer tomography (CT) or magnetic resonance imaging (MRI), had received prior therapy containing a purine analog or bendamustine and an anti-CD20 monoclonal antibody, experienced CLL progression less than 36 months since completion of the last prior therapy, and were fit to receive cytotoxic therapy and had Karnofsky Performance Status score of ≥60. Although not an eligibility requirement, an average life expectancy of the patients was ≥120 days.

Disease progression at inclusion was assessed by the investigator and was based on IWCLL criteria that included indications for treatment.[9] Required baseline laboratory values included serum bilirubin ≤1·5 x upper limit of normal (ULN, unless due to Gilbert's syndrome or hemolysis) and serum transaminases up to 2·5 x ULN. Grade 2 neutropenia, thrombocytopenia, or anemia were permitted only if deemed related to bone marrow involvement with CLL, documented by bone marrow biopsy. Whether patients were deemed fit to receive the BR regimen depended on the protocol eligibility requirements such as performance status, creatinine clearance ≥40 ml/min (calculated using the Cockcroft-Gault equation), and the medical judgment of the investigator with consideration for the number and severity of comorbid conditions in each patient.

Key exclusion criteria included known histological transformation to an aggressive lymphoma (eg, Richter transformation); disease refractory to bendamustine (ie, no response or progression less than six months from last dose of bendamustine); chronic active hepatitis B or C; pneumonitis; or prior therapy with inhibitors of AKT, BTK, JAK, mTOR, PI3K (including idelalisib), or SYK. All patients provided written informed consent.

Randomisation and masking

A central Interactive Web Response System (IWRS) was used to assign a unique treatment code for each patient, as well as bottle numbers and instructions for dispensing of blinded study drug matching the assigned treatment. Patients were randomized in a 1:1 ratio based on a computer-generated randomisation schedule prepared by Triangle Biostatistics (Wilmington, NC, USA) to receive either idelalisib or placebo in combination with BR. The randomisation was balanced by randomly permuted blocks with a block size of four. Patients were stratified based on the presence or absence of del(17p) and/or *TP53* mutation: either vs neither (or indeterminate), *IGHV* mutation status: unmutated or *IgHV3-21*) vs mutated (or indeterminate) and by disease status: refractory (CLL progression <6 months from completion of prior therapy) or relapsed (CLL progression ≥6 months from completion of prior therapy) disease.

Blinding was achieved through the use of a placebo that was well matched to the active drug in appearance, packaging, labeling, and schedule of administration. During the study, both patients and study personnel remained blinded to the identity of the treatment assignments, which were available only to the IWRS, the Independent Data Monitoring Committee (IDMC), and drug safety personnel. Following an interim analysis, the final study unblinding occurred upon recommendation by the IDMC.

Procedures

Study treatment consisted of twice-daily oral idelalisib 150 mg or matching placebo. In both treatment arms, bendamustine 70 mg/m^2 was administered intravenously on days 1 and 2 for six 28-day cycles. Rituximab was administered intravenously with each cycle of bendamustine at 375 mg/m^2 on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2 to 6. Bendamustine and rituximab were administered up to a maximum of 12 and six infusions, respectively. Idelalisib/placebo was administered continuously until disease progression, death, intolerable toxicity, pregnancy, substantial noncompliance with study procedures, study discontinuation, or withdrawn consent (Appendix page 6). Detailed guidelines for modifications of all study treatments can be found in our protocol online. Briefly, in case an AE was deemed related to study drug (either idelalisib/placebo), the administration of the drug was held or modified. After the AE had resolved, the study drug could be reinstituted at either the starting dose level (150 mg/dose twice daily) or at the reduced dose level (100 mg/dose twice daily).

Clinic/laboratory visits occurred every two weeks through week 24, every six weeks between weeks 24 and 48, and every 12 weeks thereafter. At each visit, safety and CLL disease status were assessed by physical and laboratory examinations. Imaging by CT or MRI was performed every 12 weeks and evaluated by the Independent Review Committee (IRC) for evidence of response or disease progression, according to IWCLL criteria.[9] At the time of discontinuation from the study, an end-of-study CT/MRI tumor assessment was performed unless the patient already had radiographic confirmation of definitive disease progression. This assessment was followed by a safety visit 30 days thereafter. Patients who permanently discontinued the study treatment for a reason other than disease progression could continue on study with regular assessments until disease progression or another anticancer or experimental therapy was initiated. Long-term follow-up for survival was conducted at approximately six-month intervals for five years. Data had been collected longitudinally for peripheral blood CD4 count, serum immunoglobulin and health-related quality of life (FACT-Leu, EuroQoL-5 Dimensions [EQ-5D]), but were not analysed at the time of this publication. The data for del 11q had also been collected but have not yet been fully collated and analysed.

Overall safety profile of each treatment was characterized by the type, frequency, severity, timing of onset, duration, and relationship to study therapy of any adverse events (AEs) or abnormalities of laboratory tests. Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0. The severity of AEs was graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

An independent central lab (Ulm University, Ulm, Germany) analysed baseline samples for the presence of del(17p) and mutations in *TP53* exons 4–10 and *IGHV* somatic mutations using previously reported techniques.[11] *IGHV* was considered unmutated if homology to corresponding germline gene was at least 98%. Loss of 17p was determined by fluorescence in situ hybridization according to standard procedures.[11]

Outcomes

The primary endpoint was PFS, defined as the interval from randomisation to the earlier of the first documentation of definitive disease progression confirmed by the IRC or death from any cause. Definitive disease progression of CLL was based on standard IWCLL criteria, other than lymphocytosis alone.[9,10] Secondary efficacy endpoints included confirmed overall response rate (ORR, the proportion of patients who achieved a complete response [CR], complete response with incomplete marrow recovery [CRi] or partial response [PR]; a confirmed response should be maintained for at least 12 weeks), lymph node response rate (the proportion of patients who achieved a ≥50% decrease from baseline in the sum of the products of the greatest perpendicular diameters [SPD] of index lesions), overall survival (OS, the interval from randomisation to death from any cause), and complete response rate (the proportion of patients who achieved a CR). Responses were categorized by the IRC as CR, CRi, PR, stable disease (SD), progressive disease (PD), or not evaluable (NE).

Statistical analysis

With a hazard ratio (HR) equal to 1 under the null hypothesis and an HR of 0·67 under the alternative hypothesis of superiority of the idelalisib treatment, 260 events of definitive CLL progressions or deaths were required to achieve a power of 0·90 based on a stratified log-rank test with a two-sided significance level of 0·05. To compensate for lost to follow-up, a sample size of approximately 195 patients/treatment arm was estimated.

A prespecified interim analysis was performed after approximately 75% of the 260 expected PFS events had occurred, with a significance level of 0·001 for the primary endpoint. To preserve the overall type I error rate across the primary and secondary endpoints, a sequential testing procedure was applied. Secondary endpoints were tested at a two-sided 0·032 significance level.[12] Incidence of treatment-emergent AEs and laboratory abnormalities was summarized with descriptive statistics.

For the primary efficacy analysis, the difference in PFS between treatment arms was assessed using Kaplan-Meier methods and the stratified log-rank test. Patients were considered not assessable for the following reasons: absence of measurable disease at baseline, required response evaluation was not performed or the patient was lost to follow up. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were calculated using a Cox proportional hazards regression model. We carried out a sensitivity analysis in which surviving, non-progressing patients who were lost to follow-up due to AEs were categorized as having an event at the time of the last known CLL tumor status assessment. Categorical variables were compared using the Cochran-Mantel-Haenszel test adjusted for stratification factors.

Efficacy analyses were performed in the intent-to-treat population including all randomised patients. All randomised patients who received at least one dose of study drug were included in the safety analyses. All statistical data were generated using SAS version 9.2 software. This trial is registered with ClinicalTrials.gov, number NCT 01569295.

Role of the funding source

The trial was designed by the sponsor, Gilead Sciences, Inc. Employees of Gilead Sciences, Inc., contributed to the study design, implementation, and data analyses. ADZ and AHA drafted the manuscript. All authors had full access to the data, critically reviewed each draft of the manuscript including the data analyses, agreed to be accountable for the accuracy and integrity of the data and analyses, and provided final approval to submit the manuscript for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between 26 June 2012 and 21 August 2014, 416 patients with R/R CLL were enrolled; 207 patients were randomized to the idelalisib and 209 to the placebo arm. A prespecified interim efficacy analysis was performed using a data cutoff date of 15 June 2015, at which time 196/260 (75%) of PFS events had occurred. Based on the results of this analysis, the IDMC recommended halting and unblinding the study. Of 416 patients enrolled, 13 (3%, ten patients in the placebo arm) were unblinded before reaching the primary endpoint of the study, and prior to the recommendation of the IDMC to halt and unblind the study. Of the 15 patients who discontinued the study due to an AE and entered long-term follow-up for survival, ten were in the idelalisib arm. Of the 24 patients who discontinued the study due to an AE and were lost to follow-up, 15 were in the idelalisib arm. In the idelalisib vs placebo arms median (95% CI) OS was 16 (8, NR) vs 7 (5, 15) months in patients who discontinued due to an AE and was not reached (NR) (24, NR) vs 32 (21, NR) months in patients who discontinued due to PD.

Updated data are presented in this manuscript with a cutoff date of 07 October 2015. At this date, 141/416 (33·9%) patients were still on study, 95/207 (45·9%) in the idelalisib group and 46/209 (22·0%) in the placebo group (Fig. 1). The primary study endpoint of PD or death had been met by 42/207 (20%) and 16/207 (8%) of patients, respectively in the idelalisib group, and 107/209 (51%) and 13/209 (6%) of patients, respectively, in the placebo group. In total 97 patients (54 in the idelalisib group and 43 in the placebo group) discontinued from the study due to other reasons (most common reasons included AEs, physician’s decision and withdrawal of consent; Fig. 1). Time since diagnosis and median number of prior regimens (two) were similar in the treatment arms (Table 1). A majority of patients had high-risk disease and most had received a fludarabine-containing regimen (idelalisib/placebo arm: 192/207 (92·8%)/189/209 (90·4%), respectively).

The median (Q1, Q3) follow-up duration for PFS was 14 (7, 18) months. Overall, the median (95% CI) PFS in the idelalisib arm was 20·8 (16·6, 26·4) months vs 11·1 (8·9, 11·1) months for the placebo arm (HR, 0·33; 95% CI, 0·25, 0·44; P<0·0001; Fig. 2A). The benefit in PFS was seen consistently across all risk groups (Fig. 2B). For patients with neither

del(17p) nor TP53mut, median PFS (95% CI) for idelalisib was 24·6 (19·5, 30·3) months vs 11·2 (11·1, 13·6) months for placebo (HR, 0·27; 95% CI, 0·18, 0·39; P<0·0001) (Fig. 3A). For patients with del(17p)/*TP53*mut CLL, the median PFS (95% CI) for idelalisib was 11·3 (8·8, 16·6) months vs 8·3 (5·9, 8·5) months for placebo (HR, 0·47; 95% CI, 0·31, 0·72; P<0·0001) (Fig 3B).

The ORR of the 78 patients with del(17p) on the study is presented in Table 2. The ORR in the idelalisib arm was 22/38 (58%) vs 9/40 (23%) in the placebo arm. Furthermore, 10/40 (25%) of patients in the placebo arm had PD as the best overall response, compared with one patient in the idelalisib arm 1/38 (3%). Median OS (95% CI) in the idelalisib arm was NR (12·2, NR) and was 20·3 (12·1, 31·6) months in the placebo arm.

The outcomes of patients with the adverse risk category of unmutated *IGHV* were superior in the idelalisib compared with the placebo arm (ORR of 122/173 [71%] vs 74/173 [43%]; the difference between arms was less apparent in patients with mutated *IGHV* Table 2). Median PFS (95% CI) for patients with unmutated *IGHV* was 19·5 (16·1, 24·6) months vs 10·9 (8·6, 11·1) months in the idelalisib vs placebo arms, and median OS was NR (26·8, NR) months vs 31·6 (22·2, NR) months. For patients with mutated *IGHV,* the median PFS (95% CI) was 26·4 (19·3, NR) months vs 13.7 (8·3, 18·5) months and median OS (95% CI) was NR (NR, NR) vs NR (15·2, NR) in the idelalisib and placebo arms, respectively.

In the ITT population, there was a statistically significant improvement in OS, after the prespecified multiplicity adjustment, in the idelalisib vs placebo arm (HR, 0·62; 95% CI, 0·42, 0·92; P = 0·031 [stratified]) (Fig. 2C). Overall survival in prespecified subgroups is presented in Fig. 2D.

The median change from baseline in the sum of the products of the perpendicular diameters (SPD) of measured lymph nodes (Q1, Q3) was 82·6% (−89·0, −73·7) in the idelalisib arm and 59·8% (−76·8, −34·0) in the placebo arm. The lymph node response rate (95% CI), the percentage of patients who achieved at least a 50% decrease from baseline in the SPD of index lymph nodes, was 96·9% (93·3, 98·8) in the idelalisib arm and 60·9% (53·7, 67·8) in the placebo arm (odds ratio, 28·7; 95% CI, 10·5, 78·7; P<0·0001; Fig. 4). Overall response rate was significantly improved in the idelalisib vs placebo arm: 145/207 (70·0%) vs 94/209 (45·0%) (P<0·0001; Table 3). The majority of responses were PRs: 142/207 (69%) vs 93/209 (45%) in the idelalisib and placebo arms, respectively (Table 3).

Complete responses were observed in 3/207 (1·4%) and 0 patients in the idelalisib and placebo arms, respectively. This may be due to the stringent requirement for both an aspirate and a biopsy to confirm CR (an additional 22 patients in the idelalisib arm and eight patients in the placebo arm met criteria for CR but did not have a bone marrow to confirm the response). These patients were deemed to have achieved PR.

The median number of cycles of BR in both arms was six; however, median (Q1, Q3) duration of exposure to idelalisib (14·8 [5·9, 18·9) months was longer vs placebo (11·1 [5·8, 15·3]) months (Table 1). Median duration (Q1, Q2) of observation from completion of 6 cycles of BR therapy to unblinding was 73 (58, 97) weeks in the idelalisib arm and 68 (56, 97) weeks in the placebo arm. The number of patients with an AE leading to dose

interruption in the idelalisib and placebo groups was 120/207 (58·0%) and 50/209 (23·9%), respectively, and the number of patients with an AE leading to dose reductions was 26/207 (12·6%) and 13/209 (6·2%), respectively. As of the data cutoff for this report, more patients continue on idelalisib vs placebo (90/207 [44%] vs 45/209 [22%], Figure 1). Reasons for treatment discontinuation are listed in Table 1. Overall, 87 patients had an AE leading to treatment discontinuation: 58/207 (28·0%) in the idelalisib arm and 29/209 (13·9%) in the placebo arm; in the idelalisib and placebo arms, the most common were pneumonia (8/207 [3·9%] vs 4/209 [1·9%]), diarrhea (5/207 [2·4%] vs 0), and pyrexia (4/207 [1·9%] vs 1/209 [0·5%]), respectively. Overall 146/207 (71) patients in the idelalisib arm and 118/209 (56%) patients in the placebo arm received growth factors during treatment. Treatment discontinuations for reasons other than disease progression or death appear higher in the idelalisib vs placebo arm (83/207 [40·1%] vs 64/209 [30·6%]), but on division by the duration of exposure, they are similar. Treatment discontinuation due to physician decision was 7/207 (3·4%) vs 24/209 (11·5%), respectively, favoring idelalisib.

The most common all-grade AEs were neutropenia and pyrexia in the idelalisib arm and neutropenia and nausea in the placebo arm (Table 4). The most frequent grade 3 or greater AEs were neutropenia (124/207 [60%]) and febrile neutropenia (48/207 [23%]) in the idelalisib arm and neutropenia (99/209 [47%]) and thrombocytopenia (27/209 [13%]) in the placebo arm (Table 4). All AEs and laboratory abnormalities grade 3 or higher are detailed in the Appendix on pages 7–11. The incidence of infections was higher in the idelalisib group, and most infections were bacterial (data not shown). All grade/grade ≥3 infections and infestations, respectively, occurred in 143/207 (69%)/80/207 (39%) of patients in the idelalisib arm and in 124/209 (59%)/52/209 (25%) of patients in the placebo arm. The frequency of AEs was not substantially different during and after completion of BR (Appendix page 12). Grade 3 or greater diarrhea was 19/207 (9·2%) with idelalisib vs 4/209 (1·9%) with placebo. Elevations in alanine aminotransferase and aspartate aminotransferase, all grade or grade 3 or greater, were more frequent in the idelalisib arm (Table 4). Serious AEs were observed in 140/207 (68%) vs 92/209 (44%) of patients in the idelalisib and placebo arms, respectively (Table 5).

Overall, 43/207 (21%) and 59/209 (28%) patients died in the idelalisib and placebo treatment arms, respectively (Appendix page 13). Treatment-emergent AEs leading to death occurred in 23/207 (11·1%) patients in the idelalisib arm and 15/209 (7·2%) in the placebo arm. Causes of death in the idelalisib arm occurring in more than one patient included pneumonia (three patients), sepsis (three patients), and septic shock (two patients). In the placebo arm, the most common causes were reported as pneumonia (four patients) and acute myocardial infarction (two patients). Adverse events leading to death, deemed by the investigator to be related to idelalisib/placebo, included herpes zoster, sepsis, bacterial and cytomegaloviral pneumonia, pulmonary mycosis and liver disorder (Table 6). Overall there was no substantial differences in the frequency of AEs leading to death observed during or after completion of BR (Appendix page 15). However, infectious AEs leading to death were high in the idelalisib arm (n=6) versus placebo (n=3). Opportunistic infections with *Pneumocystis jirovecii* (PJP) and cytomegalovirus (CMV) occurred in 4/207 (2%) and 13/207 (6%) of patients in the idelalisib arm vs 0 and 3/209 (1%) of patients in the placebo arm. Exposure analysis revealed that during the period from 0–≤6 months, >6–≤12 months

and >12 months the number of patients at risk for PJP infection was 1/207 (0·5%), 2/165 (1·2%) and 1/130 (0·8%) for the idelalisib arm vs 0 for the placebo arm. Overall 126/207 (61%) and 148/209 (71%) of patients received PJP prophylaxis (most commonly with trimethoprim-sulfamethoxazole) on the idelalisib and placebo arms respectively. One patient (on the idelalisib arm) developed PJP infection while on prophylaxis. During 0–≤6 months, >6–≤12 months and >12 months, the numbers of patients at risk for CMV infection were 9/207 (4·3%), 3/165 (1·8%) and 1/130 (0·8%) in the idelalisib arm and 2/209 (1·0%), 1/163 (0·6%) and 0 in the placebo arm.

Discussion

This phase 3 study met its primary endpoint of improved PFS. All prespecified secondary endpoints were met, including, importantly, an improvement in OS, and were consistent across prespecified patient subgroups. The results of this study add to the body of evidence demonstrating that idelalisib produces clinically meaningful outcomes in R/R CLL, as monotherapy or in combination with other agents.[13–15]

No imbalances in key baseline characteristics, such as age, sex, and median number of prior therapies, that may have confounded our results were observed in the two treatment arms. However, there were more patients with a greater tumor burden, reflected in the population of patients with Rai stages 3/4, receiving idelalisib. The median number of cycles of BR was similar in the two treatment arms, indicating that the addition of idelalisib did not negatively affect the delivery of BR and that the regimen was tolerable.

The PFS curves diverge as early as the first imaging timepoint (12 weeks), and, at each scheduled subsequent timepoint, more patients experienced disease progression on placebo vs idelalisib. These observations also hold true for OS, perhaps suggesting synergy with chemotherapy rather than an additive effect.

Patients with del(17p) were eligible for this study as there were no approved and effective therapeutic alternatives to BR at the time of the development of this trial. A prespecified analysis of patient subgroups favored the idelalisib arm, including patients with high-risk features. In patients with·del(17p), the PFS HR point estimate was 0·62 (95%CI 0·37, 1·04), although the upper limit of the CI crossed 1, which may be due to the small number of patients. Although comparisons of the clinical outcomes of patients with del(17p) on this study with those of other agents such as ibrutinib and venetoclax that have demonstrated improved clinical outcomes in patients with R/R CLL are tempting, drawing valid conclusions can be misleading due to the following confounding from co-therapy administered on this trial (including its toxicity profile), number of lines of prior therapies received, and the performance status of patients enrolled on these studies.

Patients with neither del(17p) nor *TP53* mutation derived the most benefit with respect to a reduction in the risk of a progression-defining event (HR = 0.27; 95% CI 0·18, 0·39; P≤0.0001)). This is comparable to the PFS reported in the HELIOS trial (which excluded patients with del(17p)), a similar study evaluating the efficacy and safety of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed CLL.[16] The median PFS (11

months) in the control arm on this study is comparable to that seen in the HELIOS trial control arm (13 months).

Patients randomized to the idelalisib arm achieved higher ORRs 145/207 (70·0%) vs the placebo arm 94/209 (45·0%), representing an absolute difference of 25% in favor of the idelalisib arm, which demonstrates the contribution of idelalisib to improving ORR in this patient population (Table 3). With the newly approved kinase inhibitor agents used to treat CLL, including idelalisib and ibrutinib, it is unclear if CR (including CRi) correlates as strongly with PFS and OS as it does for chemoimmunotherapy. These data are still in evolution, but this study and others suggest substantial benefit despite a low rate of CR.[16,17] Potential drawbacks of this study are that an assessment of minimal residual disease was not performed and bias due to patient unblinding prior to halting of the study, which might have negatively affected the assessment of PD in the placebo arm (of 13 patients who were unblinded, 10 were in the placebo arm). The small numbers of patients impacted by unblinding is unlikely to impact the outcome of the study. Although, 39/416 patients (9%) discontinued the study due to an AE (25 patients on the idelalisib arm), these discontinuations did not have a meaningful impact on the primary endpoint of PFS. Based on a sensitivity analysis that counted discontinuations as events, median PFS (95% CI was 19 (15, 25) and 11 (9, 11); HR 0·4 (95% CI 0·3, 0·5) P value <0.0001 (Appendix page 16).

The DOR was prolonged in patients in the idelalisib arm (22·8 vs 11·2 months) (Table 3). During the period after completion of BR to unblinding a higher proportion of patients in the placebo arm experienced a progression event, thus supporting the ongoing impact of idelalisib administered as maintenance therapy in reducing the risk of progression or death. At the time of this analysis, median OS was not reached in the idelalisib arm. Fewer patients died in the idelalisib vs placebo arm (43 vs 59). The magnitude of the survival benefit with idelalisib increased over time, suggesting that maintenance with idelalisib may be a superior strategy compared with treatment at the time of the next progression.

While the regimen was tolerable, there was an increased risk of infection (primarily bacterial infections such as pneumonia and upper respiratory tract infections, infection, which are common in patients with CLL), perhaps due to the longer duration of exposure in the idelalisib arm. Compared with placebo, more SAEs of pneumonia/sepsis, febrile neutropenia, neutropenia, diarrhea, pyrexia, and pneumonitis were reported in the idelalisib arm. After completion of 6 cycles of BR there were 9 deaths (unadjusted for exposure) on the trial (6 on the idelalisib arm) using the system organ class “infections and infestations.” The increased number of deaths was likely due to a longer median exposure on the idelalisib arm (Appendix page 15).

Prophylaxis for PJP was recommended but not mandatory, nor was monitoring for CMV. After the completion of this study, new safety data have emerged demonstrating an increased incidence of opportunistic infection and death in three ongoing randomized phase 3 studies in which idelalisib is administered in combination with BR in frontline CLL and relapsed indolent non-Hodgkin’s lymphoma (iNHL) and in combination with rituximab in relapsed iNHL. These findings have led to a mandatory PJP prophylaxis and monitoring of CMV infection during treatment with idelalisib.

The incidence of grade 3 or higher diarrhea (9.2%) was lower than previously reported (approximately 14%) when administered as a single agent or with anti-CD20 antibody.[18] The reason for this is unclear but may be related to the administration of bendamustine, which could be hypothesized to reduce inflammatory cells (FOXP3+ /TReg) in the gut.[19] It is unknown why this did not translate to a lower incidence of grade 3 or worse transaminase elevation in patients in the idelalisib arm.

This study does not address the question of whether bendamustine adds substantially to the backbone of idelalisib and rituximab or even idelalisib alone. In the study of rituximab and idelalisib compared with rituximab alone for patients not suitable for chemotherapy,[13] the median PFS of the idelalisib arm was 19·4 months.[20] In the current study in patients fit for chemotherapy, the median PFS was 20·8 months. While cross-study comparisons are not scientifically valid, it is tempting to speculate whether bendamustine adds significantly to the PFS achieved with idelalisib and rituximab alone. Further long-term follow-up may provide answers to the risk of Richter syndrome and myelodysplastic syndrome (in particular with the administration of bendamustine) in the study population. However, at the time of this data analysis, among 11 patients who had transformation of CLL (Richter syndrome), seven patients were in the placebo arm. One patient on study (idelalisib arm) was diagnosed with myelodysplastic syndrome.

In the HELIOS trial, the addition of ibrutinib also significantly improved PFS when added to BR but did not improve OS.[16] In the single-agent trials of ibrutinib,[21,22] PFS is also similar to that seen in the ibrutinib plus BR arm of the HELIOS trial, again raising the question of how much is added by the chemotherapy component.[16] However, the question of whether bendamustine adds anything in combination with a kinase inhibitor can only be addressed definitively in a randomized study designed to address this question.

In conclusion, idelalisib in combination with the standard-of-care regimen of BR is superior to BR alone, reducing the risk of both disease progression and death and OS. These results were consistent across patients with high-risk features. The safety profile confirmed an increased risk of infection and added to the experience of how best to manage and mitigate this risk while maximizing the therapeutic benefit of idelalisib. This trial provides further evidence for improved outcomes for idelalisib-based therapy in patients with R/R CLL. This regimen represents an important new treatment option for the management of R/R CLL, further establishing the role of idelalisib in this setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. National Comprehensive Cancer Network. [Accessed 2016 Jan 20] NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas. Version 1. 2016. Available at: http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf
2. Grever MR, Lucas DM, Dewald GW, et al. Comprehensive assessment of genetic and molecular features predicting outcome in patients with chronic lymphocytic leukemia: results from the US Intergroup Phase III Trial E2997. J Clin Oncol. 2007; 25:799–804. [PubMed: 17283363]
3. Zenz T, Eichhorst B, Busch R, et al. TP53 mutation and survival in chronic lymphocytic leukemia. J Clin Oncol. 2010; 28:4473–9. [PubMed: 20697090]
4. Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000; 343:1910–6. [PubMed: 11136261]
5. Hallek M. Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment. Am J Hematol. 2015; 90:446–60. [PubMed: 25908509]
6. Blunt MD, Steele AJ. Pharmacological targeting of PI3K isoforms as a therapeutic strategy in chronic lymphocytic leukaemia. Leuk Res Rep. 2015; 4:60–3. [PubMed: 26500849]
7. Full prescribing information. Foster City, CA: Gilead Sciences, Inc; 2014. ZYDELIG® (idelalisib) tablets for oral use. Available at: http://www.zydelig.com/include/media/pdf/full-prescribing-information.pdf [Accessed 2016 Feb 2]
8. European Medicines Agency. ZYDELIG. Summary of Product Characterisations. 2015. Cited 2016 Feb 2. Available at:http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003843/WC500175377.pdf
9. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. Blood. 2008; 111:5446–56. [PubMed: 18216293]
10. Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol. 2012; 30:2820–2. [PubMed: 22778323]
11. Stilgenbauer S, Schnaiter A, Paschka P, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood. 2014; 123:3247–54. [PubMed: 24652989]
12. Li, X., Wulfsohn, M., Koch, G. Statistical Considerations on Secondary Endpoints after Trial is Stopped at an Interim Analysis. Invited presentation at FDA/Industry Statistics Workshop; 2014; Washington, DC.
13. Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014; 370:997–1007. [PubMed: 24450857]
14. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110delta, for relapsed/refractory chronic lymphocytic leukemia. Blood. 2014; 123:3390–7. [PubMed: 24615777]
15. Zelenetz AD, Lamanna N, Kipps TJ, et al. A Phase 2 Study of Idelalisib Monotherapy in Previously Untreated Patients ≥65 Years with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL). Blood. 2014; 124:1986. (abstract).
16. Chanan-Khan A, Cramer P, Demirkan F, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet Oncol. 2016; 17:200–11. [PubMed: 26655421]
17. Stilgenbauer S, Eichhorst BF, Schetelig J, et al. Venetoclax (ABT-199/GDC-0199) Monotherapy Induces Deep Remissions, Including Complete Remission and Undetectable MRD, in Ultra-High Risk Relapsed/Refractory Chronic Lymphocytic Leukemia with 17p Deletion: Results of the Pivotal International Phase 2 Study. Blood. 2015; 126:LBA–6.

18. Coutre SE, Barrientos JC, Brown JR, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion. Leuk Lymphoma. 2015; 56:2779–86. [PubMed: 25726955]

19. Balfour JA, Goa KL. Bendamustine. Drugs. 2001; 61:631–8. Discussion 9–40. [PubMed: 11368287]

20. Sharman JP, Coutre SE, Furman RR, et al. Second Interim Analysis of a Phase 3 Study of Idelalisib (ZYDELIG®) Plus Rituximab (R) for Relapsed Chronic Lymphocytic Leukemia (CLL): Efficacy Analysis in Patient Subpopulations with Del(17p) and Other Adverse Prognostic Factors. Blood. 2014; 124 Abstract 330.

21. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia. N Engl J Med. 2015; 373:2425–37. [PubMed: 26639149]

22. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014; 371:213–23. [PubMed: 24881631]

Research in context

Evidence before this study

New therapies are needed that improve on clinically relevant outcomes in CLL, such as overall survival (OS) and progression-free survival (PFS), for which an unmet medical need exists for the treatment of patients that relapse following standard therapy.

Prior to initiating this study in 2012, we performed a PubMed search for the time period between 1 January, 2002 and 1 January, 2012 using the following search terms: “relapsed CLL, refractory CLL, bendamustine, chemoimmunotherapy, rituximab, phosphoinositide 3-kinase (PI3K) δ isoform (PI3Kδ), CAL-101 and idelalisib,” either singly or as part of combination, but with one of the terms being relapsed CLL or refractory CLL. We were unable to document any placebo-controlled randomized phase 3 clinical trial incorporating a PI3K δ inhibitor as part of the management of this disease. At the time of initiation of this study, the established treatment landscape for relapsed/refractory (R/R) CLL, based on several phase 1/2 studies and one phase 3 study, was the use of alkylating agents such as chlorambucil and bendamustine, as well as anti-CD-20 monoclonal antibodies (rituximab, ofatumumab). A single-arm phase 2 clinical study by Fischer (NCT00274989) demonstrated that the combination of bendamustine with rituximab is effective and safe and has notable activity in fludarabine-refractory disease. Idelalisib (CAL-101), a potent inhibitor of PI3Kδ, had been shown to inhibit B-cell receptor signaling and survival signals in CLL cells in vitro. Subsequent phase 1 studies established tolerability, clinical activity, and pharmacokinetics of idelalisib as a single agent and in combination with bendamustine or an anti-CD-20 antibody in patients with R/R CLL. Therefore, based on these promising data and an unmet medical need for more effective therapies, we initiated this randomized, phase 3, placebo-controlled study to evaluate the safety and efficacy of idelalisib in combination with bendamustine and rituximab (BR) compared to BR alone in the R/R CLL population fit enough to receive the BR backbone. There were no other published placebo-controlled, randomized, phase 3 clinical trials incorporating a PI3Kδ inhibitor with chemoimmunotherapy as part of the management of R/R CLL.

In the last year, a phase 3 clinical study published in Lancet Oncology of the targeted agent ibrutinib, which inhibits B-cell signaling via Bruton’s tyrosine kinase, demonstrated an improvement in PFS when administered in combination with BR compared with BR alone. Currently, there are several ongoing phase 3 clinical studies in CLL evaluating other targeted agents in the same class as idelalisib or ibrutinib in earlier or later lines of therapy. The results of these studies are awaited.

Added value of this study

This randomized, placebo-controlled, phase 3 study is, to our knowledge, the first to demonstrate conclusively that the addition of a small molecule targeted agent idelalisib to a standard-of-care regimen of BR leads to an improvement in OS and PFS. In so doing, it has advanced our knowledge of the field of oncology and contributed to optimizing therapy in patients with R/R CLL. Additionally, this study has added to the body of evidence that, while chemoimmunotherapy with BR has a role in the management of

patients with R/R CLL, adding idelalisib to this standard regimen should be considered when maximizing the clinically relevant endpoints of PFS, OS, and duration of response (DOR) is the goal of therapy.

Implications of all the available evidence

In this patient population, BR alone should no longer be considered the optimal therapeutic approach, since the addition of idelalisib improved PFS and OS. While the combination of idelalisib with BR is tolerable and has the benefits of reducing the risk of death and improving OS, the toxicity of this combination is not trivial. The addition of idelalisib increased the risk of infection (including opportunistic infections caused by Pneumocystis jirovecii pneumonia [PJP] and cytomegalovirus [CMV]). Therefore, PJP prophylaxis and routine CMV monitoring should be instituted with this combination. To reduce the risk of an adverse outcome, benefit/risk assessment by clinicians should be individualized for each patient for whom this regimen is being considered, such as the risk of infection, time since prior BR therapy, co-morbidities such as preexisting colitis, pneumonitis or hepatic disease and presence of adverse genetic aberrations such as del (17p) and/or TP53. In summary, the combination of idelalisib with BR is an important new therapeutic option for patients with R/R CLL.

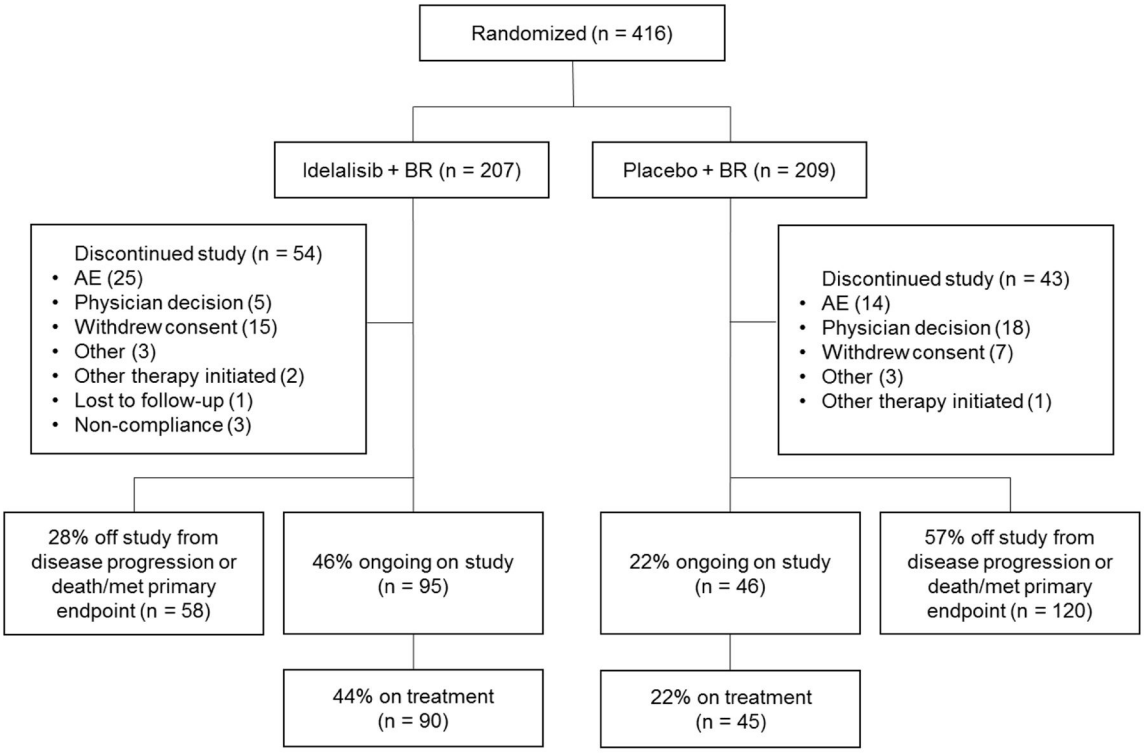
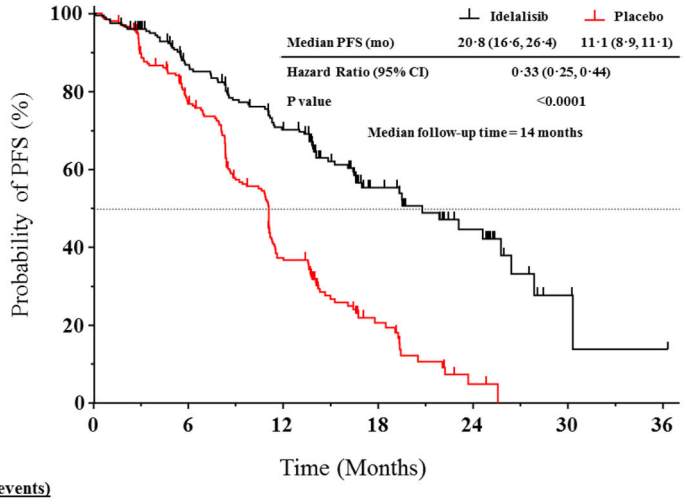


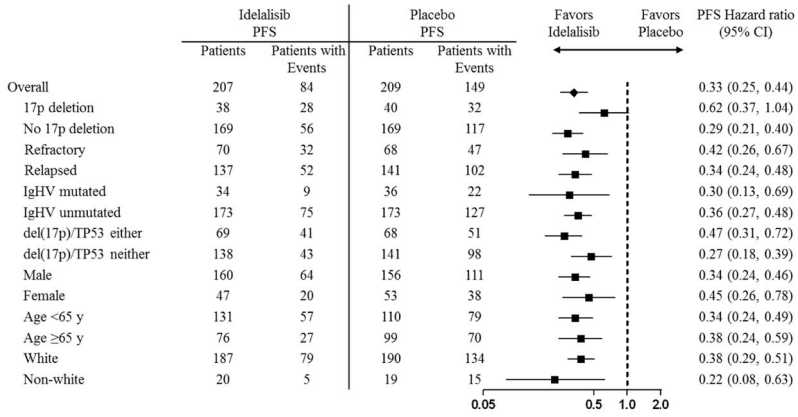
Figure 1.
Study disposition. AE, adverse event; BR, bendamustine and rituximab.

(A)



N at risk (events)							
Idelalisib + BR	207 (0)	156 (25)	118 (54)	40 (73)	18 (79)	3 (83)	1 (84)
Placebo + BR	209 (0)	146 (46)	63 (118)	16 (138)	2 (148)	0 (149)	0 (149)
N patients censored							
Idelalisib + BR	0	26	35	94	110	121	122
Placebo + BR	0	17	28	55	59	60	60

(B)



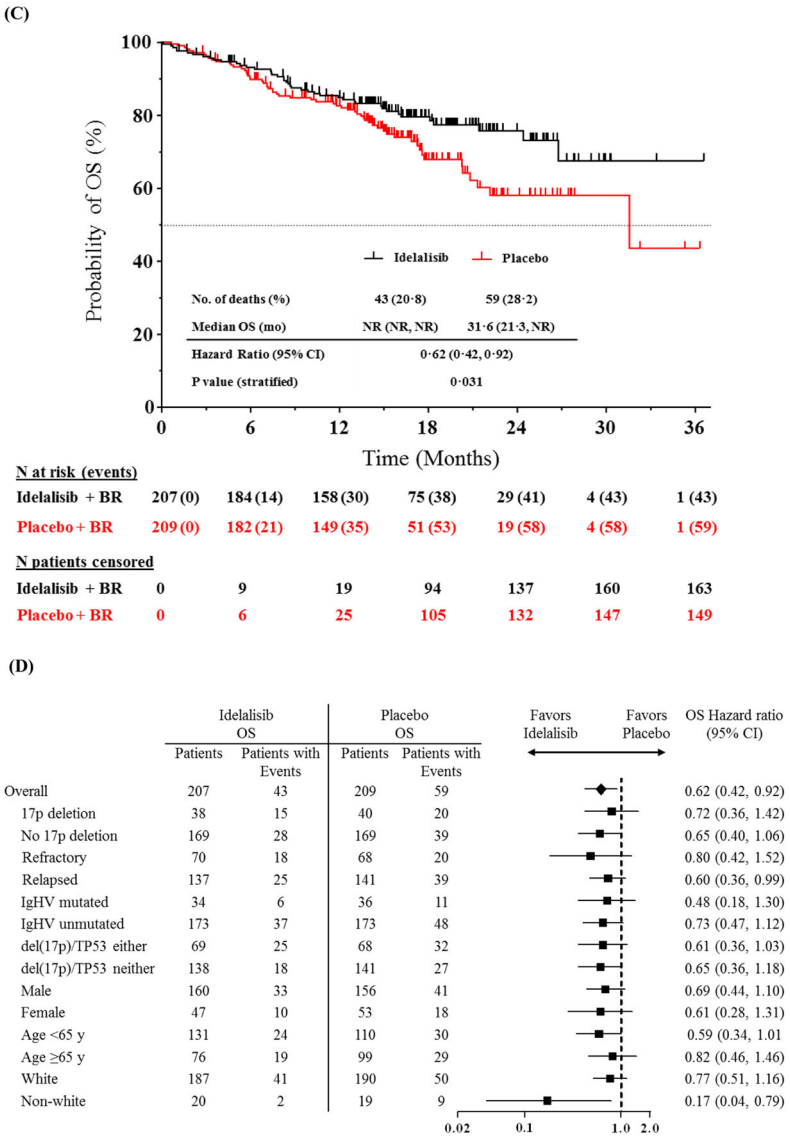


Figure 2.

Progression-free and overall survival. (A) PFS at a median follow-up of 12 months. (B) Forest plot of hazard ratios for PFS by prespecified subgroups. (C) OS. (D) Forest plot of hazard ratios for OS by prespecified subgroups. An Independent Review Committee adjudicated disease progression. BR, bendamustine and rituximab; CI, confidence interval; NR, not reached; OS, overall survival; PFS, progression-free survival.

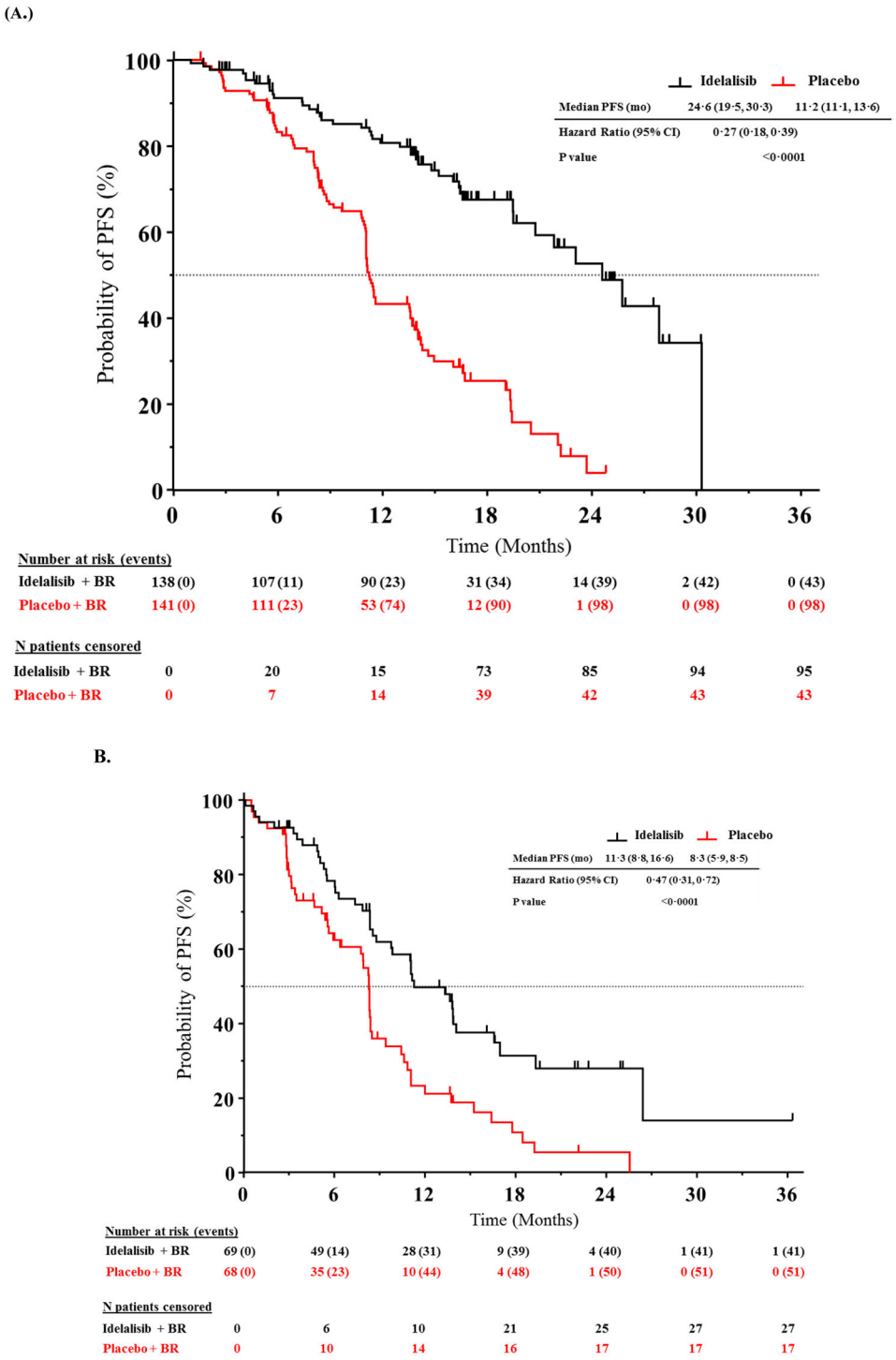


Figure 3.

Kaplan-Meier curves of PFS for patients with (A) neither del(17p) or *TP53* (B) either del(17p) nor *TP53* mutations BR, bendamustine and rituximab; CI, confidence interval; PFS, progression-free survival.

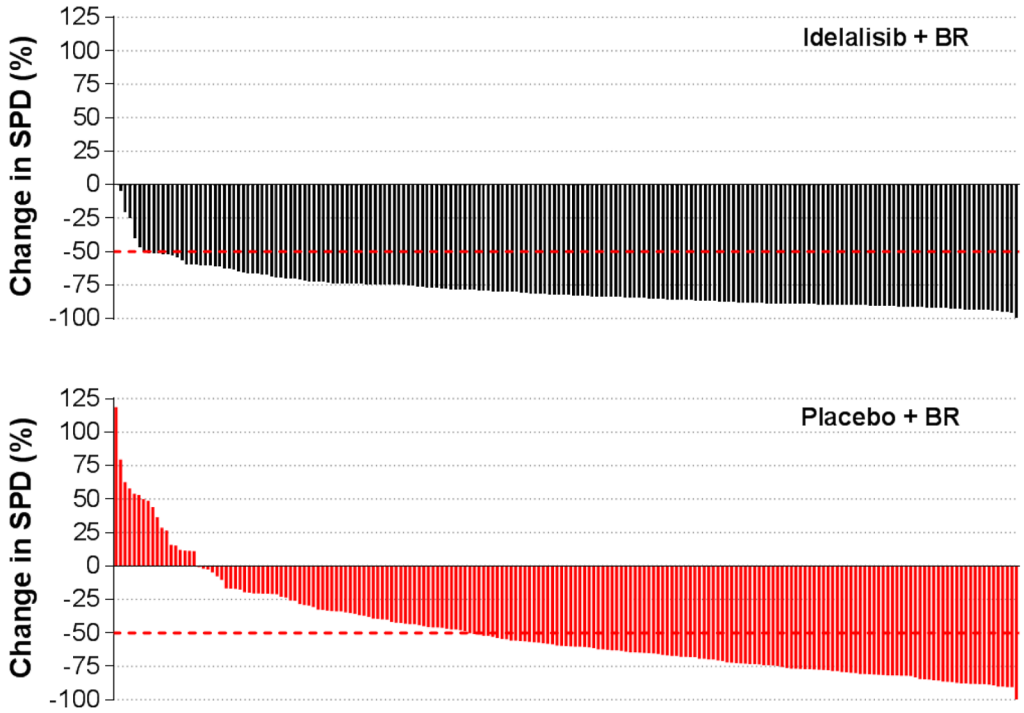


Figure 4.

Nodal response to treatment by patient. Response assessed by computed tomography scan according to standard criteria and adjudicated by an Independent Review Committee. BR, bendamustine and rituximab; SPD, sum of the products of the perpendicular diameters of measured lymph nodes.

Table 1

Patient baseline characteristics and disposition

	Idelalisib plus bendamustine and rituximab (N = 207)	Placebo plus bendamustine and rituximab (N = 209)	All Patients (N = 416)
Age, median (Q1, Q3), years	62 (56, 69)	64 (56, 70)	63 (56, 70)
Gender, male, n (%)	160 (77)	156 (75)	316 (76)
Time since diagnosis, median (Q1, Q3), months	74 (46, 120)	75 (50, 111)	75 (47, 113)
Rai stage at screening, n (%)			
I	40 (19)	41 (20)	81 (20)
II	61 (30)	71 (34)	132 (32)
III	20 (10)	16 (8)	36 (9)
IV	82 (40)	69 (33)	151 (37)
Number of prior regimens, median (Q1, Q3)	2 (1, 4)	2 (1, 4)	2 (1, 4)
Patients refractory to fludarabine, n (%)	34 (16)	37 (18)	71 (17)
Did not receive anti-CD20 antibody, n (%)	2 (1)	1 (<1)	3 (0·71)
Prior regimens, n (%)			
Fludarabine-containing regimen	192 (93)	189 (90)	381 (92)
FCR	140 (68)	138 (66)	278 (67)
FC	50 (24)	43 (21)	93(22)
Chlorambucil	38 (18)	37 (18)	75 (18)
Bendamustine-containing regimen	37 (18)	22 (11)	59 (14)
BR	30 (15)	17 (8)	47 (11)
Bendamustine alone	1 (<1)	2 (1)	3 (<1)
Disease status, n (%)			
Relapsed	137 (66)	141 (68)	278 (67)
Refractory	70 (34)	68 (33)	138 (33)
CLL genetics, n (%)			
Del17p (Yes)	38 (18)	40 (19)	78 (19)
Del17p (No)	169 (82)	169 (81)	338 (81)
Del17p and/or *TP53*	69 (33)	68 (34)	137 (33)
Unmutated *IGHV*	173 (84)	173 (83)	346 (83)
Duration of exposure, median (Q1, Q3), months	14·8 (6, 19)	11·1 (6, 15)	13·4 (6, 17)
Patient disposition, n (%)[a]			
Met primary endpoint[b]	34 (16)	100 (48)	134 (32)
Discontinued study	83 (40)	64 (31)	147 (35)
Ongoing in study	90 (44)	45 (22)	135 (33)

	Idelalisib plus bendamustine and rituximab (N = 207)	Placebo plus bendamustine and rituximab (N = 209)	All Patients (N = 416)
Reason for early discontinuation from study treatment, n (%)			
Adverse event	56 (27)	28 (13)	84 (20)
Physician decision	7 (3)	24 (12)	31 (8)
Withdrawal by patient	12 (6)	8 (4)	20 (5)
Other	4 (2)	3 (1)	7 (2)
Other therapy initiated	1 (<1)	1 (<1)	2 (<1)
Lost to follow-up	1 (<1)	0	1 (<1)
Noncompliance	2 (1)	0	2 (<1)

[a] Per investigator assessment.

[b] Disease progression or death.

BR, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; FC, fludarabine and chlorambucil; FCR, fludarabine, chlorambucil, and rituximab.

Table 2

Responses in patients with or without 17p deletion and unmutated or mutated *IGHV*

Response	Patients with 17p deletion		Patients without 17p deletion	
	Idelalisib plus bendamustine and rituximab N = 38	**Placebo plus bendamustine and rituximab N = 40**	**Idelalisib plus bendamustine and rituximab N = 169**	**Placebo plus bendamustine and rituximab N = 169**
Overall response rate, n (%), [95% CI]	**22 (58), [41, 74]**	**9 (23), [11, 39]**	**123 (73), [65, 79]**	85 (50), [43, 58]
CR, n (%)	0	0	3 (2)	0
CRi, n (%)	0	1 (3)	0	0
PR, n (%)	22 (58)	8 (20)	120 (71)	85 (50)
SD, n (%)	12 (32)	16 (40)	35 (21)	69 (41)
PD, n (%)	1 (3)	10 (25)	0	9 (5)
Odds ratio for overall response (95% CI)	4·7 (1·8, 12·7)		2·64 (1·7, 4·2)	
Lymph node response rate, n/N (%), [95% CI]	32/34 (94), [80, 99]	9/33 (27), [13, 46]	154/158 (98), [94, 99]	111/164 (68), [60, 75]

Response	Patients with unmutated *IGHV*		Patients with mutated *IGHV*	
	Idelalisib plus bendamustine and rituximab N = 173	**Placebo plus bendamustine and rituximab N = 173**	**Idelalisib plus bendamustine and rituximab N = 34**	**Placebo plus bendamustine and rituximab N = 36**
Overall response rate, n (%), [95% CI]	**122 (71), [63, 77]**	**74 (43), [35, 51]**	**23 (68), [50, 83]**	**20 (56), [38, 72]**
CR, n (%)	3 (2)	0	0	0
CRi, n (%)	0	1 (1)	0	0
PR, n (%)	119 (69)	73 (42)	23 (68)	20 (56)
SD, n (%)	40 (23)	73 (42)	7 (21)	12 (33)
PD, n (%)	1 (1)	16 (9)	0	3 (8)
Odds ratio for overall response (95% CI)	3·2 (2·1, 5·0)		1·67 (0·63, 4·43)	

CI, confidence interval; CR, complete response; CRi, complete response with incomplete marrow recovery; PD, progressive disease; PR, partial response; SD, stable disease.

Table 3

Overall treatment response

	Idelalisib plus bendamustine and rituximab	Placebo plus bendamustine and rituximab N = 209
Response Parameter	N = 207	
Overall response, n (%), [95% CI]	145 (70·0), [63, 76]	94 (44·5), [38, 52]
CR, n (%)	3 (1·4)	0
CRi, n (%)	0	1 (0·5)
PR*, n (%)	142 (68·6)	93 (44·5)
≥50% reduction in lymph nodes, n/N (%), [95% CI]	186/192 (97), [93, 99]	120/197 (61), [54, 68]
Duration of response, months	22·8 (19·1, 27.2)	11·2 (8·5, 13·7)
Organomegaly response, n/N (%), [95% CI]		
Spleen	125/148 (85), [78, 90]	80/141 (57), [48, 65]
Liver	57/99 (58), [47, 68]	47/109 (43), [34, 53]
Hematologic response, n/N (%), [95% CI]		
Hemoglobin	58/66 (88), [78, 95]	50/71 (70),[58, 81]
Neutrophils	24/28 (86), [67, 96]	26/32 (81), [64, 93]
Platelets	71/80 (89), [80, 95]	49/63 (78), [66, 87]

*22 patients in the idelalisib arm and 8 patients in the placebo arm met laboratory and imaging criteria for CR but did not have a bone marrow aspiration and biopsy to confirm the response. CI, confidence interval; CR, complete response; CRi, complete response with incomplete marrow recovery; PR, partial response.

Table 4

Incidence of treatment emergent adverse events and laboratory abnormalities (≥10% of patients)

	Idelalisib plus bendamustine and rituximab (N = 207)				Placebo plus bendamustine and rituximab (N = 209)			
Treatment-emergent adverse events, n (%)	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Neutropenia	8 (4)	44 (21)	80 (39)	0	16 (8)	55 (26)	44 (21)	0
Pyrexia	72 (35)	13 (6)	0	1 (0·5)	56 (27)	7 (3)	0	0
Diarrhea	61 (29)	19 (9)	0	0	43 (21)	4 (2)	0	0
Nausea	54 (26)	2 (1)	0	0	71 (34)	2 (1)	0	0
Anemia	24 (12)	18 (14)	2 (1)	0	23 (11)	24 (12)	2 (1)	0
Febrile neutropenia	0	28 (14)	20 (10)	0	0	9 (4)	3 (1)	1 (0·5)
Cough	46 (22)	1 (0·5)	0	0	44 (21)	2 (1)	0	0
Thrombocytopenia	19 (9)	15 (7)	12 (6)	0	24 (12)	18 (9)	9 (4)	0
Fatigue	36 (17)	6 (3)	1 (0·5)	0	47 (23)	14 (7)	5 (2)	0
Pneumonia	14 (7)	16 (8)	5 (2)	3 (1)	9 (4)	12 (6)	0	4 (2)
Vomiting	32 (16)	2 (1)	0	0	29 (14)	2 (1)	0	0
Rash	27 (13)	6 (3)	0	0	27 (13)	0	0	0
Constipation	31 (15)	1 (0·5)	0	0	35 (17)	0	0	0
ALT increased	10 (5)	18 (9)	4 (2)	0	2 (1)	0	1 (0·5)	0
Infusion-related reaction	26 (13)	5 (2)	0	0	45 (22)	3 (1)	1 (0·5)	0
Upper respiratory tract infection	27 (13)	2 (1)	0	0	21 (10)	3 (1)	0	0
Arthralgia	23 (11)	2 (1)	0	0	16 (8)	0	0	0
Chills	23 (11)	0	0	0	13 (6)	0	0	0
Dyspnea	16 (8)	5 (2)	1 (0·5)	0	19 (9)	8 (4)	0	0
Asthenia	21 (10)	1 (0·5)	0	0	14 (7)	6 (3)	0	0
Decreased appetite	16 (8)	5 (2)	0	0	15 (7)	0	0	0
Abdominal pain	16 (8)	5 (2)	0	0	12 (6)	1 (0·5)	0	0
Headache	19 (9)	1 (0·5)	0	0	21 (10)	1 (0·5)	0	0
Laboratory abnormalities, n (%)	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Neutrophil count decreased	35 (17)	45 (22)	106 (51)	0	56 (27)	62 (30)	70 (34)	0
Neutrophils, segmented (GI/L)	42 (20)	46 (22)	93 (45)	0	56 (27)	62 (30)	70 (34)	0

	Idelalisib plus bendamustine and rituximab (N = 207)				Placebo plus bendamustine and rituximab (N = 209)			
Treatment-emergent adverse events, n (%)	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
White blood cell decreased	75 (36)	67 (32)	27 (13)	0	76 (36)	72 (34)	19 (9)	0
Lymphocyte count decreased	50 (24)	82 (40)	21 (10)	0	50 (24)	76 (36)	18 (9)	0
Alanine aminotransferase increased	82 (40)	34 (16)	10 (5)	0	60 (29)	6 (3)	0	0
Hyperglycemia	105 (51)	19 (9)	1 (0·5)	0	102 (49)	13 (6)	1 (0·5)	0
Hypertriglyceridemia	108 (52)	17 (8)	0	0	97 (46)	13 (6)	0	0
Anemia	82 (40)	41 (20)	0	0	95 (46)	34 (16)	0	0
Aspartate aminotransferase increased	79 (38)	31 (15)	1 (0·5)	0	54 (26)	5 (2)	2 (1)	0
Gamma glutamyl transferase increased	93 (45)	16 (8)	0	0	50 (24)	8 (4)	0	0
Platelets count decreased	63 (30)	21 (10)	21 (10)	0	73 (35)	23 (11)	12 (6)	0
Alkaline phosphatase increased	74 (36)	3 (1)	0	0	43 (21)	0	0	0
Hyponatremia	43 (21)	9 (4)	0	0	29 (14)	3 (1)	0	0
Hypokalemia	38 (18)	11 (5)	1 (0·5)	0	21 (10)	7 (3)	0	0
Blood bilirubin increased	48 (23)	1 (0·5)	0	0	36 (17)	2 (1)	0	0
Hypoalbuminemia	45 (22)	3 (1)	0	0	29 (14)	0	0	0
Hypophosphatemia	17 (8)	26 (12)	0	0	19 (9)	14 (7)	0	0
Hypoglycemia	28 (14)	0	0	0	30 (14)	0	0	0
Hyperuricemia	21 (10)	0	1 (0·5)	0	32 (15)	0	6 (3)	0
Creatinine clearance decreased	18 (9)	1 (0·5)	0	0	21 (10)	0	0	0
Creatinine increased	14 (7)	0	0	0	23 (11)	0	0	0

Treatment emergent adverse events were classified by preferred term using Medical Dictionary for Regulatory Activities, version 18·0, as reported by the investigator. Patients who experienced multiple events within the same preferred term were counted once per preferred term. ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 5

Incidence of serious adverse events (≥2% of patients)

	Idelalisib plus bendamustine and rituximab (N = 207)	Placebo plus bendamustine and rituximab (N = 209)
	Any grade n (%)	Any grade n (%)
Any serious adverse event	**140 (68)**	**92 (44)**
Febrile neutropenia	41 (20)	10 (5)
Pneumonia	29 (14)	15 (7)
Pyrexia	24 (12)	11 (5)
Sepsis	10 (5)	3 (1)
Diarrhea	10 (5)	1 (0·5)
Neutropenia	9 (4)	3 (1)
Lower respiratory tract infection	6 (3)	5 (2)
Anemia	5 (2)	5 (2)
Neutropenic sepsis	3 (1)	6 (3)
Urinary tract infection	5 (2)	3 (1)
Pulmonary embolism	2 (1)	5 (2)
Respiratory tract infection	2 (1)	5 (2)
Abdominal pain	4 (2)	2 (1)
Bronchitis	1 (0·5)	5 (2)
Cough	4 (2)	2 (1)
Septic shock	5 (2)	1 0·5)
Squamous cell carcinoma	1 (0·5)	5 (2)
Cellulitis	4 (2)	0

Treatment emergent adverse events were classified by preferred term using Medical Dictionary for Regulatory Activities, version 18·0, as reported by the investigator. Patients who experienced multiple events within the same preferred term were counted once per preferred term.

Table 6

Treatment-related adverse events leading to death, per investigator assessment

Treatment	Adverse event by preferred term	Related to idelalisib/placebo	Related to rituximab	Related to bendamustine	Related to study procedure
Idelalisib + BR	Septic shock	No	No	Yes	No
	Multi-organ failure	Yes	Yes	Yes	No
	Herpes zoster	Yes	No	No	No
	Sepsis	Yes	No	No	No
	Pyrexia	No	Yes	Yes	No
	Septic shock	No	Yes	Yes	No
	Respiratory distress	No	No	No	Yes
Placebo + BR	Liver disorder	Yes	No	No	No
	Pneumonia bacterial	Yes	No	Yes	No
	Pneumonia	Yes	No	Yes	No
	cytomegaloviral				
	Pulmonary mycosis	Yes	No	Yes	No
	Pneumonia	No	Yes	Yes	No
	Respiratory tract infection	No	Yes	Yes	No
	Urosepsis	No	Yes	Yes	No

BR, bendamustine and rituximab.