Idelalisib in Combination with Bendamustineand Rituximab Improves Overall Survival in Patients with Relapsed/refractory CLL – Interim Results of a Phase 3 Randomized Placebo-Controlled Trial.

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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) wherean 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 between2002and 2012 using the following search terms: "relapsed CLL, refractory CLL, bendamustine, chemoimmunotherapy, rituximab, adenosine triphosphatidylinositol 3-kinase (PI3K) δ isoform (PI3Kδ), CAL-101 andidelalisib," either singly or as part of combination, but with one of the terms being relapsed CLL or refractory CLL.The established treatment landscape for relapsed/refractory CLL based on several phase 1/2 studies and one phase 3 studywas the use of alkylating agents such as chlorambucil andbendamustine, as well asanti CD-20 monoclonal antibodies (rituximab, ofatumumab).A single-arm phase 2 clinical study by Fischer demonstrated that the combination of bendamustine with rituximab was safe and effective and had significant activity in fludarabine-refractory patients. Idelalisib (CAL-101), a potent inhibitor ofPI3Kδ, had been shown to inhibit B-cell receptor signaling and survival signals in CLLcells in vitro. Subsequent phase 1 studies established tolerability,clinical activity and pharmacokinetics of idelalisibas a single agent and in combination with bendamustine or an anti CD-20 antibody in patients with relapsed/refractory 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 relapsed/refractory 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 relapsed or refractory CLL.

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

Added value of this study:

This randomized placebo-controlled phase 3 study is the first to demonstrate conclusively that the addition of a small molecule targeted agent idelalisib to a standard-of-care regimen of bendamustine and rituximab 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 relapsed/refractory CLL. Additionally, this study has added to the body of evidence that,while chemoimmunotherapy with bendamustine and rituximab has a role in the management of patients with relapsed or refractory CLL,adding idelalisib to this standard regimen should be consideredwhen maximizing the clinically relevant endpoints of PFS,duration of response (DOR), and OS are the goals of therapy.

Implications of all the available evidence:

In this patient population, bendamustine in combination with rituximab alone should no longer be considered the optimal therapeutic approach since the addition of idelalisib improved

PFS and OSt.While the combination of idelalisib with bendamustine and rituximab is tolerable and has the positive benefitsof 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 jiroveci*pneumonia [PJP]andcytomegalovirus [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. In summary, the combination of idelalisib with bendamustine and rituximab is an important new therapeutic option for patients with relapsed/refractory CLL.

Abstract

Background: Bendamustine and rituximab has been a standard of care for the management of patients with relapsed/refractory chronic lymphocytic leukemia (CLL). We evaluated the impact of adding idelalisib, a first-in-class targeted PI3K delta inhibitor, to bendamustine/rituximab in patients with relapsed/refractory CLL.

Methods: Between June 2012 and August 2014, 416 patients with relapsed/refractory CLL were randomized (207 received idelalisib and 209 placebo). This multicenter phase 3, randomized, double-blind studyevaluated the addition of twice-daily oral idelalisib 150 mg or placebo to six cycles of bendamustine/rituximab. Treatment with idelalisib or placebo continued until progression or intolerance. Patients were randomized 1:1 and stratified based on high-risk features (*IGHV*, del(17p)/*TP53*mutation) and refractory disease. The primary endpoint was progression-free survival and a key secondary endpoint was overall survival. A prespecified interim analysis was completed after 75% of the anticipated primary events.

Findings: After the prespecified interim analysis, the Independent Data Monitoring Committee recommended discontinuation and unblinding of the trial due to "overwhelming" efficacy.The data presented herein is from the last cutoff date prior to unblinding. Median progression-free survival was 20.8 and 11.1 months in the idelalisib and placebo arms, respectively (hazard ratio [HR], 0·33; 95% CI, 0·25 to 0·44; P<0·0001) at a median follow-up of 14months. Median overall survival was not reached in the idelalisib arm and was 32 months in the placebo arm, with adjusted HR of 0.62; 95% CI 0.42, 0.92; P = 0.0309. An increased risk of infection was observed in the idelalisibvs placebo arm.

Interpretation: Idelalisib plus bendamustine/rituximab is superior to bendamustine/rituximab alone, improving progression-free and overall survival. This regimen represents an important

new treatment option for patients with relapsed/refractory CLL.

Funding: This study was funded by Gilead Sciences, Inc.

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,unmutatedimmunoglobulin heavy chain variable region (*IGHV*) genes, *TP53* mutations (*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/rituximab would improve efficacy as defined by progression-free survival with tolerable toxicity in patients with relapsed/refractory disease.

Methods

Study design and participants

In this phase 3, randomized, multicenter, double-blind, placebo-controlled study (NCT01569295), patients were enrolled at total of 110 sites in the following 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. The trial was conducted according to principles of Good Clinical Practice and the Declaration of Helsinki. Institutional review boards at each study site approved the protocols.

Eligible adult patients had previouslytreated CLL requiring therapy,[9]measurable adenopathy, received prior therapy containing a purine analog or bendamustineand an anti-CD20 monoclonal antibody, serum bilirubin less than 1·5x upper limit of normal (unless due to Gilbert'ssyndrome or hemolysis), serum transaminases up to 2·5 x upper limit of normal, experienced CLL progression less than 36 months sincecompletion of the last prior therapy, and werefit to receive cytotoxic therapy.

Exclusion criteria included known histological transformation to an aggressivelymphoma(eg, Richter transformation); disease refractory to bendamustine (ie, no response or progression less than 6 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.

Randomization and masking

An Interactive Web Response System (IWRS) was usedtodocument screening and to implement stratification and randomization. Eligible patients were randomized in a 1:1 ratio to receive idelalisib or placebo in combination with bendamustine and rituximab. In order to balance treatment allocation by potentially important predictive factors, a fixed-block centralized

randomization allocated patients based on the presence or absence of del(17p), and/or TP53mut, and IGHV mutation status, and by refractory (progression less than 6 months from completion of prior therapy) or relapsed (progression at least 6 months from completion of prior therapy) disease. The IWRS assigned bottle numbers and instructions for dispensing of blinded study drug.

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 data monitoring committee (DMC) and drug safety personnel. Following an interim analysis, the final studyunblindingoccurred upon recommendation by the DMC.

Procedures

Study treatment consisted oftwice-daily oral idelalisib150 mgor matching placebo. In both treatment arms, bendamustine70 mg/$m^2$was administered on days 1 and 2 for six28-day cycles. Rituximab was administered 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. Rituximab and bendamustinewere administered up to a maximum of 6 and 12 infusions, respectively.Idelalisib/placebo was administered continuouslyuntil disease progression, death, intolerable toxicity, or withdrawn consent. Study visits occurred every 2 weeks through week 24, every 6 weeks between weeks 24 and 48 and every 12 weeks thereafter. At each visit, safety and CLL disease status wasassessed by physical and laboratory examinations. Imaging by computed tomography (CT)or magnetic resonance imaging (MRI) was performed every 12 weeks and evaluated by the Independent Review

Committee(IRC) for evidence of disease progression.At the time of discontinuation from the study, an end-of-study CT/MRI tumor assessment was performedunless the patient already had radiographic confirmation of definitive disease progression. This assessment wasfollowed 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 6-month intervals for 5 years.

An independent central lab (Ulm University, Ulm, Germany) analyzed 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 progression-free survival, defined as the interval from randomization to the earlier of the first documentation of definitive disease progression confirmed by the Independent Review Committee or death from any cause. Definitive disease progression of CLL was based on standard International Workshop on Chronic Lymphocytic Leukemia criteria,[9,10] other than lymphocytosis alone. Secondary efficacy endpoints included confirmed overall response rate (iemaintaining a response for at least 12 weeks), lymph node response rate, overall survival, and complete response rate.Responses were categorized by the IRC as complete response (CR), complete response withincomplete marrow recovery (CRi), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE).

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; serious adverse events (SAEs); or AEs leading to discontinuation of study drug(s). Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.0 and graded according to Common Terminology Criteria for Adverse Events (version 4·03).

Statistical analysis

Efficacy analyses were based on an intent-to-treat analysis.Safety endpoints were analyzed for patients receiving at least one dose of study treatment. For the primary efficacy analysis, the difference in progression-free survival between treatment arms was assessed using Kaplan-Meier methods and the stratified log-rank test. Hazard ratios (HRs) and the corresponding 95% confidence intervals (CIs) were calculated using a Cox proportional hazards regression model. Categorical variables were compared using the Cochran-Mantel-Haenszel test adjusted for stratification factors.

With an 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 2-sided significance level of 0.05. Further considering lost to follow-up, sample size of 195 patients/treatment arm was estimated.

A prespecified interim analysis was performed after approximately 75% of the 260 expected progression-free survival 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 atwo-sided 0·032 significance level.[12]Incidence of treatment-emergent adverse events and laboratory abnormalities was summarized with descriptive statistics.

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 allthe data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 2012 and August 2014, 416 patients with relapsed/refractory 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 75% of PFS events had occurred. Based on the results of this analysis, the independent Data Monitoring Committee recommended to halt and unblind the study.Updated data are presented in this manuscript with a cutoff dateof 07 October 2015. Time since diagnosis and median number of prior regimens were similar in the treatment arms. (**Table 1**). A majority of patients had high-risk disease and most had received a fludarabine-containing regimen.

Overall, the median (95% CI) progression-free survival 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. 1A**). The benefit in progression-free survival was seen consistently across all risk groups (**Fig. 1B**). For patients with del(17p)/*TP53mut* CLL, the median progression-free survival (95% CI) was 11·3 (8·8, 16·6) months for the idelalisib arm vs 8·3 (5·9, 8·5) months for the placebo arm (hazard ratio, 0·47; 95% CI,0·31, 0·72; P = 0·0004) (**Fig S2A**). For patients with neither del(17p) nor *TP53mut*, median progression-free survival for idelalisibwas 24·6 months vs 11·2 months for placebo (hazard ratio, 0·27; 95% CI, 0·18, 0·39; P<0·0001) (**Fig. S2B**).

Median overall survival was not reachedin the idelalisib arm and was 32 months in the placebo arm. There was a statistically significant improvement in overall survival, after the prespecified multiplicity adjustment, in the idelalisibvs placebo arm (hazard ratio, 0·62; 95% CI, 0·42, 0·92; P = 0.0309[stratified] (**Fig. 1C**). Overall survival in prespecified subgroups is presented in **Fig. 1D**.

The median change in sum of the products of the perpendicular diameters (SPD) of measured lymph nodes was −82·6% in theidelalisibarm and −59·8% 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 theidelalisibarm 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. 2**). Overall response rate was significantly improved in the idelalisibvs placebo arm; 70·0% vs 45·0% (P<0·0001; **Table 2**). Complete responses were observed in three (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 complete response (an additional 22 patients in the idelalisib and eight patients in the placebo arm met criteria for complete response,

but did not have a bone marrow to confirm the response)..

The median number of cycles of bendamustineand rituximabin both arms was six, however, median duration of exposure to idelalisib (14·8 months) was longer vsplacebo (11·1 months) (**Table 1**). The number of patients with an AE leading to dose interruption in the idelalisib and placebo groups was 120 (58·0%) and 50 (23·9%), respectively. As of the data cut for this report, more patients continueon idelalisibvs placebo (44% vs22%). Reasons for treatment discontinuation are listed in **Table 1**. Overall, 87patients had an adverse event leading to treatment discontinuation: 58(28·0%) in theidelalisibarm and 29(13·9%) in the placebo arm; in the idelalisib and placebo arms, the most common werepneumonia (8 [3·9%] and 4 [1·9%]), diarrhea (5 [2·4%] vs 0), pyrexia (4 [1·9%] vs 1 [0·5%]) respectively.Treatment discontinuations were similar in the idelalisibvs placebo arm (40·1% vs 30·6%) after accounting for the difference in duration of exposure. Treatment discontinuation due to physician decision was 3·4% vs 11·5%, respectively, favoring idelalisib.

The most common all-grade adverse events were neutropenia and pyrexia in theidelalisibarm and neutropenia and nausea in the placebo arm (**Table 3**). The most frequentGrade 3 or greateradverse events were neutropenia and febrile neutropenia in the idelalisiband neutropenia and thrombocytopenia in the placebo arm. The incidence of infections was higher in the idelalisib group. Opportunistic infections with *Pneumocystis jirovecii*(PJP)and cytomegalovirus were observed more commonly in the idelalisib arm (**Table 4**).The frequency of adverse events was not substantially different during and after completion of bendamustine/rituximab (**Table S1**). Grade 3 or greater diarrhea was9·2% with idelalisibvs1·9% with placebo. Elevations in alanine aminotransferase and aspartate aminotransferase, all-grade or Grade 3 or greater, were more frequent in the idelalisib arm (**Table 3**). Serious adverse events

were more frequent in theidelalisibarm (**Table 3**).

Overall, 43 and 59 patients died in the idelalisib and placebo treatment arms, respectively. Treatment-emergent adverse events leading to death occurred in 23 (11·1%) patients in the idelalisibarm and 15 (7·2%) in the placebo arm. Causes of death in the idelalisibarm occurring in greater than one patient included pneumonia (3 patients), sepsis (3 patients), and septic shock (2 patients). In the placebo arm, the most common causes were reported as pneumonia (4 patients) and acute myocardial infarction (2 patients). No substantial differences in the frequency of adverse events leading to death were observed during or after completion of bendamustine/rituximab (**Table S2)**.

Discussion

This phase 3 study met its primary endpoint of improved progression-free survival. All secondary endpoints were met, including, importantly, an improvement in overall survival, and were consistent across pre-specified patient subgroups. The results of this study add to the body of evidence demonstrating that idelalisib produces clinically meaningful outcomes in R/R CLL.asmonotherapy 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 bendamustineand rituximab was similar in the two treatment arms, indicating that the addition of idelalisib did not negatively impact the delivery of bendamustine/rituximab and that the regimen was tolerable.

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

A prespecified analysis of patient subgroups favored the idelalisibarm, including patients with high-risk features. In patients with del(17p), the progression-free survival hazard ratio point estimate was 0·62, although the upper limit of the CI crossed 1, which may be due to the small number of patients. 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). This is comparable to the progression-free survival reported in the HELIOS trial (which excluded patients with del(17p)), asimilar study evaluating the efficacy and safety of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed CLL without del(17p).[16] The median progression-free survival (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 overall response rates (70%) vs the placebo arm (45%), representing an absolute difference of 25% in favor of the idelalisibarm, demonstrating the contribution of idelalisib to improving overall response rate in this patient population (Table 2). With the newly approved kinase inhibitor agents used to treat CLL, including idelalisib and ibrutinib, it is unclear if complete response (including CRi) correlates as strongly with progression-free survival and overall survival as it does for chemoimmunotherapy. These data are still in evolution, but this study and others suggest substantial benefit despite a low rate of complete responses.[16,17]A drawback of this study is that an assessment of MRD was not performed.

The duration of response was prolonged in patients on the idelalisib arm (22·8vs11·2 months). After completion of bendamustine/rituximab, a higher proportion of patients on 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 overall survival was not reached in the idelalisib arm. Fewer patients died on the idelalisibvs placebo arm (43 vs59). The magnitude of the survival benefit with idelalisib increased over time suggesting that maintenance with idelalisibmay be a superior strategy compared with treatment at the time of the next progression, as the magnitude of the survival benefit increases with time.

While the regimen was tolerable, there was an increased risk of infection (primarily bacterial infection, common in patients with CLL), perhaps due to the longer duration of exposure on the idelalisib arm. Compared with placebo, more serious adverse events of pneumonia/sepsis, febrile neutropenia, neutropenia, diarrhea, pyrexia, and pneumonitis were reported in the idelalisib arm. Prophylaxis for *Pneumocystis jiroveci* pneumonia (PJP) was recommended but not mandatory, nor was monitoring for cytomegalovirus (CMV) mandatory. After the completion of this study, new safety data have emerged demonstrating an increased incidence of opportunistic infection and death in 3 ongoing randomized phase 3 studies in which idelalisib is administered in combination with bendamustine and rituximab in frontline CLL and relapsed indolent non-Hodgkin's lymphoma (iNHL) and in combination with rituximab in relapsed iNHL**.** These findings have led to 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%)[18] when administered as a single agent or with anti-CD20 antibody. 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]

The study does not address the question 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 progression-free survival of the idelalisib arm was 19·4 months.[20]In the current study in patients fit for chemotherapythe median progression-free survival was 20·8 months.While cross-study comparisons are not scientifically valid, it is tempting to speculate whether bendamustine is adding significantly to the progression-free survival achieved with idelalisib and rituximab alone.In the HELIOS trial,the addition of ibrutinib also significantly improved progression-free survival when added tobendamustineand rituximab,as was shown in the HELIOS trial, but did not improve overall survival.[16] In the single-agent trials of ibrutinib,[21,22] progression-free survival is also similar to that seen in the ibrutinib plus bendamustine/rituximab arm of the HELIOS trial, again raising the question of how much is added by the chemotherapy component.[16] However, the question whether bendamustineadds 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 bendamustineand rituximab is superior to bendamustineand rituximab alone, reducing the risk of both disease progression and death, increasing progression-free and overall survival. 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 the improved outcomes for

idelalisib-based therapy in patients with relapsed and refractory CLL. This regimen represents an important new treatment option for the management of relapsed/refractory CLL, further establishing the role of idelalisib in this setting.

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

ADZ, AI, ASP, BC, ME, PH, and WJhave received institutional research grants from Gilead Sciences. AHA, LKD, XL, and YK are employees of Gilead Sciences, Inc. DS received grants from Amgen; personal fees from Celgene, Janssen, and Roche; and non-financial support from Celgene. FM received personal fees from Celgene, Genentech/Roche, Gilead, and Janssen. JCB received research support from Gilead and participated in Gilead Advisory Boards. JD received consulting and lecturing fees from Gilead, Janssen, Roche, and GSK-Novartis. JRB received personal fees from Sun Biopharma, Janssen, Gilead, Pharmacyclics, Infinity, Celgene, and Roche/Genentech. JPS has received research funding, honoraria, and speaking fees from Gilead. LS received research support from Roche and also received honoraria, advisory boards fees, and travel grants from Gilead, Janssen, Novartis, and GlaxoSmithKline. MM received research grants, personal fees, and non-financial support from Gilead; and personal fees from Janssen, Roche, and Novartis. PG has received personal fees from Adaptive Biotechnologies, AbbVie, Gilead, Janssen, and Pharmacyclics; and grants from Gilead, Celgene, and Roche. ET and SS have received honoraria for consulting or serving on an advisory board, research report, and travel support from AbbVie, Amgen, Boehringer-Ingelheim, Celgene, Genentech, Genzyme,

Gilead, GlaxoSmithKline, Janssen, Mundipharma, Novartis, Pharmacyclics, Hoffmann La-Roche, and Sanofi. TR received research support and personal fees from Gilead. PM received personal fees from Gilead,Pfizer and Amgen, and personal fees and advisory board support from Roche, Janssen, Novartis, and Takeda.

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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 (range), years	62 (38–83)	64 (32–82)	63 (32–83)
Gender, male, n (%)	160 (77)	156 (75)	316 (76)
Time since diagnosis, median (range), months	74 (7-281)	75 (1-280)	75 (1-281)
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)
Prior regimens, n (%)			
FCR	140 (68)	138 (66)	278 (67)
FC	50 (24)	44 (21)	93(22)
Chlorambucil	38 (18)	37 (18)	75 (18)
Disease status, n (%)			
Relapsed	137(66)	141(68)	278(67)
Refractory	70(34)	68(33)	138(33)
CLL genetics, n (%)			
Del17p and/or *TP53*	69 (33)	68 (33)	137 (33)
Unmutated*IGHV*	173 (84)	173 (83)	346 (83)
Duration of exposure, median (range), months	14·8 (0·0–36·6)	11·1 (0·5–27·6)	13·4 (0·00–36·6)
Patient disposition, n (%)			
Met primary endpoint*	34(16)	100(48)	134(32)
Discontinued study	83(40)	64(31)	147(35)
Ongoing in study	90(44)	45(22)	134(32)
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)
Non-compliance	2 (1)	0	2 (<1)

*Disease progression or death.

Table 2. Treatment response

Response Parameter	Idelalisibplus bendamustine and rituximab N = 207 % (95% CI)	Placebo plus bendamustine and rituximab N = 209 % (95% CI)
Overall response	70(63, 76)	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	97(93, 99)	61 (54, 68)
Duration of response, months	22·8(19·1, 27.2)	11·2(8·5, 13·7)
Organomegaly response		
Spleen	85(78,90)	57 (48,65)
Liver	58(47, 68)	43(34, 53)
Hematologic response		
Hemoglobin	88 (78, 95)	70 (58, 81)
Neutrophils	86(67, 96)	81(64, 93)
Platelets	89 (80, 95)	78 (66, 87)

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

Table 3. Incidence of treatment emergent adverse events (≥10% of patients), serious adverse events (≥2% of patients), and key laboratory abnormalities

	Idelalisibplus bendamustine and rituximab(N = 207)		Placebo plus bendamustine and rituximab(N = 209)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Treatment-emergent adverse events, n (%)	207 (100)	192 (93)	203 (97)	159 (76)
Neutropenia	132 (64)	124 (60)	115 (55	99(47)
Pyrexia	86 (42)	14 (7)	63 (30)	7 (3)
Diarrhea	80 (39)	19 (9)	47(23)	4 (2)
Nausea	56 (27)	2 (1)	73 (35)	2 (1)
Anemia	54 (26)	30 (15)	49 (23)	26 (12)
Febrile neutropenia	48 (23)	48 (23)	13 (6)	13(6)
Cough	47 (23)	1 (1)	46 (22)	2 (1)
Thrombocytopenia	46 (22)	27 (13)	51(24)	27 (13)
Fatigue	43 (21)	7 (3)	52 (25)	5 (2)
Pneumonia	38 (18)	24 (12)	25 (12)	16 (8)
Vomiting	34 (16)	2 (1)	31 (15)	2 (1)
Rash	33 (16)	6 (3)	27 (13)	0
Constipation	32 (16)	1 (1)	35 (17)	0
ALT increased	32 (16)	22 (11)	3 (1)	1 (1)
Infusion-related reaction	31 (15)	5 (2)	49(23)	4 (2)
URT infection	29 (14)	2 (1)	24(12)	3 (1)
Arthralgia	25 (12)	2 (1)	16 (8)	0
Chills	23 (11)	0	13 (6)	0
Dyspnea	22 (11)	6 (3)	27 (13)	8 (4)
Asthenia	22 (11)	1 (1)	20 (10)	6 (3)
Decreased appetite	21 (10)	5 (2)	15 (7)	0
Abdominal pain	21 (10)	5 (2)	13 (6)	1 (1)
Headache	20 (10)	1 (1)	22 (11)	1 (1)
AST increased	20 (10)	12 (6)	2 (1)	0
Serious adverse events, n (%)	137 (66)	-	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 (1)	-
Neutropenia	9 (4)	-	3 (1)	-
LRT infection	6 (3)	-	5 (2)	-
Anemia	5 (2)	-	5 (2)	-
Neutropenic sepsis	3 (1)	-	6 (3)	-
Laboratory abnormalities, n (%)				
Neutrophils, decreased	186 (90)	151 (73)	188 (90)	132 (63)
ALT, increased	126 (61)	44 (21)	66 (32)	6 (3)
Hemoglobin, decreased	123 (59)	41(20)	129 (62)	34(16)
AST, increased	111 (54)	32 (16)	61 (29)	7 (3)
Platelets, decreased	105 (51)	42 (20)	108 (52)	35 (17)

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. URT, upper respiratory tract; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4.Opportunistic infections

	Idelalisibplus bendamustine and rituximab(N = 207) n (%)	Placebo plus bendamustine and rituximab(N = 209) n (%)
Patients with PJP	5(2)	0
Patients on prophylaxis for PJP	0	0
Patients on prophylaxis for PJP who developed PJP	0	0
Patients who died due to PJP	0	0
Patients with CMV	13 (6)	3(1)
Patients who died due to CMV	0	1 (<1)

CMV, cytomegalovirus; PJP, Pneumocystis jirovecii pneumonia

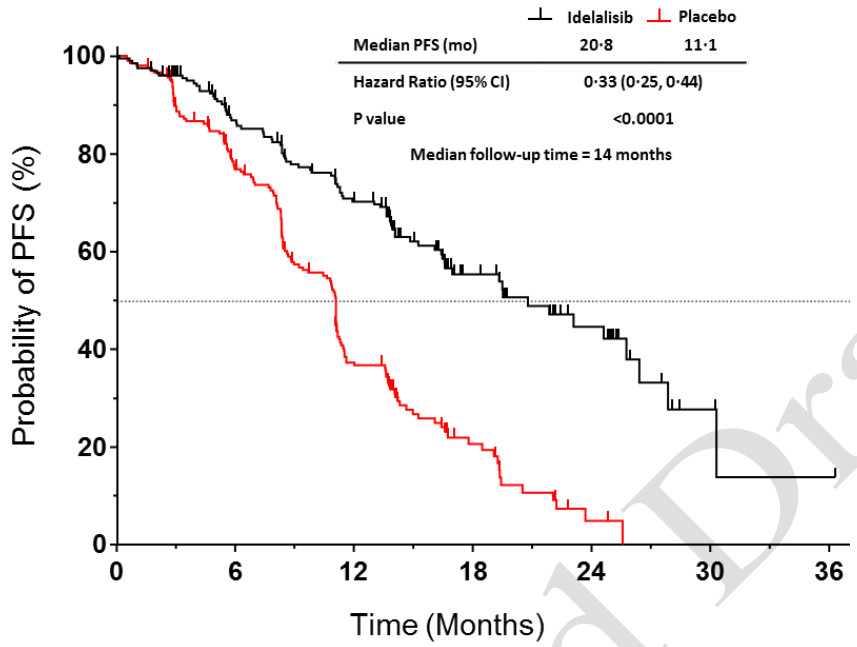
FIGURE LEGENDS

Figure 1. Progression-free and overall survival. (A) Progression-free survival (PFS) at a median follow up of 12 months. (B) Forest plot of hazard ratios for progression-free survival by prespecifiedsubgroups.(C) Overall survival (OS).(D) Forest plot of hazard ratios for overall survival by prespecifiedsubgroups. An Independent Review Committee adjudicated disease progression. BR, bendustamine and rituximab.

Figure 2. Nodal response to treatment by patient. Response assessed by computed tomography scan according to standard criteria and adjudicated by an Independent Review Committee. BR, bendusatmine and rituximab; SPD, sum of the products of the perpendicular diameters of measured lymph nodes.

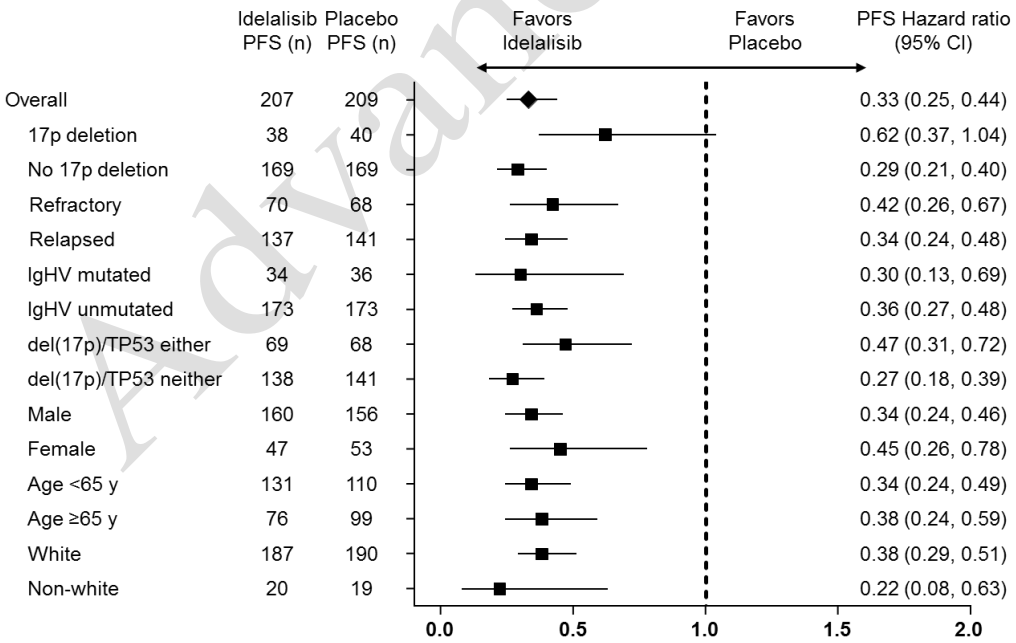
Figure 1.

(A)

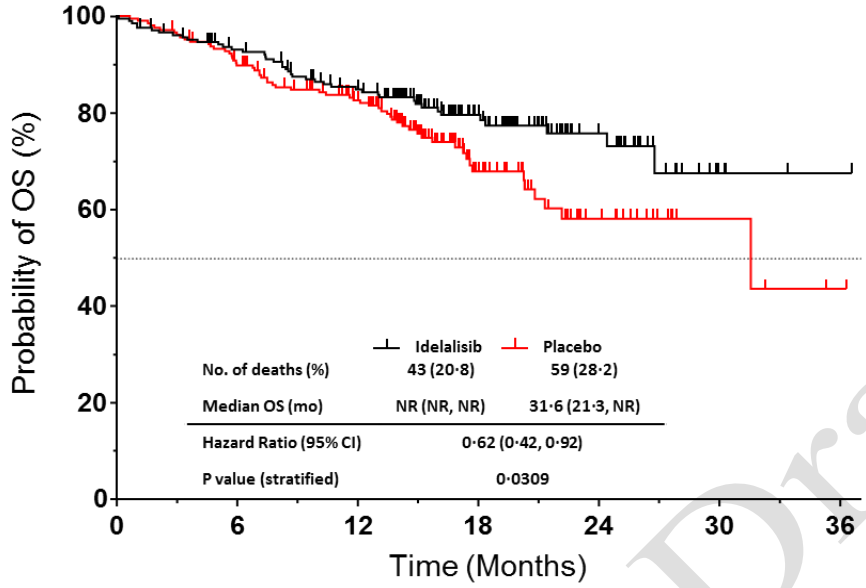


N at risk (events)							
Idelalisib + BR	207 (0)	156 (25)	118 (54)	40 (73)	18 (79)	3 (83)	1 (84)
Placebo + BR	209 (0)	146 (46)	63 (118)	16 (138)	2 (148)	0 (149)	0 (149)

(B)



(C)



N at risk (events)							
Idelalisib + BR	207 (0)	184 (14)	160 (30)	92 (41)	38 (44)	6 (46)	1 (46)
Placebo + BR	209 (0)	182 (21)	153 (35)	64 (55)	27 (62)	5 (62)	1 (63)

(D)

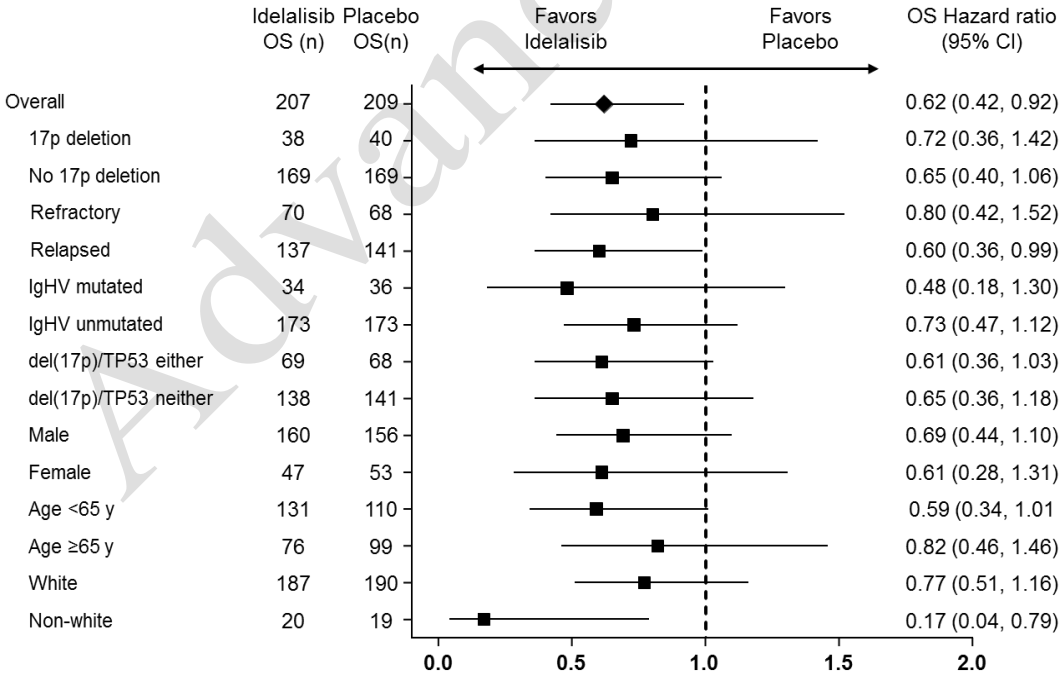
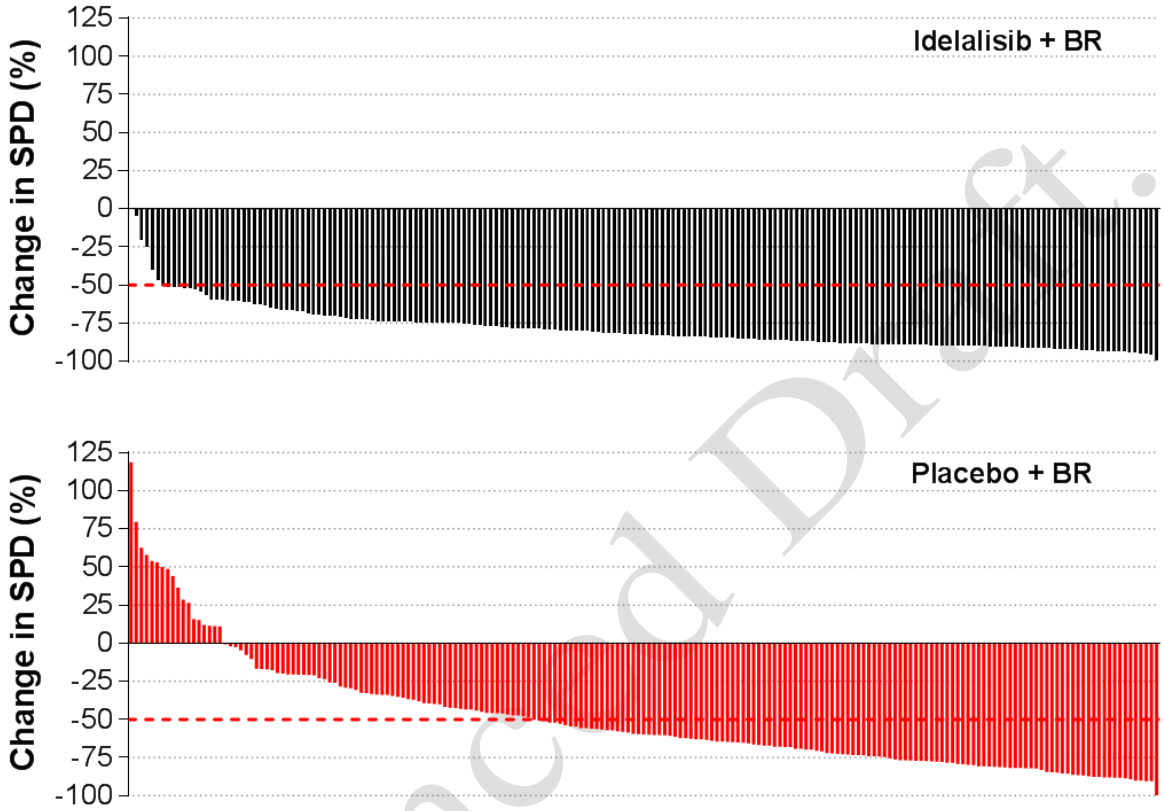


Figure 2.



Supplementary Materials

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to:Zelenetz AD, Barrientos J, Brown JR, et al. Idelalisib, bendamustine and rituximab in relapsed/refractory CLL.

Contents:

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Fig. S1. CONSORT Diagram. Patient disposition based on investigator assessment. AE, adverse event; BR, bendamustine and rituximab.

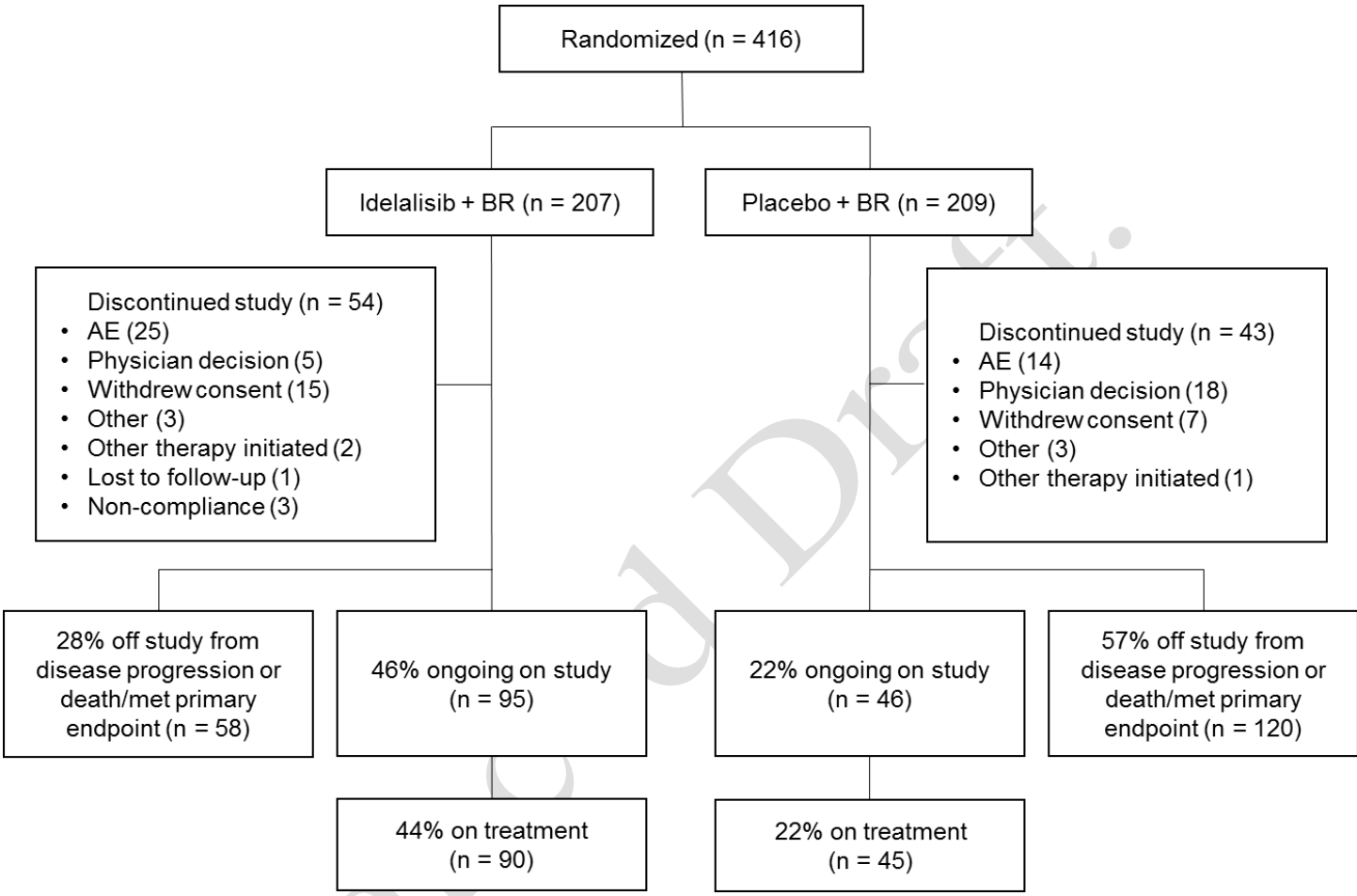
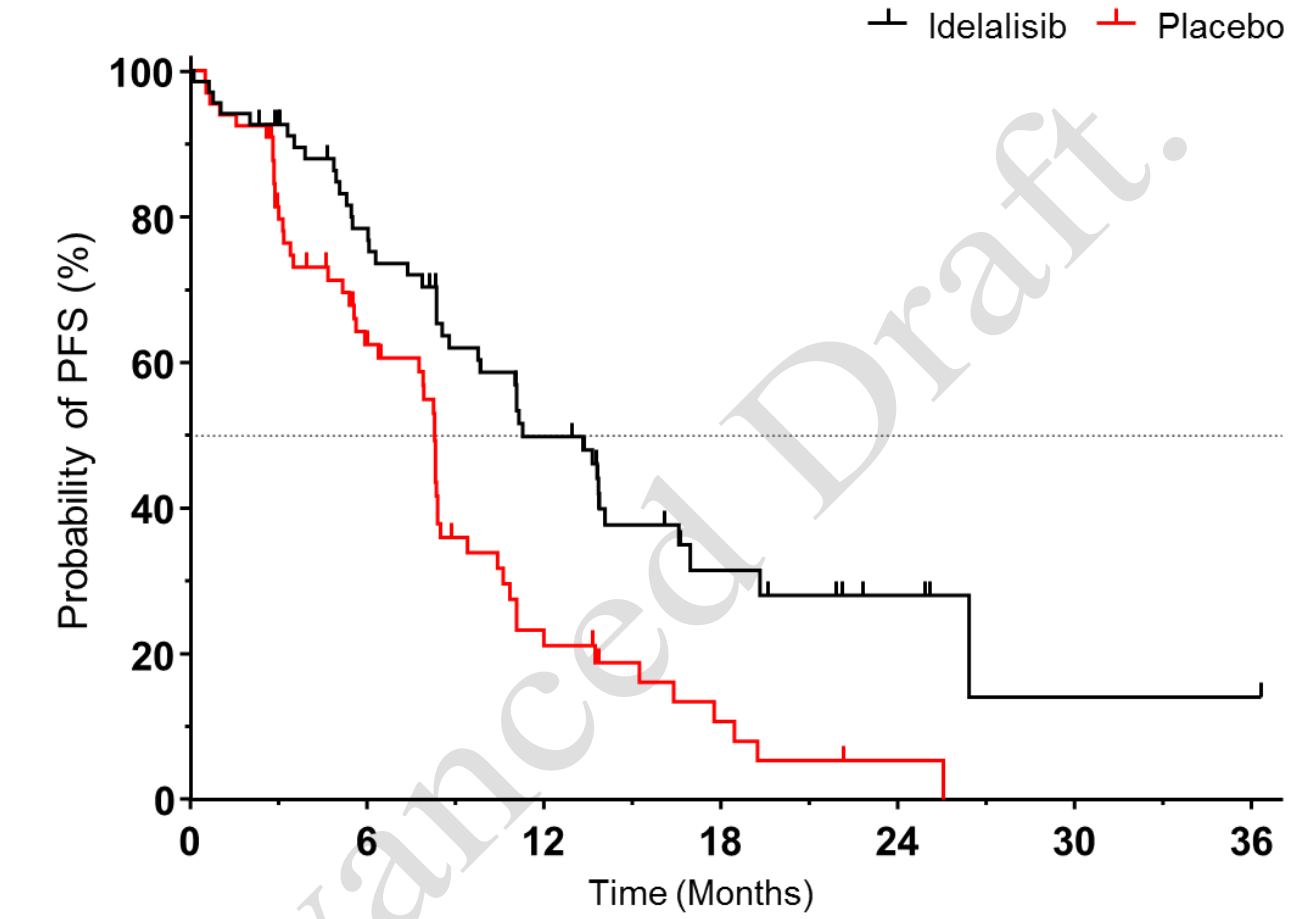


Fig. S2. Kaplan-Meier curves of progression-free survival for patients with (A) either del(17p) or *TP53* mutations and (B) neither del(17p) nor *TP53* mutations.

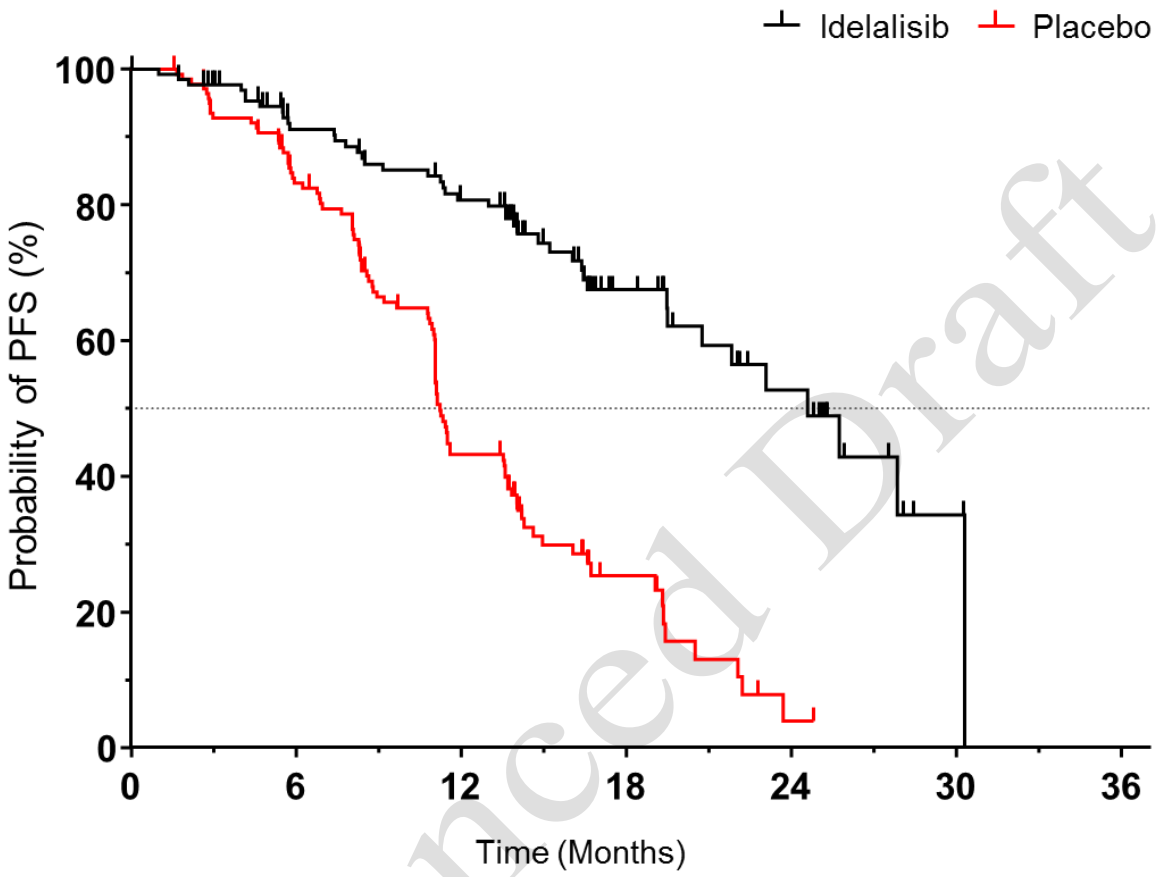
A)



Number at risk (events)

Idelalisib + BR	69 (0)	49 (14)	28 (31)	9 (39)	4 (40)	1 (41)	1 (41)
Placebo + BR	68 (0)	35 (23)	10 (44)	4 (48)	1 (50)	0 (51)	0 (51)

B)



Number at risk (events)

Idelalisib + BR	138 (0)	107 (11)	90 (23)	31(34)	14 (39)	2 (42)	0 (43)
Placebo + BR	141 (0)	111 (23)	53 (74)	12 (90)	1 (98)	0 (98)	0 (98)

Table S1. Adverse events of infections and infestations by System Organ Class - during and after completion of study treatment with bendamustine, rituximab.*

	Idelalisib plus bendamustine and rituximab	Placebo plus bendamustine and rituximab
Infections and infestations		
All grade	143 (69%)	124(59%)
≥Grade 3	80(39%)	52(25%)
Infections and infestations during bendamustine/rituximab study treatment		
All grade	90 (43%)	77 (37%)
≥Grade 3	30 (14%)	21 (10%)
Infections and infestations after completion of bendamustine/rituximab		
All grade	53 (26%)	47(22%)
≥Grade 3	50(24%)	31(15%)

*No adjustment made for duration of exposure in either treatment arm.

Table S2. Summary of adverse events leading to death*.

Arm	Deaths due to Adverse Events			Death by System Organ Class of infections/infestations		
	Total	Before completion of 6-cycle cotherapy with BR	After completion of 6-cycle cotherapy with BR	Total	Before completion of 6-cycle cotherapy with BR	After completion of 6-cycle cotherapy with BR
Idelalisib	23	14	9	12	6	6
Placebo	15	7	8	9	6	3

BR, bendustamine and rituximab.*No adjustment made for duration of exposure in either treatment arm