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Journal

Leukemia & Lymphoma, 56(10)

ISSN

1042-8194

Authors

Kipps, Thomas J
Eradat, Herbert
Grosicki, Sebastian
et al.

Publication Date

2015-10-03

DOI

10.3109/10428194.2015.1030638

Peer reviewed

HHS Public Access

Author manuscript

Leuk Lymphoma. Author manuscript; available in PMC 2015 November 20.

Published in final edited form as:

Leuk Lymphoma. 2015 October ; 56(10): 2826–2833. doi:10.3109/10428194.2015.1030638.

A phase 2 study of the BH3 mimetic BCL2 inhibitor navitoclax (ABT-263) with or without rituximab, in previously untreated B-cell chronic lymphocytic leukemia

Thomas J. Kipps[1], **Herbert Eradat**[2], **Sebastian Grosicki**[3], **John Catalano**[4], **Walter Cosolo**[5], **Iryna S. Dyagil**[6], **Sreeni Yalamanchili**[7], **Akiko Chai**[7], **Srikumar Sahasranaman**[7], **Elizabeth Punnoose**[7], **Deborah Hurst**[7], and **Halyna Pylypenko**[8]

[1]Department of Hematology-Oncology, UCSD School of Medicine, San Diego, CA, USA [2]Division of Hematology-Oncology, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA [3]Department of Hematology, Community Hospitals, Chorzow, Poland [4]Frankston Hospital and Monash University, Frankston, Australia [5]John Fawkner Cancer Trial Centre, Coburg, Australia [6]Department of Hematology, National Research Center for Radiation Medicine of National Medical Academy of Sciences of Ukraine, Kyiv, Ukraine [7]Genentech, Inc., South San Francisco, CA, USA and [8]Department of Hematology, Cherkassy Regional Oncological Center, Cherkassy, Ukraine

Abstract

We evaluated the safety and biologic activity of the BH3 mimetic protein, navitoclax, combined with rituximab, in comparison to rituximab alone. One hundred and eighteen patients with chronic lymphocytic leukemia (CLL) were randomized to receive eight weekly doses of rituximab (arm A), eight weekly doses of rituximab plus daily navitoclax for 12 weeks (arm B) or eight weekly doses of rituximab plus daily navitoclax until disease progression or unacceptable toxicity (arm C). Investigator-assessed overall response rates (complete [CR] and partial [PR]) were 35% (arm A), 55% (arm B, $p = 0.19$ vs. A) and 70% (arm C, $p = 0.0034$ vs. A). Patients with del(17p) or high levels of BCL2 had significantly better clinical responses when treated with navitoclax. Navitoclax in combination with rituximab was well tolerated as initial therapy for patients with CLL, yielded higher response rates than rituximab alone and resulted in prolonged progression-free survival with treatment beyond 12 weeks.

Keywords

B-cell; BH3; chronic lymphocytic leukemia; rituximab; clinical trial; ABT-263; BCL2; navitoclax

Correspondence: Thomas J. Kipps, MD, PhD, University of California San Diego, 3855 Health Sciences Dr, La Jolla, CA 92093, USA. Tel: 858-534-5400. Fax: 858-534-5620. tkipps@ucsd.edu.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

Supplementary material available online
Supplementary Table and figure showing further results

Introduction

Apoptosis is an interplay between pro-survival proteins and pro-apoptosis proteins in the *BCL2* family of proteins [1]. The overexpression of BCL2 anti-apoptotic proteins sequesters pro-apoptotic proteins of the same family, leading to enhanced cell survival. Chronic lymphocytic leukemia (CLL) cells express high levels of the anti-apoptotic protein BCL2, thereby enhancing the capacity of CLL cells to resist spontaneous or drug-induced apoptosis [2].

BH3 mimetics are a class of drugs designed to compete for the BH3-binding pocket in pro-survival proteins to displace sequestered pro-apoptosis proteins [3]. ABT-737 is a small molecule inhibitor that mimics the BH3 protein, BAD, by binding to BCL2, BCLXL or BCLW, and thereby antagonizing their capacity to sequester pro-apoptosis proteins [4]. CLL is responsive to ABT-737, and a mechanistic dissection points specifically to its ability to displace BIM from BCL2 where it is constitutively sequestered [5]. ABT-737 has been developed into a second-generation, orally available therapeutic agent, ABT-263 (navitoclax), with similar binding properties [6]. In addition to expressing high levels of the anti-apoptotic protein BCL2, CLL cells also express high levels of the pro-apoptotic protein BIM, making CLL cells particularly sensitive to inhibition of BCL2 by navitoclax [5].

Navitoclax can enhance the anti-leukemia activity of rituximab [7], either alone or in combination with chemotherapy, *in vitro* [4,6,8,9]. CLL cells that express high levels of BCL2, or that have a high ratio of BCL2 to MCL1 or other *BCL2* family members, appear most sensitive to navitoclax or ABT-737 [10,11]. In a phase 1 study, patients with relapsed/refractory CLL who were treated with navitoclax had a 35% overall response rate (ORR) [12]. Study-emergent thrombocytopenia was managed through the implementation of a lead-in period, and neutropenia was reversible with dose reduction or administration of granulocyte colony stimulating factor. Based on the single-agent data [12], the present study evaluated the safety, pharmacokinetics and biologic activity of navitoclax and rituximab versus rituximab alone, in the initial therapy of patients with CLL.

Materials and methods

Study design

An open-label phase 2, randomized three-arm, multicenter trial was performed in patients with CLL (ClinicalTrials.gov: NCT01087151). Patients provided written informed consent, and protocol approvals were obtained from national health authorities and independent ethics committees for each site. The study was conducted at 47 sites in nine countries in accordance with International Conference on Harmonization Good Clinical Practice Guidelines. The primary efficacy outcome measure was progression-free survival (PFS) defined by the International Workshop on CLL (iwCLL) criteria as the time from study entry until objective disease progression or death [13].

Patients and study treatments

Patients aged ≥ 18 years were eligible if they had previously untreated CLL that required treatment according to iwCLL criteria [13]; Eastern Cooperative Oncology Group (ECOG)

performance status of 0 or 1 due to CLL [14]; and adequate marrow, renal and hepatic function (baseline platelet counts > 75 000/mm to allow for drug-related thrombocytopenia [15], hemoglobin ≥ 9 g/dL, absolute neutrophil count ≥ 1000/μL, serum creatinine ≤ 2.0 mg/dL or measured clearance ≥ 50 mL/min, alanine transaminase/aspartate transaminase/alkaline phosphatase [ALT/AST/ALP] ≤3.0 times the upper limit of normal [ULN], bilirubin ≤1.5 × ULN unless Gilbert syndrome present, activated partial thromboplastin time/prothrombin time ≤1.2 × ULN). Exclusion criteria included receiving therapeutic anticoagulation (heparin, warfarin), drugs that affect platelet function (e.g. aspirin, clopidogrel), active infection or chronic viral infection (human immunodeficiency virus [HIV], hepatitis C virus [HCV], hepatitis B virus [HBV]). Patients were stratified by Binet stage and high-risk cytogenetic features (17p deletion and/or 11q deletion) [13,16–18].

Patients self-administered ABT-263 in liquid or tablet form, on a daily basis. Rituximab infusion occurred on a weekly basis in the infusion room of each participating site. Patients were randomized 1:1:1 to arm A (rituximab 375 mg/m^2 week 1, 500 mg/m^2 weekly for weeks 2–8), arm B (rituximab 375 mg/m^2 week 1, 500 mg/m^2 weekly for weeks 2–8, plus navitoclax 100 mg daily × 1 week [week 1], then 250 mg daily × 12 weeks) and arm C (rituximab 375 mg/m^2 week 1, 500 mg/m^2 each week 2–8, plus navitoclax 100 mg daily × 1 week [week 1], then 250 mg daily until disease progression or unacceptable toxicity).

The rituximab dose chosen for investigation (500 mg/m^2 subsequent to an initial dose of 375 mg/m^2) is similar to that used in combination with fludarabine and cyclophosph-amide, which resulted in statistically significant and clinically meaningful improvement in patient outcomes [19]. Patients randomized to ABT-263 arms B and C received the “lead-in” dose of 100 mg/day ABT-263 identified in the phase 1 study [20], followed by the final dose of 250 mg/day. The lead-in dose period lasted 8–15 days and was intended to allow for monitoring of the effects of low-dose ABT-263 on the platelet counts of treated patients [15]. Patients enrolled in arm A who experienced disease progression at least 2 months after the last rituximab infusion were eligible for cross-over to arm B (rituximab for 8 weeks plus navitoclax daily for 12 weeks). Due to the mechanistic and early effect of navitoclax on platelet counts, it was not practical to treat patients enrolled in the rituximab-only arm with a placebo in blinded fashion.

Patients on arm C who were responding to navitoclax were given the option to continue on a roll-over protocol for continued navitoclax treatment once they discontinued from the study. The ABT-263 was continued until disease progression or for 1 year, whichever came first. No further efficacy outcomes were collected on these patients.

Safety assessments

Safety was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.0) for the standardized classification of adverse events (AEs) of drugs used in cancer therapy [21]. Special emphasis was focused on grade ≥ 3 AEs, serious AEs (SAEs) and grade ≥ 3 laboratory toxicities, and relationship to study treatment.

An Internal Monitoring Committee (IMC) conducted a formal safety data review from the first 30 patients treated on the combination arms B and C before additional enrollment was allowed. Thereafter, safety review meetings by the IMC were required approximately every 6 months.

Pharmacokinetic evaluations

Navitoclax and rituximab pharmacokinetic (PK) samples were obtained at multiple visits throughout the study. Navitoclax plasma PK samples were obtained coincident with the week 1, lead-in day 5 dose: pre-dose and at 2, 4, 6 and 8 h post-dose; and on week 8, day 1: pre-dose and at 2, 4, 6, 8 and 24 h post-dose in arm B and arm C. Pre-infusion and post-infusion rituximab samples were obtained on day 1 at weeks 2, 4 and 8, and rituximab concentrations were subsequently followed at weeks 12, 16, 20 and 24. Navitoclax concentrations in plasma were determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS-MS) method [22]. Rituximab concentrations in serum were analyzed using a validated immunoassay [23].

Biomarker assessments

Baseline bone marrow aspirates (BMAs) were collected by optional consent from patients randomly assigned to one of the three arms of this study. Protein expression of BCL2 and related family proteins were measured by intracellular staining after gating on CD19/CD5 positive CLL cells in a flow assisted cell sorting assay on fresh samples run at a central laboratory (Esoterix, Inc.) (LabCorp Clinical Trials, Cranford, NJ) within 72 h of sample collection [24]. The following analytes were evaluated in BMAs by flow cytometry for statistical analysis: BCL2, BCLXL, MCL1, A1, BIM and NOXA, and the ratios of BCL2/MCL1 and BCLXL/MCL1. BMAs were also examined by interphase fluorescence *in situ* hybridization (FISH) analyses for cytogenetic features (17p deletion and/or 11q deletion) [18].

Efficacy outcomes

Progression-free survival (PFS) was defined as the time from randomization to progressive disease (PD), relapse or death on study from any cause within 12 weeks of last tumor assessment. The study investigators assessed for clinical response using the updated iwCLL criteria [13]. Response was assessed at week 12, and every 12 weeks during follow-up.

Statistical analysis

This trial was designed to estimate the magnitude of treatment effect rather than for formal hypothesis testing. The study was originally planned to enroll 120 patients to observe approximately 72 investigator-assessed PFS events across the three treatment arms combined. Due to early discontinuation of the trial, the final study data for analysis included only 27 patients who had experienced a PFS event instead of the planned 72 patients. Kaplan–Meier methods were used to estimate the median PFS for each treatment arm [25]. Objective response, defined as a complete or partial response according to the modified iwCLL criteria, was estimated, and corresponding 95% confidence intervals were calculated for each treatment arm. The difference in objective response rate between the treatment arms

was also calculated along with the 95% confidence intervals. *p*-Values for treatment group comparison were based on χ^2 tests. Due to the explorative nature of the study, no adjustment was made for multiple comparisons.

Biomarker subgroups were derived by the median value of expression for each biomarker. Biomarker analysis was intended to evaluate the correlation between BCL2 levels with efficacy outcomes. Since biomarker data were available for only a small subset of patients, arms B and C were pooled to provide a larger number of patients receiving combination treatment for comparison with rituximab alone. Odds ratios of an objective response were calculated between treatment arms (arm A vs. arm B and arm C combined) for biomarker low and high groups. Logistic regression was used for each biomarker and expression subgroup. Baseline characteristics were compared between treatment arms.

Role of the funding source

The sponsor provided study drug and collaborated with investigators on study design, collection, analysis and interpretation of data, writing the report and the decision to submit the paper for publication. The corresponding author had full access to all the data.

Results

This study enrolled a total of 118 patients (Figure 1), who had (Table I) a median baseline lymphocyte count of 53 000/mm^3 (range 7000–552 000/mm^3), median age of 63 years and 55% Binet stage B + C disease. Baseline characteristics and prognostic factors of patients randomly assigned to each arm were generally balanced between each of the treatment groups. FISH analyses of pretreatment samples revealed that 31% or 28% of patients had CLL cells with deletions in 11q or 17p, respectively.

While neither safety nor toxicity was an issue, the study ended prematurely, as the sponsor decided instead to develop a more selective BCL2 inhibitor, ABT-199, which appeared less likely than navitoclax to induce thrombocytopenia, but that still could selectively dissociate BCL2/BIM heterodimers [26]. All patients had either completed their treatment period or were allowed to continue on navitoclax at the time the trial was closed. Only the follow-up was discontinued early, but not the treatment. It is noteworthy that given the small sample size, this trial is hypothesis-generating and is able to detect only a large benefit of combination therapy with rituximab and ABT-263. It does not have adequate power to detect minimal clinically meaningful differences between the combination treatment arms and arm A. Thus, formal hypothesis testing is limited in that statistically negative outcomes do not necessarily rule out clinically significant effects. Ninety-one patients (77%) completed the navitoclax study; four patients crossed over to arm B from arm A. The median time on study was 34 weeks; arm A: 24 weeks (range 12–83 weeks); arm B: 33 weeks (1–105 weeks); and arm C: 44 weeks (2–86 weeks). More patients withdrew from study due to AEs in arm C (8 [20%]) than in arm A (0 [0%]) or arm B (4 [11%]). Patients in arm C, who were randomized to continue daily navitoclax after completing six cycles of rituximab, had a longer time on study (median of 44 weeks) than patients in either arm B (33 weeks) or arm A (24 weeks), because this study arm stayed open longer than the other two study arms to allow for continued administration of navitoclax.

Safety

The percentages of patients who experienced grade ≥ 3 AEs was greater in arms B and C than in arm A. Grade ≥ 3 AEs (with an incidence of 5% or greater, Table II) included thrombocytopenia, neutropenia, leukopenia, anemia, gastrointestinal symptoms (diarrhea, abdominal pain), chills, fatigue, ALT/AST/bilirubin elevations and infusion-related reactions to rituximab. Two patients had grade 5 AEs, one each (3%) in arms A and B, neither of which was assessed by the investigator as being related to treatment with navitoclax.

The incidence of SAEs was not increased in patients treated with navitoclax compared to patients treated with rituximab alone. One patient had grade 3 bleeding (epistaxis). A total of 12 patients discontinued navitoclax due to an AE, four (11%) in arm B and eight (20%) in arm C. AEs leading to discontinuation of therapy with navitoclax included elevations in AST and/or ALT (six patients), pain (n = 1), hyperbilirubinemia (n = 1), neutropenia (n = 1), thrombocytopenia (n = 1), serum sickness (n = 1) or reaction to the infusion of rituximab (n = 1). While liver function test (LFT) abnormalities usually responded to dose adjustments, of the six patients who discontinued navitoclax, four patients in arm B discontinued at study days 37, 43, 56 and 58, while two patients on arm C discontinued at day 170 and day 316, respectively. Most of the LFT-associated discontinuations (four of the six) occurred within the first 2 months of treatment. Other reasons for discontinuation of therapy were less common: physician decision (n = 5 [4%]), sponsor decision (n = 2 [2%]) and subject/guardian decision (n = 6 [5%]).

Grade ≥ 3 infusion-related reactions were uncommon, but more often were observed in patients treated in arm B (n = 3 [8%]) or C (n = 2 [5%]), one of which was an SAE; no patient in arm A had such an AE. Two patients died while on study, one in arm A, who died on day 163 with a pulmonary embolism, judged by the treating physician as being unrelated to rituximab treatment. One patient in arm B died on day 8 due to hypotension, which was viewed by the site investigator as being related to the infusion of rituximab.

Pharmacokinetics

Plasma concentrations of navitoclax are shown in Table III. The maximum navitoclax concentrations (C_{max}) were observed approximately 6 h after oral administration. The C_{max} and area under the curve (AUC) of navitoclax in this study were similar to those observed in patients treated with single-agent navitoclax in prior phase 1 studies, indicating that co-treatment with rituximab does not alter the PK of navitoclax [20]. Patients treated in arm A had serum concentrations of rituximab that were comparable to those measured in patients treated in arm B or arm C, indicating that navitoclax does not affect the PK of rituximab. Rituximab levels were consistent across the three arms at other sampling visits from week 2 to week 24 as well (Supplemental Table I, Supplemental Figure 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/10428194.2015.1030638). The rituximab concentration levels achieved in this study using weekly dosing were higher than those observed in patients with CLL treated with rituximab given once every 28 days [27].

Biomarker assessments

Achievement of clinical response correlated significantly with BCL2 levels (interaction effect $p = 0.048$), but did not correlate with levels of other BCL2 family members tested. Patients with CLL cells that had high-level expression of BCL2 protein had significantly higher odds of achieving a favorable clinical response when treated with navitoclax and rituximab, than when treated with rituximab alone (Table IV). In comparison, patients with low BCL2 had similar odds of achieving a favorable response when treated with navitoclax and rituximab as when treated with rituximab alone. The data on patients treated with navitoclax in arms B and C were combined for this analysis and compared to the data on patients treated with rituximab alone (arm A). This was done to help identify biomarkers that correlated with a favorable outcome to treatment with navitoclax and rituximab versus treatment with rituximab alone. Similar effects were also observed when comparing arms A vs. B and also arms A vs. C (data not shown).

Efficacy

The ORR for patients treated in arm C was 70% (Table V). This compared favorably to the ORR of patients treated in arm B (55%) and was significantly greater than the ORR of patients treated in arm A (35%; $p = 0034$). Two patients in arm C (5%) achieved a complete response ($n = 2$, 5%), which was not observed for patients in other treatment arms.

Twenty-seven PFS events had occurred at the time of study closure (38% of 72 events planned). These events included one patient who died (arm A), 24 patients who had stable disease or objective response (11 patients in arm A, 10 in arm B and three in arm C) and two patients (arm A) who had stable disease or objective response but subsequently went on to have progressive disease. PFS was significantly longer for arm C than for arm B or arm A (Figure 2). Arm B trended toward longer PFS than arm A. Response duration and median PFS cannot be quantified precisely due to the limited follow-up and patient numbers.

Four patients crossed over from arm A to arm B. No exploratory analyses of efficacy data were performed on the cross-over period for these four patients. However, one patient had a partial response while on arm A while three patients had stable disease while on arm A and subsequently had progressive disease.

Discussion

Patients treated with navitoclax in combination with rituximab achieved higher ORR than patients treated with rituximab alone as initial therapy for CLL. The improved treatment outcome with navitoclax was also evident for patients who had CLL with del(17p). Similarly, improvement in treatment outcomes with navitoclax was seen in patients with CLL with other prognostic features such as del(11q) or unmutated immunoglobulin heavy chain variable gene (IgVH) (data not shown). Disease progression after therapy was observed earliest in patients treated with rituximab alone (arm A). Patients in arm C appeared to have the longest PFS.

Treatment with navitoclax and rituximab was well tolerated. First, we did not observe any interactions between navitoclax and rituximab that altered the PK of either drug. Second,

there were few grade ≥ 3 AEs that were observed more frequently in patients treated with both agents than in those treated with rituximab alone. Those AEs noted more frequently by patients treated with navitoclax included thrombocytopenia, neutropenia and elevations in hepatic transaminases. Navitoclax-related thrombocytopenia is caused by shortened platelet survival due to inhibition of $BCLX_L$, a protein necessary for normal platelet survival [28,29]. This was managed by initiating therapy with a lead-in dose of 100 mg navitoclax 1 week before advancing to the 250 mg daily dose, to allow time for the marrow to increase platelet production and provide a steady-state platelet count sufficient for hemostasis. Thereafter, platelet counts were closely monitored and treatment was temporarily held or given at a reduced dose if the counts dropped. Patients also were cautioned not to use aspirin or non-steroidal anti-inflammatory drugs while on treatment. This management appears to have mitigated risk, as the only report of bleeding among the navitoclax-treated patients was a single AE of self-limited epistaxis. Neutropenia, another mechanistic-based effect of navitoclax, was managed with dose reductions, temporary discontinuation and administration of granulocyte stimulating factor. There was no increase in infections or febrile neutropenia compared with treatment with rituximab alone. These on-target AEs and the liver function abnormalities were manageable in most cases with dose adjustments, use of granulocyte stimulating growth factor or temporary discontinuation. Nonetheless, cytopenias (one each of thrombocytopenia and neutropenia) and transaminase elevations (six patients) led to the discontinuation of navitoclax in a minority of patients. Two additional patients discontinued navitoclax due to hyperbilirubinemia and hepatic transaminase elevations, respectively.

Earlier studies hypothesized that the high expression of BCL2 and BIM and their association in pre-existing complexes in CLL cells would make these cells particularly sensitive to navitoclax [5,12]. We found BCL2 to be well expressed in patients on this study. We further tested whether quantitative levels of BCL2, BIM and related family members would be associated with improved responses to the combination of navitoclax and rituximab. Patients with CLL cells that expressed high levels of BCL2 (above the median) appeared to have had a more favorable response to therapy with navitoclax and rituximab than with rituximab alone. These data suggest that the benefit from the addition of navitoclax to rituximab is associated with high-level CLL-cell expression of BCL2 protein. It further supports the use of baseline BCL2 protein expression as a predictive biomarker of response to navitoclax. A similar relationship was not identified for the pretreatment levels of $BCLX_L$ or MCL1, making it appear sufficient to use a more selective BCL2 antagonist.

In contrast to the findings here, no significant correlation between level of expression of BCL2 and response was observed in the phase 1 study of navitoclax in relapsed/refractory CLL [12]. This could be explained by potential biological differences between the relapsed/refractory and frontline patient population. It is also worth noting that the use of a standardized assay that was run real-time in a central laboratory on fresh patient samples may have improved quantification of protein biomarkers in the present study. However, the magnitude of the benefit from navitoclax treatment versus rituximab alone in patients with high BCL2 protein levels would need to be confirmed prospectively. The caveat to the results is the small sample size in this study, and that the analysis is exploratory. To compensate for the limited availability of data, arms B and C were pooled for the biomarker

analysis where time/duration was different in arms B and C, but was not a parameter that influenced bio-marker data outcome. It must be noted that data for arms B and C were not pooled when analyzing PFS, for the PFS out-come is dependent on time/duration, which were different in the three arms.

Patients treated with navitoclax and rituximab in either arm C or arm B had a significantly higher response rate than did patients treated with rituximab alone on arm A. Patients treated in arm C, who continued treatment with navitoclax, appeared to have a longer PFS than patients treated in the other study arms. Although these differences were statistically significant, caution should be exercised in interpreting these data in view of the limited follow-up period due to the study's premature discontinuation. In any case, the results of this study indicate that a high-affinity BCL2 inhibitor combined with rituximab can potentially result in high ORRs in the frontline therapy of patients with CLL, and that a combination with monoclonal antibodies may further increase the response rate. Of note, the observed response rate of patients with del(17p) was similar to that of patients without this adverse prognostic marker; in arm C, 60% of patients with del(17p) CLL had either a complete or partial response, while in the ITT population 70% of patients showed an overall response.

Overall, the regimen of navitoclax and rituximab was well tolerated, with the principal toxicities being dose-related thrombocytopenia, presumably due to inhibition of $BCLX_L$, and transient elevations in hepatic transaminases. Preliminary results indicate that a BH3-mimetic inhibitor of BCL2 could be highly effective when used in combination with rituximab for treatment of patients with CLL. Although the combination of ABT-263 and rituximab was deemed tolerable and offered a high response rate, the thrombocytopenia caused by $BCLX_L$ inhibition limited increases to optimize drug levels and complicated combinations with other drugs. At the same time, a highly selective BCL2 inhibitor, ABT-199, had been developed with very high affinity for BCL2 and effectively no $BCLX_L$ inhibition. This study provided additional data supporting the concept of BCL2 inhibition as an effective treatment approach for CLL and demonstrated that an increased response may be possible with a monoclonal antibody combination. Based on these promising data with navitoclax, clinical trials of ABT-199 alone and in combination with rituximab and obinutuzumab are ongoing to further explore the potential for BCL2-targeted therapy for patients with CLL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors wish to thank the patients and the investigators who participated in this study. We thank William Ho and Beiyao Zheng for contributions to the study at the time they were employed by Genentech. We also thank Surai Jones and Yuanyuan Xiao for additional statistical assistance. Writing assistance was provided by Genentech.

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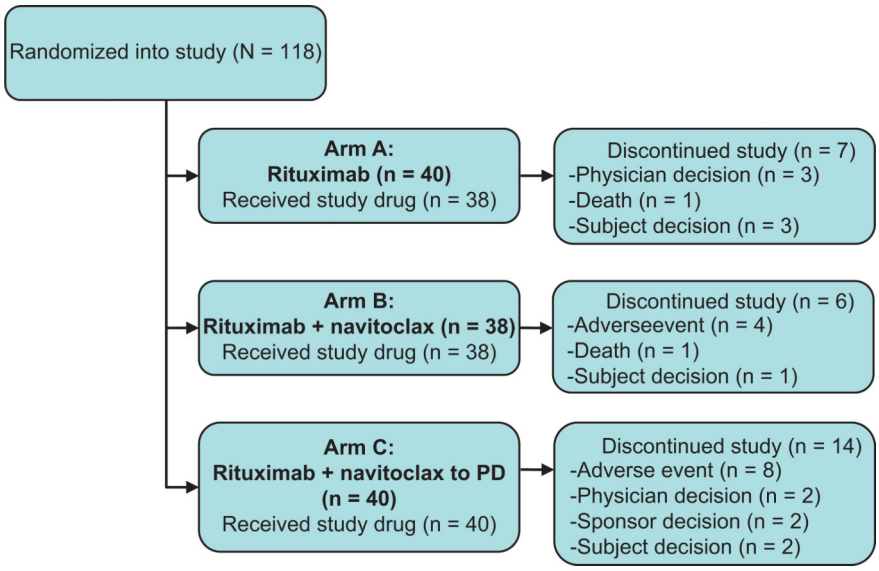
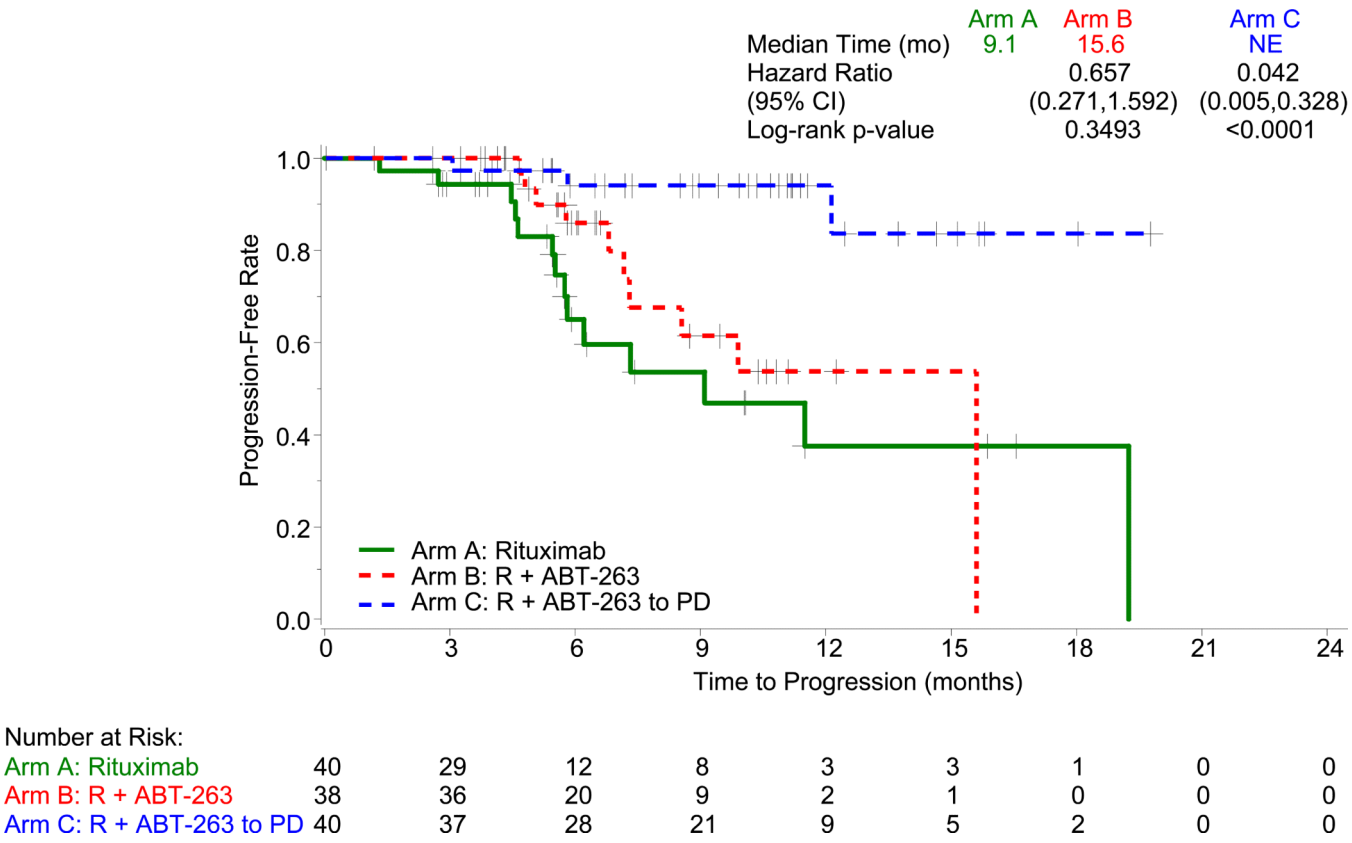


Figure 1.
Patient flow diagram.



Number at Risk:

Arm A: Rituximab	40	29	12	8	3	3	1	0	0
Arm B: R + ABT-263	38	36	20	9	2	1	0	0	0
Arm C: R + ABT-263 to PD	40	37	28	21	9	5	2	0	0

Figure 2.

Progression-free survival (PFS). Kaplan–Meir estimates of PFS after treatment in the three arms is shown. PFS was measured from the date of enrollment to the first date of documented relapsed or progressive disease (PD) or death related to any cause, whichever came first.

Table I

Patient demographics and disease characteristics.

Characteristic	Arm A: rituximab (*n* = 40)	Arm B: rituximab + ABT-263 (*n* = 38)	Arm C: rituximab + ABT-263 to PD (*n* = 40)	Total (*n* = 118)
Age in years, median (range)	65 (48-94)	62 (41-82)	63 (38-80)	63 (38-94)
Sex, *n* (%)				
Male	23 (58)	24 (63)	27 (68)	74 (63)
Female	17 (42)	14 (37)	13 (32)	44 (37)
Race, *n* (%)				
White	39 (98)	37 (97)	39 (98)	115 (97)
Country				
Australia	10 (25)	6 (16)	3 (8)	19 (16)
Brazil	0 (0)	0 (0)	3 (8)	3 (3)
France	1 (3)	0 (0)	0 (0)	1 (1)
Israel	1 (3)	0 (0)	2 (5)	3 (3)
Italy	0 (0)	0 (0)	1 (3)	1 (1)
Poland	1 (3)	3 (8)	6 (15)	10 (8)
Russia	0 (0)	2 (5)	0 (0)	2 (2)
Ukraine	13 (33)	14 (37)	14 (35)	41 (35)
United States	14 (35)	13 (34)	11 (28)	38 (32)
ECOG status ≤ 1, *n* (%)	37 (93)	36 (95)	39 (98)	112 (95)
Binet stage, *n* (%)				
A	22 (55)	16 (42)	15 (38)	53 (45)
B	15 (38)	16 (42)	21 (53)	52 (44)
C	3 (8)	6 (16)	4 (10)	13 (11)
Lymphocytes × 1000/mm^3, median (range)	47 (7-283)	84 (10-347)	54 (7-552)	53 (7-552)
Prognostic features				
Unmutated IgVH	13 (33)	8 (21)	16 (40)	37 (31)
FISH: del(17p)	11 (28)	12 (32)	10 (25)	33 (28)
FISH: del(11q)	11 (28)	11 (29)	15 (38)	37 (31)
FISH: + 12	8 (20)	5 (13)	6 (15)	19 (16)
FISH: del(13q)	21 (53)	22 (58)	21 (53)	64 (54)
CD38 (≥ 30%)	9 (23)	15 (39)	11 (28)	35 (30)
β_2-Microglobulin elevated > 2 × nl	29 (73)	34 (89)	33 (83)	96 (81)

ECOG, Eastern Cooperative Oncology Group; IgVH, immunoglobulin heavy chain variable gene; FISH, fluorescence *in situ* hybridization; nl, normal; PD, progressive disease.

Table II

Summary of adverse events.

Adverse event (AE)	Arm A: rituximab (*n* = 40)	Arm B: rituximab + ABT-263 (*n* = 38)	Arm C: rituximab + ABT-263 to PD (*n* = 40)
Any SAEs, *n* (%)	5 (13)	5 (13)	4 (10)
Any AEs, *n* (%)	33 (87)	37 (97)	40 (100)
AEs grade ≥ 3 occurring in > 5% of patients, *n* (%)			
Neutropenia	3 (8)	11 (29)	18 (45)
Thrombocytopenia	0 (0)	7 (18)	13 (33)
Anemia/worsening of anemia	2 (5)	2 (5)	1 (3)
Leukopenia	1 (3)	2 (5)	1 (3)
Liver enzyme increase	0 (0)	3 (8)	10 (25)
Hyperbilirubinemia	0 (0)	2 (5)	1 (3)
Diarrhea	0 (0)	2 (5)	1 (3)
GI and abdominal pain	0 (0)	0 (0)	2 (5)
Chills	0 (0)	2 (5)	1 (3)
Asthenia	0 (0)	2 (5)	0 (0)
Respiratory tract infection	3 (8)	1 (3)	1 (3)
Procedural complications (infusion-related reactions)	0 (0)	3 (8)	2 (5)
Vascular hypertensive disorders (hypertension)	0 (0)	2 (5)	1 (3)

SAE, serious adverse event; GI, gastrointestinal; PD, progressive disease.

Table III

Summary of PK parameters for navitoclax and rituximab concentration levels (pooled data from arms A and B)[*].

Navitoclax dose (visit)	*n*	T_{max} (h)	C_{max} (μg/mL)	AUC (h*μg/mL)
100 mg (lead-in day 5)	39	6.0 (3.6-8.0)	2.3 ± 0.9	10.5 ± 4.1
250 mg (week 8, day 1)	28	6.1 (2.0-8.0)	3.7 ± 2.0	61.2 ± 31.2

	Week 8 mean ± SD rituximab concentration (μg/mL)	
	Pre-infusion	Post-infusion
Arm A: rituximab	296 ± 175 (*n* = 33)	576 ± 264 (*n* = 33)
Arm B: rituximab + ABT-263	296 ± 100 (*n* = 33)	553 ± 145 (*n* = 31)
Arm C: rituximab + ABT-263 to PD	323 ± 116 (*n* = 35)	572 ± 161 (*n* = 31)

PK, pharmacokinetics; PD, progressive disease; T_{max}, time to maximum concentration; C_{max}, maximum concentration; AUC, area under the curve; SD, standard deviation.

[*] T_{max} presented as median (range); C_{max} and AUC as mean ± SD; AUC on lead-in day 5 is AUC(0-8 h) and on week 8, day 1 is AUC(0-24 h).

Table IV

Association of BCL2 protein expression with best response.

Biomarker	Response	Arm A (*n* = 24), *n* (%)	Arms B + C (*n* = 31), *n* (%)	Odds ratio
Low BCL2 protein	PR	6 (43%)	6 (43%)	1.0
	SD or PD	8 (57%)	8 (57%)	
High BCL2 protein	PR	3 (33%)	14 (82%)	10.89
	SD or PD	7 (66%)	3 (l8%)	

PR, partial response; SD, stable disease; PD, progressive disease.

Table V

Best response.

Assessment	Arm A: rituximab	Arm B: rituximab + ABT-263	Arm C: rituximab + ABT-263 to PD
ITT population, *n* (%)	*n* = 40	*n* = 38	*n* = 40
Overall response (PR + CR)* [95% CI (%)]	14 (35) [21, 52]	21 (55) [39, 71]	28 (70) [53, 82]
Complete response (CR)	0 (0)	0 (0)	2 (5)
Partial response (PR)	14 (35)	21 (55)	26 (65)
Stable disease	21 (53)	15 (40)	10 (25)
Progressive disease	2 (5)	0 (0)	0 (0)
Missing	3 (8)	2 (5)	2 (5)
Patients with del(17p)	*n* = 11	*n* = 12	*n* = 10
Overall response (PR + CR)* [95% CI (%)]	2 (18) [2, 52]	8 (67) [35, 90]	6 (60) [26, 88]
Complete response (CR)	0 (0)	0 (0)	1 (10)
Partial response (PR)	2 (18)	8 (67)	5 (50)
Stable disease	8 (73)	3 (25)	4 (40)
Progressive disease	1 (9)	0 (0)	0 (0)
Missing	0 (0)	1 (8)	0 (0)

ITT, intention to treat; CI, confidence interval; PD, progressive disease; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; CT, computed tomography; BM, bone marrow.

*Responses according to 2008 iwCLL criteria: required CT assessment, plus BM for CRs. All responses were confirmed with repeat assessment after ≥ 8 weeks.