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Phase 1 Study of the Safety, Pharmacokinetics, and Antitumour Activity of the BCL2 Inhibitor Navitoclax in Combination With Rituximab in Patients With Relapsed or Refractory CD20+ Lymphoid Malignancies

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Summary

The oral BCL2 inhibitor navitoclax has moderate single-agent efficacy in chronic lymphocytic leukaemia (CLL) and minor activity in lymphoma in Phase 1 trials. Navitoclax synergizes with rituximab in preclinical models of B-cell lymphoid cancers. We report the safety, pharmacokinetics, and clinical activity of this combination. Patients received navitoclax (200–325mg) daily and four standard weekly doses of rituximab. Twenty-nine patients were enrolled across three dose-escalation cohorts and a safety expansion cohort (250mg/day navitoclax). The combination was well tolerated. Common toxicities were mild diarrhoea (79%) and nausea (72%). Grade 4 thrombocytopenia occurred in 17% of patients (dose limiting at 325mg/day). CD19+ counts were severely reduced, while CD3+ cells (~20%), and serum immunoglobulin M levels (~33%) were also reduced during the first year. The maximum tolerated dose for navitoclax in combination was 250mg/day. Pharmacokinetic analyses revealed no apparent interactions between the drugs. The response rate in patients with follicular lymphoma was 9/12, including five complete responses. All five patients with CLL/SLL achieved partial responses. One of nine patients with aggressive lymphoma responded. The addition of rituximab to navitoclax 250mg/day is safe; the combination demonstrates higher response rates for low-grade lymphoid cancers than observed for either agent alone in previous Phase 1 trials.

Keywords

BCL2; navitoclax; rituximab; B-cell malignancy

Introduction

Evasion of apoptosis is a common property of a wide range of cancers (Hanahan & Weinberg, 2011). In many B-cell lymphoid malignancies, this evasion is mediated by overexpression of BCL2 (Kitada *et al*, 2002), which inhibits the activity of the intrinsic (mitochondrial) pathway to apoptosis (Adams & Cory, 1998; Kitada *et al*, 2002; Vaux *et al*, 1988). The small molecule navitoclax (originally known as ABT-263) was developed by structure–function design to inhibit BCL2 and two closely related proteins, BCL-xL and BCLw (Park *et al*, 2008). Navitoclax binds these cytoplasmic proteins in the “BH3-binding domain” with higher affinities than their natural inhibitory ligands, the BH3-only proteins. In doing so, navitoclax displaces the BH3-only protein BIM from BCL2, making it available to initiate apoptosis through activation of BAX and BAK on the outer mitochondrial membrane (Merino *et al*, 2012; Park *et al*, 2008).

In Phase 1 studies in patients with relapsed and/or refractory lymphoma (Wilson *et al*, 2010) or chronic lymphocytic leukaemia (CLL) (Roberts *et al*, 2012), oral daily administration of navitoclax, either continuously or on a 2-week-on and 1-week-off schedule, displayed clinically important antitumour activity in several B-cell lymphoid malignancies. An objective response rate (ORR) of 31% was observed for patients with CLL or small lymphocytic lymphoma (SLL), including those with del17p and resistance to fludarabine-based therapy (Roberts *et al*, 2012). Responses in patients with CLL/SLL were often

durable, with a median progression-free survival (PFS) of 25 months. Antitumour activity was also observed against follicular lymphoma (FL) but was less frequent, with six of 16 patients with FL demonstrating reduction in tumour burden radiologically but only one patient having a > 50% reduction (Wilson *et al*, 2010). Thrombocytopenia was the major dose-limiting toxicity (DLT) across the two studies (Roberts *et al*, 2012; Wilson *et al*, 2010). Navitoclax induced a highly predictable, dose-dependent acute fall in platelet counts in all patients due to its on-target activity against BCL-xL, which is required for the survival of platelets (Mason *et al*, 2007). Thrombocytopenia was a significant barrier to dose escalation in patients with impaired marrow function, either due to CLL infiltration or previous extensive cytotoxic therapy (Roberts *et al*, 2012).

We hypothesized that combination of navitoclax and another active agent with a different mechanism of action and nonoverlapping toxicity profile would deliver greater efficacy without significant additional toxicity. Rituximab has moderate single-agent activity against previously treated CLL/SLL (Nguyen *et al*, 1999; Winkler *et al*, 1999) and FL (Foran *et al*, 2000; McLaughlin *et al*, 1998), as well as other indolent B-cell lymphoid cancers (Foran *et al*, 2000). It improves response rates and both PFS and overall survival (OS) when combined with cytotoxic agents as compared with cytotoxic agents alone in patients with CLL (Hallek *et al*, 2010), FL (Hiddemann *et al*, 2005; Marcus *et al*, 2008), and diffuse large B-cell lymphoma (DLBCL) (Coiffier *et al*, 2002; Pfreundschuh *et al*, 2006). Unlike with navitoclax, thrombocytopenia is rarely seen with rituximab treatment (Rituxan[®], 2014).

Rituximab can induce death of CD20+ cells through several mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and direct induction of apoptosis (Cartron *et al*, 2004). Although the relative importance of each of these pathways in vivo remains uncertain, studies in patients with CLL treated with rituximab have shown a correlation with caspase (−9/−3) activation and the depletion of B lymphocytes (Byrd *et al*, 2002), linking efficacy of this agent to activation of the intrinsic apoptotic pathway. In vitro, rituximab-resistant lymphoma clones demonstrate upregulated expression of prosurvival BCL2 family members relative to wild-type cells and exhibit a higher degree of resistance to numerous chemotherapeutic agents (Jazirehi *et al*, 2007). Cutaneous B-cell lymphoma samples obtained after clinical relapse following rituximab treatment also exhibit a strong upregulation of BCL2 compared with before therapy (Wobser *et al*, 2007), potentially linking antiapoptotic BCL2 proteins to therapy resistance.

These data suggest that by lowering the apoptotic threshold, a BCL2 inhibitor may act synergistically with rituximab in a spectrum of B-cell malignancies. Consistent with these theoretical considerations, navitoclax increased antitumour activity when added to rituximab or rituximab-containing regimens in several murine preclinical models (Park *et al*, 2008). In the DoHH-2 xenograft model of DLBCL, neither navitoclax nor rituximab alone was able to achieve sustained tumour regression. However, the combination of navitoclax and rituximab achieved complete responses (CRs) in 70% of animals (Park *et al*, 2008).

Based on the rationale of anticipated synergistic efficacy and nonoverlapping toxicity, a Phase 1b study of rituximab in combination with navitoclax was initiated for patients with relapsed or refractory CD20+ lymphoid malignancies.

Methods

Study Design

Study M10-166 (ClinicalTrials.gov identifier: NCT00788684) was an open-label, multicentre, dose-escalation Phase 1b study of navitoclax in combination with four weekly doses of rituximab in patients with CD20+ lymphoproliferative disorders. The study comprised a navitoclax dose-escalation phase, a safety expansion phase following definition of the maximum tolerated dose (MTD) for navitoclax, and an extension phase (Fig 1). The primary objectives were to assess the safety profile of the combination, to characterize the pharmacokinetics of each drug when used together, and to determine the MTD of navitoclax and a recommended dose and schedule for Phase 2 assessment when used in combination with rituximab. The secondary objectives were to evaluate preliminary data regarding ORR, PFS, duration of response, and OS when navitoclax was administered in combination with rituximab. The study enrolled patients between July 2009 and November 2010 and concluded 1 year after the last patient was enrolled. At that time, patients continuing to benefit from ongoing navitoclax were able to continue this therapy in an extension study. The aims of the extension study were to define the safety of navitoclax and to continue to evaluate the efficacy measures included in the main study. The data cutoffs for this report were August 2014 for safety and November 2012 for efficacy.

The study was conducted according to the Declaration of Helsinki and relevant International Conference on Harmonisation Good Clinical Practice guidelines, and with approval from the local Institutional Review Board, Independent Ethics Committee, or Research Ethics Board of all participating study sites. All participants provided written and dated informed consent before participating in this study.

Patients

Patients with a histologically documented diagnosis of a CD20+ lymphoproliferative disorder (World Health Organization classification) requiring further treatment were considered eligible if they: (1) provided written informed consent, (2) were 18 years of age, (3) had bidimensionally measurable disease with at least one lesion 1.0 cm, (4) had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, (5) had adequate bone marrow function (absolute neutrophil count $1.0 \times 10^9/L$; platelet count $100 \times 10^9/L$; haemoglobin concentration 90 g/L), (6) had adequate renal (serum creatinine 2.0mg/dL or calculated creatinine clearance 50 mL/min) and hepatic function (aspartate aminotransferase and alanine aminotransferase $3.0 \times$ upper limit of normal [ULN]; bilirubin $1.5 \times$ ULN), (7) had normal coagulation (activated partial thromboplastin time and prothrombin time $1.2 \times$ ULN), and did not meet any exclusion criteria. Patients with a history of autologous bone marrow transplant had to be > 6 months posttransplant and have absolute neutrophil count $1.5 \times 10^9/L$ and platelet count $125 \times 10^9/L$ unsupported by

growth factors (which were otherwise allowed if there was > 80% disease infiltration of the bone marrow).

Patients were excluded if any of the following applied: (1) a history of immune thrombocytopenia, (2) known refractoriness to platelet transfusions in the preceding year, (3) ongoing use of an antiplatelet agent or anticoagulant therapy (with the exception of low-dose anticoagulation medications used to maintain the patency of a central venous catheter), (4) current bleeding or history of active peptic ulcer disease or erosive gastritis/oesophagitis, (5) active infection, (6) history of significant cardiovascular disease (e.g., myocardial infarction, thrombotic or thromboembolic event in the last 6 months), (7) current pregnancy or breast-feeding, or (8) previous allogeneic stem cell transplantation. Patients could not have received any chemotherapy, immunotherapy, radiotherapy, hormonal therapy, or investigational therapy within 14 days, or monoclonal antibody therapy within 30 days, of the first dose of navitoclax.

Treatment

Navitoclax—All patients received a 7-day lead-in course of navitoclax 150mg/day (Week 0) and then increased to the cohort dose on Day 2 of Week 1 if their platelet count exceeded $50 \times 10^9/L$. Patients were assigned sequentially to navitoclax dose-escalation cohorts of three or more patients; 200mg, 250mg, and 325mg dose levels were studied with this schedule. Patients continued daily navitoclax treatment as long as there was clinical benefit in the absence of prohibitive toxicity or progressive disease. Dose reductions were allowed for toxicity.

Rituximab—Four doses of rituximab $375\text{mg}/\text{m}^2$ were administered by standard intravenous infusion on a weekly basis to all patients, commencing on Week 1 Day 1, the day before navitoclax escalation to the designated cohort dose. On days when rituximab was administered, navitoclax was taken 1 hour after commencement of the rituximab infusion.

Patients received prophylaxis against tumour lysis, premedication before rituximab, and supportive care as per standard institutional practices.

Dose Escalation

The first dose level studied was 200mg/day, being the highest dose cleared at that time in the two concurrent Phase 1 studies of navitoclax monotherapy in patients with lymphoma or CLL (Roberts *et al*, 2012; Wilson *et al*, 2010). Dose escalation of 25% to 40% was planned for subsequent cohorts after a minimum of three patients had completed 4 weeks of combined treatment without experiencing a DLT. If one of three patients at any dose level experienced a DLT, a minimum of six patients were planned for enrollment at that dose level. If at least 2/3 or 2/6 patients at a dose level experienced a DLT, then the MTD was considered exceeded. The MTD was defined as the highest dose level at which <33% of patients experience a DLT during the lead-in phase and the first 4 weeks of combined therapy.

Study Assessments

Safety—Safety assessments included medical history, physical examination, vital signs, ECOG performance status, 12-lead electrocardiogram, echocardiogram, blood chemistry, haematology, urinalysis, platelet count, and lymphocyte subset enumeration. In general, safety assessments were performed at screening, weekly during the lead-in and combined therapy periods, and then monthly. Echocardiograms were performed every 6 weeks, approximately 6 hours after dosing. Platelet counts were monitored daily or every other day during the first 2 weeks of navitoclax dosing.

Adverse event (AE) severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 (NCI CTCAE) (Cancer Therapy Evaluation Program, 2006). AEs that were judged possibly or probably related to the study drugs were considered to be DLTs if they satisfied any of the following criteria: grade 4 thrombocytopenia (platelet count $< 25 \times 10^9/L$), grade 2 bleeding associated with thrombocytopenia, or all other grade 3 AEs with certain protocol-defined exceptions (grade 3 or 4 leukopenia or lymphopenia; grade 3 thrombocytopenia or neutropenia; grade 4 neutropenia without fever, if lasting < 7 days; grade 3 infusion reactions). Each DLT required interruption and possible discontinuation of navitoclax and rituximab if during the combined therapy phase. Navitoclax could be reintroduced at a reduced dose providing toxicity grades resolved to grade 1 or to baseline if grade 2 at study entry. Following a DLT of thrombocytopenia, navitoclax could be reintroduced at a reduced dose if the platelet count returned to $50 \times 10^9/L$ (grade 2 toxicity).

Pharmacokinetics—Plasma samples for navitoclax assay were collected on Week 1 Day 2 at 0 (predose), 2, 4, 6, 8, and 24 hours. Serum samples for rituximab were collected on Week 1 Day 1 (before and immediately following first rituximab infusion), Week 4 Day 1 (before and immediately following fourth rituximab infusion), Week 5 Day 1 (1 week after fourth infusion), Week 8 Day 1 (1 month after fourth infusion), and Week 17 Day 1 (3 months after fourth infusion). Plasma concentrations of navitoclax were determined using a validated liquid chromatography method with tandem mass spectrometric detection. Serum concentrations of rituximab were determined using a validated sandwich enzyme-linked immunosorbent assay method. Pharmacokinetic parameters of navitoclax and rituximab were estimated using noncompartmental methods with Phoenix[®] WinNonlin[®]-Professional[™], version 6.2 (Pharsight Corporation, Mountain View, CA).

Efficacy—Exploratory efficacy endpoints included ORR, PFS, and OS, and analysis by tumour type was planned. ORR was evaluated using clinical, computed tomography, and as appropriate, blood count and bone marrow biopsy data according to International Working Group criteria for patients with lymphoma (Cheson *et al*, 1999) or the 2008 International Workshop on Chronic Lymphocytic Leukaemia update of the National Cancer Institute-Working Group for patients with CLL (Hallek *et al*, 2008). Responses were assessed while patients continued treatment with navitoclax.

Statistical Analysis

Safety data were summarized by navitoclax dose level. Descriptive statistics such as medians, standard errors, and ranges for continuous parameters were calculated, as well as frequencies and percentages for categorical parameters. Summary statistics including the mean and standard deviation were calculated for each parameter. Time-to-event analyses used the method of Kaplan and Meier. Comparisons between baseline and later timepoints for immune parameters were performed by one way analysis of variance followed by Dunnett's test for multiple comparisons. The specific tests used are stated in the text or the relevant figure legends.

Results

Patient Characteristics

Twenty-nine patients enrolled in this trial (Table I). FL represented the largest subgroup of CD20+ disease with 12 patients, followed by aggressive lymphomas (DLBCL, transformed SLL, mantle cell lymphoma, lymphoblastic lymphoma) with nine and CLL/SLL with five. All patients were navitoclax naive and 23 had prior exposure to rituximab-containing regimens. Eight were considered to have rituximab-refractory disease having failed to respond or progressed within 6 months of their most recent rituximab-containing regimen (four with aggressive lymphoma and two each with FL or CLL/SLL). Six patients had undergone prior autologous stem cell transplantation, four had received radioconjugated antibody therapies, and seven had previous exposure to other investigational therapies. Thirteen patients had achieved at least a partial response (PR) to their last treatment regimen, seven had stable disease, while nine had progressed without response.

A significant proportion of the patients were heavily immunocompromised at study entry: seven (24%) had peripheral blood (PB) CD3 T-cell counts < 500/ μ L, eight (28%) had PB CD4 counts < 300/ μ L, nine (31%) were hypogammaglobulinaemic, and 20/24 (83%) non-CLL/SLL patients had PB CD19+ B-cell counts < 100/ μ L.

Patient Flow/Disposition

Fourteen patients were treated in three dose-escalation cohorts of 200mg, 250mg, and 325mg, and 15 patients were treated in the safety expansion phase (Fig 1B). The median duration on study was 170 days (range, 1–1826+). At data cutoff, 26 had discontinued treatment, with the majority ($n = 17$) ceasing because of progressive disease after a median of 108 days (range, 12–743) on treatment. Seven patients did not complete all four doses of rituximab (progressive disease, $n=5$; DLT before starting rituximab, $n=1$; withdrawal of consent, $n=1$). Three patients remained on navitoclax in the extension study at the safety data cutoff, 46 to 60 months from study entry.

Pharmacokinetics

Table II presents the pharmacokinetic profile of navitoclax on the day after the first rituximab infusion (Week 1 Day 2). Maximum concentrations ($C_{\max}$) were observed approximately 6 to 7 hours postdose. Navitoclax exposure ($C_{\max}$ and area under the curve) observed in this combination study was comparable with that observed in the monotherapy

Phase 1/2a study of navitoclax in patients with relapsed or refractory lymphoid malignancies (Wilson *et al*, 2010), indicating that rituximab did not affect navitoclax pharmacokinetics. Serum concentrations of rituximab following the first infusion through 3 months posttreatment are also presented in Table II. The serum concentrations of rituximab were comparable with the values reported in the literature for single-agent treatment (Berinstein *et al*, 1998; Iacona *et al*, 2000). Overall, the results indicated that there was no apparent pharmacokinetic interaction between navitoclax and rituximab.

Toxicity

Toxicities defined by the protocol as dose limiting (i.e., from the commencement of navitoclax to the completion of four doses of rituximab during combined therapy) were observed in five patients. Two of three patients treated with 325mg navitoclax daily experienced DLTs (grade 3 fatigue, grade 4 thrombocytopenia), while only one of seven patients treated with 250mg daily experienced a DLT (grade 3 diarrhoea); therefore, 250mg daily was considered the MTD. Subsequently during the safety expansion phase, two of 15 patients treated with 250mg daily experienced DLTs (grade 3 hypoadrenalism, grade 3 elevation of alanine transaminase).

Treatment was generally well tolerated. Table III summarizes the emergent toxicities of any grade experienced in 15% of patients, by system and grade, regardless of causality. The most common toxicities were mild diarrhoea, nausea, and fatigue. Grade 3 or 4 toxicities of note were neutropenia ($n = 8$, including febrile neutropenia), thrombocytopenia ($n = 5$), and abnormal liver function tests ($n = 4$). Two patients experienced febrile neutropenia, and one patient developed separate episodes of *Escherichia coli* and *Pseudomonas* sepsis during neutropenia. Thirty-seven episodes of infection were recorded in 15 patients (Table IIIB). The exposure-adjusted average rate of infection was 0.14 per patient-year for grade 3 infections, and 1.3 per patient-year for all infections. Serious adverse events are presented in the supplementary table (Supporting information). Twelve patients (41%) required reduction in navitoclax dosing during the study, with neutropenia, thrombocytopenia, and diarrhoea being the main reasons for reduction.

Peripheral blood CD3+ cell counts declined to approximately 80% of baseline within two weeks of initiation of navitoclax, as did CD4+ cell counts, and remained stable while patients remained on study drug (Fig 2A). PB CD19+ B-cell counts in non-CLL/SLL patients fell to zero after two weeks on study (i.e., after two weeks of navitoclax and a single dose of rituximab), and remained essentially undetectable for the duration of the study in most patients. Serum immunoglobulin (Ig) G and IgA levels were not significantly reduced compared with baseline during combined therapy or ongoing navitoclax (Fig 2B), but IgM levels were reduced by approximately one third at four months and remained suppressed during ongoing therapy.

Efficacy

Objective responses were observed at all dose levels studied, and so are reported in aggregate. Sixteen of 29 (55%) patients achieved an objective response (Table IV). The combination induced responses in patients with indolent CD20+ lymphoproliferative

diseases predominantly, but no responses were seen in patients with mantle cell lymphoma, transformed FL, or lymphoblastic lymphoma, and in only one patient with relapsed DLBCL. Although all patients with CLL/SLL achieved a response, no CRs were observed. The ORR in patients with FL was 9/12 (75%), with five CRs (42%). The combination was active in the four patients with rituximab-refractory CLL/SLL or FL, with partial responses observed in all, but not in the remaining four rituximab-refractory patients who had aggressive lymphomas, where no responses were achieved. The median PFS for the whole group was 11 months (range, 0–36+), and the median duration of response was 10 months (range, 1.5–29+). Too few deaths have been documented to provide any survival estimate.

Discussion

This trial was conducted to determine whether it is feasible to combine the BH3-mimetic BCL2 inhibitor navitoclax with the anti-CD20 monoclonal antibody rituximab. Overall, the data confirm that addition of four weekly doses of rituximab to navitoclax at the recommended Phase 2 dose of 250mg/day is deliverable to patients with relapsed CD20+ lymphoid malignancies. There was no apparent pharmacokinetic interaction between navitoclax and rituximab observed in this study. The exposures of rituximab and navitoclax following combination treatment were comparable with that observed in monotherapy studies of each drug (Berinstein *et al*, 1998; Iacona *et al*, 2000; Wilson *et al*, 2010).

Navitoclax induced reductions in platelet counts in all patients consistent with its action to inhibit BCL-xL and thereby reduce the platelet survival. Grade 4 thrombocytopenia was observed in five patients over the duration of the trial. However, there were no instances of clinically important bleeding. The most common patient-relevant AEs were infections. These were minor in the majority of instances, although two episodes of gram-negative sepsis were observed in association with neutropenia. Opportunistic infections such as invasive fungal infections, disseminated viral infections, and atypical organism infections were not observed in this group of heavily pretreated patients, suggesting that the combination and ongoing use of navitoclax did not substantially diminish clinically relevant immune function.

Circulating T- and B-cell numbers were reduced congruent with the mechanism of action of each drug. Combined BCL2 and BCL-xL inhibition results in depletion of immature and mature peripheral T and B cells in murine models (Khaw *et al*, 2014). While navitoclax induced a mean 20% reduction in PB CD3 cells in patients in the lymphoma Phase 1 trial (Wilson *et al*, 2010), lymphopenia was uncommon with navitoclax monotherapy in patients with relapsed small-cell lung cancer (Gandhi *et al*, 2011; Rudin *et al*, 2012). In the current trial, combination therapy was associated with a very similar reduction in circulating CD3 and CD4 cells to that observed for navitoclax alone in lymphoma patients (Wilson *et al*, 2010).

As expected given the experience with rituximab monotherapy, PB CD19+ cells in lymphoma patients (CLL patients were excluded) were dramatically reduced within two months and remained undetectable in the majority of patients for the duration of the study. Serum IgG and IgA levels remained stable, while IgM levels fell by approximately 25% and

remained low throughout the study. Whether ongoing treatment with navitoclax slows the recovery of mature B cells and IgM production following rituximab-induced reductions cannot be determined in this study given its single-arm design.

The combination showed substantial efficacy in patients with indolent CD20+ lymphoproliferative malignancies, despite extensive prior treatment and rituximab resistance in four responding patients. The 75% response rate in 12 patients with FL, with five (42%) CRs, compares very favourably with the results observed in the navitoclax Phase 1 monotherapy study where only one of 11 patients treated with > 200mg/day achieved > 50% reduction in nodal size on CT evaluation. Similarly, while aware of the small numbers treated, the 100% response rate in five CLL/SLL patients compares favourably with the 8/17 (47%) response rate observed in patients receiving 200mg/day of navitoclax in the CLL Phase 1 monotherapy trial. Recognizing the caveats about comparisons across early-phase trials and varied dosing regimens and the limited follow-up data from this trial, conclusions cannot be drawn about superiority without a randomised trial. Nonetheless, the apparent pattern of more frequent and deeper responses in patients with FL is similar to that seen when rituximab was added to cytotoxic regimens such as cyclophosphamide, vincristine, and prednisone (Coiffier *et al*, 2002) and cyclophosphamide, doxorubicin, vincristine, and prednisone (Marcus *et al*, 2008). In contrast to the observed efficacy in indolent CD20+ lymphoid malignancies, the combination of navitoclax and rituximab demonstrated minimal efficacy in the small number of patients with aggressive lymphomas evaluated. Finally, emerging preliminary data with the BCL2-selective BH3 mimetic venetoclax (ABT-199) indicate high response rates, including CRs in heavily pretreated patients with CLL and follicular lymphoma, reinforce the potential of BCL2 inhibitors to advance care for patients with these diseases (Anderson *et al*, 2014).

We conclude that the recommended Phase 2 dose for navitoclax when combined with rituximab is 250mg/day. This regimen has been incorporated as an investigational arm in a recently completed randomized Phase 2 trial in patients with CLL (clinical trial identifier: NCT01557777).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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A. **B.** **Fig 1.**

(A) Schema of treatment. Navitoclax was initiated at 150mg on Week 0 Day 1, and rituximab 375mg/m² was initiated on Week 1 Day 1, on the day before navitoclax increase to the designated cohort dose. Four doses of rituximab were given at weekly intervals. Navitoclax continued until off study or interrupted because of toxicity. (B) Flow of patients into trial, number of DLTs, and patient disposition at end of study. DLT, dose-limiting toxicity.

Fig 2.

(A) Percent change from baseline in PB CD3+ (left), CD4+ (middle), and CD19+ cells (right) during first year of the trial. Mean $\pm$ SD of data available from 8–29 patients at each time point. For CD19+ cells, data from CLL patients have been excluded. (B) Percent change from baseline in serum IgG (left), IgA (middle), and IgM (right) concentrations during first year of the trial. Mean $\pm$ SD of data available from 6–29 patients at each time point. IgM data for patients with an IgM paraprotein at baseline have been excluded. ANOVA, analysis of variance; CLL, chronic lymphocytic leukaemia; Ig, immunoglobulin; PB, peripheral blood. * $P < 0.05$ for comparison with baseline (ANOVA, followed by Dunnett's test for multiple comparisons).

Table I

Patient Characteristics

Characteristic, n (%)	Patients (N=29)
Age	
Median (range), y	60 (35–92)
< 60	13 (45%)
60	16 (55%)
Sex	
Male	17 (59%)
Female	12 (41%)
ECOG performance status	
0	15 (52%)
1	14 (48%)
Diagnosis	
Follicular lymphoma	12 (41%)
Aggressive lymphomas	9 (31%)
Diffuse large B-cell lymphoma	6 (21%)
Transformed SLL, mantle cell, lymphoblastic	3 (10%)
CLL/SLL	5 (17%)
Other lymphomas	3 (10%)
Hodgkin lymphoma	1 (3%)
Lymphoplasmacytic lymphoma	2 (7%)
Prior systemic therapies	
Median (range)	3 (1–8)
Autologous stem cell transplant	6 (21%)

CLL, chronic lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group; SLL, small lymphocytic lymphoma.

Table II

Pharmacokinetic Parameters of Navitoclax After Oral Administration and Serum Concentrations of Rituximab Following Intravenous Infusion

A.				
Dose	N	Navitoclax (Week 1 Day 2)		
		t_{max}, h	C_{max}, µg/mL	AUC₂₄, µg•h/mL
200mg	4	6.5 ± 1.0	3.35 ± 1.45	46.4 ± 16.2
250mg	20	7.5 ± 4.3	3.70 ± 1.36	59.1 ± 24.2
325mg	3	5.5 ± 2.8	3.94 ± 1.55	57.8 ± 26.2
All doses	27	7.1 ± 3.9	--	--

B.		
Time point	N	Rituximab Serum Concentration, µg/mL
After first infusion	27	220 ± 69.4
Before fourth infusion	23	178 ± 63.0
After fourth infusion	22	387 ± 104
1 week posttreatment	20	240 ± 77.8
1 month posttreatment	18	107 ± 52.1
3 month posttreatment	10	30.8 ± 38.2

A. Mean ± SD pharmacokinetic parameters for navitoclax. B. Mean ± SD serum concentrations of rituximab following first, third, and fourth infusions. Postinfusion samples were taken immediately after completion of the infusion. AUC₂₄, area under the curve from time zero to 24 h; C_{max}, maximum plasma concentration; t_{max}, time to C_{max}.

Table III**Adverse Events**

A. All Emergent Adverse Events Observed in 15% of Patients					
System	Adverse Event	n%	Grade 1	Grade 2	Grade 3 4
Gastro-intestinal	Diarrhoea	23 (79)	13	8	2 0
	Nausea	21 (72)	15	5	1 0
	Decreased appetite	7 (24)	6	0	1 0
	Constipation	6 (21)	4	2	0 0
	Vomiting	5 (17)	5	0	0 0
	Flatulence	5 (17)	5	0	0 0
General	Fatigue	15 (52)	8	4	3 0
	Headache	7 (24)	7	0	0 0
	Chills	6 (21)	4	2	0 0
Blood	Neutropenia	8 (28)	0	0	3 5
	Thrombocytopenia	6 (21)	0	1	0 5
Respiratory	Cough	8 (28)	4	4	0 0
	Upper RTI	6 (21)	2	4	0 0
Pain	Back pain	6 (21)	4	0	2 0
Other	Elevated ALT	6 (21)	2	2	2 0
	Hypokalaemia	5 (17)	3	1	1 0
B. Infectious Adverse Events in All Patients					
Upper respiratory tract	Upper RTI	6 (21)	2	4	0 0
	Nasopharyngitis	2 (6)	2	0	0 0
	Sinusitis	2 (6)	0	1	1 0
Lower respiratory tract	Lower RTI	2 (6)	0	2	0 0
	Bronchitis	2 (7)	0	2	0 0
	Influenza	1 (3)	1	0	0 0

B. Infectious Adverse Events in All Patients									
Ear	Ear infection	1 (3)	0	1	0	0			
	Labyrinthitis	1 (3)	0	1	0	0			
Urinary	Urinary tract infection	3 (10)	1	2	0	0			
	Cystitis	1 (3)	1	0	0	0			
Gastro-enterological	Campylobacter enteritis	2 (6)	0	1	1	0			
	Gastroenteritis	1 (3)	1	0	0	0			
Skin/Mucosa	Oral candidiasis	2 (6)	1	1	0	0			
	Zoster	2 (6)	1	1	0	0			
	Fungal skin infection	1 (3)	1	0	0	0			
	Herpes simplex labialis	1 (3)	1	0	0	0			
	Molluscum contagiosum	1 (3)	0	1	0	0			
	Gingivitis	1 (3)	1	0	0	0			
	Paronychia	1 (3)	1	0	0	0			
	Cellulitis	1 (3)	0	1	0	0			
Neutropenic	<i>Escherichia coli</i>	1 (3)	0	0	1	0			
Sepsis	<i>Pseudomonas</i>	1 (3)	0	0	1	0			
General									
	Viral infection	1 (3)	0	1	0	0			

RTI, respiratory tract infection; ALT, alanine aminotransferase.

Table IV

Summary of Responses

	CLL/SLL (<i>n</i> = 5)	Follicular (<i>n</i> = 12)	Aggressive ^{<i>a</i>} (<i>n</i> = 9)	Other ^{<i>b</i>} (<i>n</i> = 3)
CR	0	5	1	0
PR	5 ^{<i>c</i>}	4	0	1
Overall response	5 (100%)	9 (75%)	1 (11%)	1 (33%)

CLL, chronic lymphocytic leukaemia; CR, complete response; PR, partial response; SLL, small lymphocytic lymphoma.

^{*a*}CR in one patient (of six) with diffuse large B-cell lymphoma.

^{*b*}PR in patient (one of two) with lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia.

^{*c*}Confirmed by follow-up assessments 2–3 months later in four patients; unconfirmed in one patient.