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Title: Prospective multicentre phase II study of voxtalisib (XL765) in patients with relapsed or refractory non-Hodgkin lymphoma or chronic lymphocytic leukaemia


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Research in context

Evidence before this study

Constitutive activation of the phosphoinositide 3-kinase (PI3K) pathway is nearly universal in B-cell malignancies including lymphoma and chronic lymphocytic leukaemia (CLL). PI3Kδ-specific inhibitors, pan-PI3K inhibitors and mammalian target of rapamycin (mTOR) inhibitors have all shown clinical activity in B-cell malignancies. Pubmed was searched for applicable clinical and preclinical studies of PI3K pathway inhibitors in lymphoma and CLL. Preclinical data suggest that inhibition of both PI3Kα and PI3Kδ may lead to more complete inhibition of the PI3K pathway, and that concurrent inhibition of mTOR and PI3K may increase antitumour activity, providing rationale for investigating pan-PI3K/mTOR inhibitors in lymphoma and CLL. Voxtalisib (SAR245409, XL765) is a reversible, potent inhibitor of all four class I PI3Ks and a weaker inhibitor of mTOR. Voxtalisib’s impact on the PI3K/mTOR pathway, cell proliferation and apoptosis was documented in serial biopsies obtained from patients with lymphoma in prior studies. In a phase I, first-in-human trial in solid tumours, voxtalisib monotherapy showed clinical activity and an acceptable safety profile. Preliminary clinical activity was also observed in a phase I MTD-expansion cohort performed in 16 patients with relapsed/refractory lymphoma.

Added value of this study

This phase II study (NCT01403636) investigated voxtalisib in patients with relapsed/refractory lymphoma or CLL/small lymphocytic leukaemia (SLL). Single-agent voxtalisib (50 mg twice daily) had an acceptable safety profile in patients with lymphoma and CLL/SLL. Efficacy of single-agent voxtalisib was limited in patients with mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL) or CLL/SLL; however, voxtalisib showed efficacy in the follicular lymphoma group, with an ORR of 41.3% (19 patients out of 46), complete response rate of 10.9% (5 patients) and median progression-free survival (PFS) of 58.0 weeks (95% CI 26.0 to not calculated). These findings compare favourably, particularly for complete response rate, to those reported with the PI3Kδ inhibitor idelalisib, which had a 47% ORR, 1.6% complete response rate and PFS of 8 months in its original phase I study.
Implications of all the available evidence

The observed activity of voxtalisib in relapsed/refractory follicular lymphoma, notable for inducing 11% complete responses, warrants further studies. Voxtalisib showed no pharmacodynamic impact on cytokine/chemokine levels in patients with CLL/SLL, despite its strong proapoptotic activity in vitro. Insufficient exposure of voxtalisib may have led to limited PI3Kδ inhibition in patients with CLL, and may explain the limited antitumour activity observed in this patient subgroup as well as the MCL and DLBCL subgroups. Consistent with previous studies, molecular analyses indicated that responses were independent of mTOR/PI3K pathway alterations, which may be because the pathway is constitutively activated in most lymphomas independent of molecular alterations.
Abstract [MAX 250 words, currently 248]

Background
The aim of this phase II trial was to investigate the efficacy and safety of voxtalisib (SAR245409), a pan-phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) (PI3K/mTOR) inhibitor, in patients with relapsed or refractory lymphoma, or chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL).

Methods
Patients with relapsed or refractory mantle cell lymphoma (MCL), follicular lymphoma, diffuse large B-cell lymphoma (DLBCL) or CLL/SLL were treated with voxtalisib 50 mg twice daily (BID) until progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR). Secondary endpoints included safety and progression-free survival (PFS). Molecular profiling of lymphoma tissue and CLL cells was performed. This study is registered with ClinicalTrials.gov, number NCT01403636, and has been completed.

Findings
One hundred sixty-seven patients were enrolled (42 with MCL, 47 with follicular lymphoma, 42 with DLBCL and 36 with CLL/SLL). The median number of prior anticancer regimens was three (IRQ 2–4). Of 164 patients evaluable for efficacy, 30 patients achieved a partial (n=22) or complete response (n=8) (ORR 18.3%; 41.3% [19/46] in follicular lymphoma, 11.9% [5/42] in MCL, 4.9% [2/41] in DLBCL and 11.4% [4/35] in CLL/SLL). The safety profile was consistent with previous studies of voxtalisib. The most frequently reported adverse events were diarrhoea (35.3%, in 59 of 167 patients), fatigue (31.7%, in 53 patients), nausea (26.9%, in 45 patients) and pyrexia (26.3%, in 44 patients). The most frequently reported grade ≥3 adverse events were anaemia (12.0%, in 20 patients), pneumonia (8.4%, in 14 patients) and thrombocytopenia (7.8%, in 13 patients). Serious adverse events occurred in 97 of 167 patients (58.1%).

Interpretation
Voxtalisib 50 mg BID had an acceptable safety profile, with encouraging efficacy in patients with follicular lymphoma and limited efficacy in patients with MCL, DLBCL or CLL/SLL.

Funding
This study was funded by Sanofi.
Introduction

Although recent advances in chemoimmunotherapy have improved the prognosis of B-cell non-Hodgkin’s lymphoma (NHL) and chronic lymphocytic leukaemia (CLL), relapsed/refractory disease still carries a poor prognosis. Multiple targeted therapies are in development for these diseases, including agents targeting the phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR)-signalling pathway. While constitutive activation of the PI3K pathway is nearly universal in B-cell malignancies, activating molecular alterations of the PI3K pathway are relatively rare. \textit{PIK3CA} is mutated in only 8\% of patients with DLBCL, and rare in CLL, with \textit{PIK3CA} amplification detected in only 6\% of CLL patients, but in 68\% of mantle cell lymphoma (MCL) patients. Phosphatase and tensin homolog (PTEN) loss has been reported in 14–55\% of diffuse large B-cell lymphoma (DLBCL), 21\% of follicular lymphoma, and 16\% of MCL patients.

Idelalisib (GS-1101, CAL-101), a PI3K\(\delta\) isoform-selective inhibitor, is FDA approved for the treatment of follicular lymphoma patients who relapsed after \(\geq 2\) prior therapies, or in combination with rituximab in relapsed patients with CLL. In patients with relapsed CLL, adding idelalisib to rituximab increased the progression-free survival (PFS) compared with rituximab alone (median 19.4 vs 7.3 months despite crossover; p<0.0001) in a heavily pretreated patient population, approximately half of whom had 17p deletion. In a phase II study of idelalisib monotherapy in refractory indolent B-cell NHL, the ORR was 57\%.

Preclinical evidence suggests that targeting more than one isoform of PI3K may increase antitumour activity in B-cell lymphoma and CLL. In MCL cell lines, concurrent inhibition of PI3K\(\alpha\) and PI3K\(\delta\) is required to abolish constitutive PI3K activation, and is more effective than PI3K\(\delta\) inhibition alone, especially in tumour samples taken at relapse. Preclinical data also suggest that concurrent inhibition of mTOR and PI3K may increase antitumour activity, as inhibition of mTOR leads to paradoxical activation of PI3K via release of a negative feedback control loop.

Voxtalisib (SAR245409, XL765) is a reversible, potent inhibitor of all four class I PI3Ks and a weaker inhibitor of mTOR. Voxtalisib is highly selective, with no cross-reactive inhibitory activity in a panel of 130 protein kinases at concentrations below 1·5 mM. In patient-derived primary CLL cells, voxtalisib led to caspase-dependent apoptosis in unstimulated primary CLL cells with an IC\(_{50}\) value of 0·86 \(\mu\)M, with a maximum impact
at 48h. In addition, voxtalisib blocked CLL cell adhesion, proliferation and survival *in vitro* and was also a potent inhibitor of T-cell-mediated production of cytokines, which support CLL survival.\textsuperscript{14}

Voxtalisib’s pharmacological properties were documented in serial biopsy samples from patients with lymphoma enrolled on prior studies.\textsuperscript{16–18} In a MCL patient with a partial response after two cycles who remained on study for 29 cycles, inhibition of PI3K, mTORC1 and mTORC2 pathways was evident after two cycles, with decreases of 73\% in pAKT(S4730), 88\% in pAKT(T308) and 60\% in p4EBP1(T70), which coincided with near-complete inhibition of proliferation.\textsuperscript{18} In patients with recurrent glioblastoma enrolled on a pharmacokinetic/pharmacodynamic study, treatment with voxtalisib at 90 mg once daily for at least 10 days led to a median maximal intratumoural concentration of 170 nM in surgically accessible recurrent tumour tissue (n=6)\textsuperscript{16} (Kubek et al. submitted). Pathway inhibition correlating with impaired tumour cell proliferation was observed in 3/6 patients with recurrent glioblastoma treated with voxtalisib 50 mg twice daily (BID) and in 5/7 patients treated with voxtalisib 90 mg daily, with inhibition documented downstream of mTORC1, on pS6RP(S235/236), pS6K1(T389) and p4EBP1(T37/46), and downstream of mTORC2 on pPRAS40(T246).

In a phase I, first-in-human trial in solid tumours, voxtalisib monotherapy showed an acceptable safety profile, with a maximum tolerated dose (MTD) of voxtalisib capsules of 50 mg BID or 90 mg once daily.\textsuperscript{17} Preliminary clinical activity was observed in an expansion cohort in patients with relapsed/refractory lymphoma (n=16); responses included one complete response (transformed lymphoma, duration of response [DoR] 125+ weeks) and two partial responses (MCL and DLBCL).\textsuperscript{18} The safety profile in lymphoma was similar to that observed in solid tumours, except for an expected higher incidence of cytopenias.\textsuperscript{17,18} This phase II study (NCT01403636) aimed to determine the efficacy and safety of voxtalisib monotherapy in patients with relapsed/refractory lymphoma or CLL/SLL.
Methods

Study population

Eligible patients were aged ≥18 years with Eastern Cooperative Oncology Group (EGOG) performance status ≤2 and had relapsed or refractory MCL, follicular lymphoma, DLBCL or CLL/SLL (see Supplementary Methods). Refractory disease was defined as being unresponsive to a standard regimen or progressing within 6 months of completing a standard regimen. All patients were required to have an estimated life expectancy of >3 months; adequate organ and marrow function, including absolute neutrophil count ≥1,000/mm³, platelets ≥30,000/mm³ with no active bleeding; alanine aminotransferase, aspartate aminotransferase and bilirubin ≤1.5 × upper limit of normal; and fasting plasma glucose <160 mg/dL. Patients were enrolled at 30 study centres in the USA, Belgium, Germany, France, The Netherlands and Australia (appendix p x).

Study design

This was a multicentre, non-randomised, open-label, phase II trial with four disease-specific cohorts, three of which had their own two-stage design (MCL, follicular lymphoma, CLL/SLL) and one had a single-stage design (DLBCL; cohort added after protocol amendment). Patients received voxtalisib 50 mg capsules BID (in the morning and evening), with a preferred interval of 12 (±1) hours between doses, with no food allowed for at least 2 hours before and 1 hour after dosing, in 28-day continuous dosing cycles until disease progression or unacceptable toxicity. After the cut-off date, patients with clinical benefit were allowed to continue treatment in an extension study (NCT01587040). It was recommended that immunocompromised patients and patients with CLL and a CD4 lymphocyte count <200 cells/µL be given prophylactic medications against reactivation of viral diseases and opportunistic infections, primarily Pneumocystis carinii.

The primary objective was to determine the ORR in patients in each disease-specific cohort. Secondary objectives were to assess PFS, progression-free rate at 24 weeks, DoR and safety. Exploratory objectives included assessing the pharmacodynamic effects of voxtalisib and defining predictive markers of response and/or resistance to voxtalisib based on molecular profiling of tumour tissue. Samples were collected for pharmacokinetic analysis, but were not analysed because clinical development is not ongoing.

This study was conducted in compliance with the recommendations of the Helsinki Declaration, all relevant international guidelines, and national laws and regulations of the countries in which the clinical trial was performed. The study was approved by the Human Protections Committees at each site, and informed consent was obtained from all patients prior to any study-related procedures.
**Efficacy assessments**

In patients with MCL, follicular lymphoma or DLBCL, response was based on investigator assessment using modified revised International Working Group response criteria. In these patients, response was defined as complete response or partial response. In patients with CLL/SLL, response was assessed using modified IWCLL guidelines, and objective response was defined as complete response (with or without minimal residual disease), complete response with incomplete marrow recovery, nodular partial response or partial response. No independent radiological review or central review was conducted. Although a rising lymphocyte count in the setting of at least a 50% nodal reduction was not considered to be progressive disease, a partial response with lymphocytosis response category had not been defined at the time the study was designed and therefore was not included in the design of this study. Patients with a discordant response (i.e. a decrease in lymph node size by >50% without meeting partial response criteria for peripheral blood lymphocyte count) were considered to have stable disease. It was recommended, but not required, that any patients with MCL, follicular lymphoma, or DLBCL meeting the criteria for complete response have a confirmatory FDG-PET scan no less than 6 weeks after the complete response assessment. Of five patients with follicular lymphoma who had complete response, all five were confirmed at least two months apart, four by CT scan and one by PET scan.

**Statistical methodology and sample size determination**

To evaluate the antitumour efficacy within each disease group, 162 efficacy-evaluable patients (41 with MCL, 45 with follicular lymphoma, 38 with DLBCL and 38 with CLL/SLL) were needed to achieve 90% power with an alpha of 0.05. A Simon’s minimax two-stage design was used for patients with MCL, follicular lymphoma and CLL/SLL, and a single-stage design was used for patients with DLBCL. The primary efficacy analysis of ORR was performed within each disease group when the required number of evaluable patients had been followed for a minimum of 6 months or discontinued from the study (appendix p x). ORR was calculated based on the proportion of patients with response in the efficacy population, with corresponding 95% CI. Median PFS (defined as time from study Day 1 to date of progressive disease or death regardless of cause), and proportion of patients progression free at 6 months, were estimated using the Kaplan–Meier method.

**Tumour molecular profiling and pharmacodynamic analyses**

Tumour alterations were documented by targeted next-generation sequencing (NGS) and PTEN immunohistochemistry of archival diagnosis formalin-fixed paraffin-embedded tumour tissue collected from
patients with follicular lymphoma, MCL and DLBCL and in buffy coat samples collected at screening from patients with CLL (appendix p x). The pharmacodynamic effect of voxtalisib was evaluated in serial plasma samples from patients with CLL (see Supplementary Methods).

Role of the funding source

This study was sponsored by Sanofi. Sanofi contributed to the study design, data analysis and interpretation, and critically reviewed the manuscript. All authors had full access to study data and were responsible for the decision to submit for publication.

Results

Patient population

In total, 167 patients were enrolled in the study between 19 October 2011 and 24 July 2013 (42 with MCL, 47 with follicular lymphoma, 42 with DLBCL and 36 with CLL/SLL; figure 1). The median age was 67 years (IRQ 60–74; table 1). The median number of prior anticancer regimens was three for patients with lymphoma (IQR 2–4) and four for patients with CLL/SLL (IQR 2–5). Three patients were not eligible for efficacy analysis as they did not have a post-baseline assessment, two (one with follicular lymphoma and one with DLBCL) due to withdrawal of consent, and one (with SLL) due to investigator decision. Thus, 164 patients were evaluable for efficacy. Duration of follow up was analysed for 33 patients with MCL, 43 patients with FL, 35 patients with DLBCL and 32 patients with CLL/SLL; patients who died, had symptomatic progression or discontinued due to adverse events were considered non-responders in the efficacy analysis, but were excluded from the duration of follow up analysis.

Patient disposition

The median duration of treatment was 11 weeks overall (IQR 5.9–31.9) and 8 weeks (IQR 5.6–19.9) for MCL, 29 weeks (IQR 8.1–64.0) for follicular lymphoma, 6 weeks (IQR 3.6–8.1) for DLBCL and 20 weeks (IQR 11.8–36.9) for CLL/SLL, respectively. The primary reasons for treatment discontinuation were disease progression (107 patients of 167, 64·1% overall; 73·8% [31/42], 42·6% [20/47], 76·2% [32/42] and 66·7% [24/36] in the MCL, follicular lymphoma, DLBCL and CLL/SLL groups, respectively) and adverse events (33 patients, 19·8% overall; 19·0% [8/42], 23·4% [11/47], 11·9% [5/42] and 25·0% [9/36] in the MCL, follicular lymphoma, DLBCL and CLL/SLL groups, respectively). Eighteen patients (10·8%) continued treatment with...
voxtalisib in a treatment extension study (NCT01587040; 4.8% [2/42], 25.5% [12/47], 7.1% [3/42] and 2.8% [1/36] in the MCL, follicular lymphoma, DLBCL and CLL/SLL groups, respectively). Twenty-four patients died during the on-treatment period (within 30 days of the last dose of voxtalisib), of which 16 deaths were due to disease progression and eight were due to adverse events (two due to cardio-respiratory arrest (both sudden deaths at home, one at 13 days and one at 22 days after study drug discontinuation, one of which was in the setting of severe aortic stenosis), three due to infectious pneumonia, one due to sepsis with Streptococcal bacteraemia, one due to pulmonary haemorrhage and one due to renal failure.

Efficacy

Thirty of 164 evaluable patients achieved a partial or complete response (ORR 18.3%): five/42 with MCL (11.9%), 19/46 with follicular lymphoma (41.3%), two/41 with DLBCL (4.9%) and four/35 with CLL/SLL (11.4%; table 2; figure 2). Eight patients (4.9%) achieved complete response (three [7.1%] in the MCL group, and five [10.9%] in the follicular lymphoma group). For the three patients with complete response in the MCL group, the median DoR was 23.4 weeks (IQR 9.3–37.4). For the five patients with complete response in the follicular lymphoma group, the median DoR was 85 weeks (IQR 71.6–88.3); all five follicular lymphoma patients were still responding at the time of data cut-off.

Median follow-up was 16.4 weeks overall (IQR 8.1–36.0), and 12.6 weeks (IQR 8.1–26.6) for MCL, 32.0 weeks (IQR 15.9–64.2) for follicular lymphoma, 8.1 months (IQR 4.9–11.0) for DLBCL and 27.9 months (IQR 14.7–50.1) for CLL/SLL. Of note, in the follicular lymphoma group, two patients were censored due to early discontinuation with adverse events, with no follow-up data available. In the MCL group, three patients had progressive disease at 3.3, 3.7 and 3.9 weeks, and a further two patients were censored due to early discontinuation with adverse events, with no follow up data available. Median PFS was 14.4 weeks (95% CI 9.0–19.4) overall [and 8.9 weeks (7.9–12.9) for MCL, 58.0 weeks for follicular lymphoma (26.0–not calculated), 7.1 weeks for DLBCL (5.1–8.1) and 24.1 weeks for CLL/SLL (16.6–31.6) (figure 3). Progression-free rate at 6-months was 38.6% (30.9–46.3); 24.5% (11.1–38.0) for MCL, 65.7% (51.6–79.8) for follicular lymphoma, 10.5% (0.3–20.7) for DLBCL and 51.9% (34.8–69.0) for CLL/SLL.
**Molecular profiling of tumour tissue and pharmacodynamic analysis**

Targeted NGS was performed on 37/47 (79%) of the tumour samples from patients with follicular lymphoma. Alterations in components of the mTOR/PI3K pathway in follicular lymphoma samples were rare. A PIK3CA E545Q mutation (with concomitant KRAS G12C mutation) was observed in one patient with complete response. PTEN deficiency was found in 28% (10/36) of the follicular lymphoma samples without any evidence of PTEN deleterious mutation (appendix p x). PTEN deficiency was also not associated with response. Alterations were identified in genes involved in epigenetic control, B-cell receptor/NFκB signalling, immune response, tumour suppression, apoptosis, cell cycle, DNA mismatch repair and JAK/STAT signalling (appendix p x), as previously reported in follicular lymphoma.21 The most prevalent alterations were in the epigenetic regulators CREBBP, MLL2 and EZH2 (in 73% [27/37], 70% [26/37] and 32% [12/37] of the samples, respectively) and in the apoptosis regulator BCL2 (49% [18/37] of samples). MCL1 alterations (gene amplification or mutations) were present in five patients; none of these patients achieved clinical benefit. Due to the diversity of alterations observed, there is insufficient evidence to suggest that response was associated with the presence or absence of any of the alterations documented.

Similar molecular profiling was performed on tumour samples from 27/42 (64%) of MCL patients and 17/42 (43%) of DLBCL patients. No alteration in components of the mTOR/PI3K pathway was observed in the MCL or DLBCL tumour samples. PTEN deleterious mutation was not identified in MCL or DLBCL samples, but PTEN deficiency was found in 26% (8/31) of MCL samples and in 20% (5/25) of DLBCL samples. The most prevalent alterations in MCL samples were in the ATM (33% [9/27]), MLL2 (30% [8/27]) and TP53 (33% [9/27]) genes (appendix p x). A single alteration was found in four of the five MCL patients achieving clinical benefit (ATM mutation, MLL2 mutation, MCL1 gene amplification and PTEN deficiency, appendix p x). The most prevalent alterations in DLBCL samples were MLL2 mutation and CDKN2A/B gene loss. Molecular profiling of buffy coat samples collected at screening from 36 patients with CLL identified alterations in TP53 (22% [8/36]) and ATM (17% [6/36]), as might be expected in patients with recurrent relapsed CLL3,22 (appendix p x). The pharmacodynamic impact of voxtalisib on cytokines/chemokines important in lymphocyte trafficking and function was evaluated in serial plasma samples collected from a subset of CLL patient treated (n=14) (appendix p x). This limited analysis failed to identify a post-treatment change in plasma cytokine or chemokine levels in patients with CLL.
Safety

The most frequently reported adverse events regardless of causality were diarrhoea (35·3%, in 59 of 167 patients), fatigue (31·7%, in 53 patients), nausea (26·9%, in 45 patients), pyrexia (26·3%, in 44 patients), cough (24·0%, in 40 patients) and decreased appetite (21·0%, in 35 patients; table 3). The most frequently reported grade ≥3 adverse events regardless of causality were anaemia (12·0%, in 20 patients), pneumonia (8·4%, in 14 patients) and thrombocytopenia (7·8%, in 13 patients).

Adverse events in the liver toxicity grouping occurred in 32 of 167 patients (19·2%), including grade 3/4 events in 13 patients (7·8%). Treatment-related adverse events in the liver toxicity grouping occurred in 20 patients (12·0%), including grade 3/4 events in nine patients (5·4%), all of which resolved with drug hold and patients were able to resume drug. Adverse events in the rash grouping (e.g. rash or pruritus) occurred in 47 patients (28·1%), including grade 3/4 events in seven patients (4·2%). Treatment-related adverse events in the rash grouping occurred in 27 patients (16·2%), including grade 3/4 events in six patients (3·6%). Only two treatment-related grade ≥3 hyperglycaemia adverse events were reported (1·2%).

Serious adverse events (SAEs) occurred in 97 of 167 patients (58·1%), most frequently pneumonia (9·6%, in 16 patients), general physical health deterioration (6·6%, in 11 patients), disease progression (6·0%, in 10 patients) and pyrexia (5·4%, in 9 patients). Twenty-nine patients (17·4%) had treatment-related SAEs. Adverse events leading to treatment discontinuation occurred in 33 patients (19·8%), most frequently nausea (2·4%, in 4 patients) and pyrexia (2·4%, in 4 patients). Overall, 123 patients (73·7%) had at least one dose modification (dose reduction and/or dose interruption).

The most frequently reported haematological laboratory abnormalities were anaemia (80·5% [132/164]; grade 3/4 in 12·2% [20/164]), decreased platelets (75·2% [124/165]; grade 3/4 in 17·0% [28/165]), decreased lymphocytes (67·1% [110/164]; grade 3/4 in 39·0% [64/164]), leukopenia (54·5% [90/165]; grade 3/4 in 12·7% [21/165]) and decreased neutrophils (46·3% [76/164]; grade 3/4 in 21·3% [35/164]). The most frequently reported biochemical laboratory abnormality was hyperglycaemia (63·0% [102/162]; grade 3/4 in 5·6% [9/162]). Overall, there were 53 deaths in 167 patients (31.7%), with 43 directly attributed to disease progression. Eight deaths were due to adverse events, with all assessed as not related to voxtalisib treatment.
Discussion

In this phase II study in 167 patients with relapsed/refractory aggressive lymphoma (MCL and DLBCL), indolent lymphoma (follicular lymphoma), or CLL/SLL, voxtalisib monotherapy had an acceptable safety profile, with encouraging efficacy in patients with follicular lymphoma but limited efficacy in those with MCL, DLBCL or CLL/SLL. In the follicular lymphoma group, single-agent voxtalisib resulted in an ORR of 41.3%, complete response rate of 10.9% and median PFS of 58.0 weeks. These findings are comparable, particularly for complete response rate, to those reported with the PI3Kδ inhibitor idelalisib, which received accelerated approval from the FDA based on a 57% ORR, 6% complete response rate and PFS of 11 months in a phase II study in patients with indolent B-cell NHL who were refractory to both rituximab and alkylating agents. Patients with follicular lymphoma in the current study had all received prior chemotherapy and 98% had received prior rituximab, although the percentage with refractory disease is not known. The observed activity of voxtalisib in relapsed/refractory follicular lymphoma, notable for inducing 10.9% complete responses, warrants further study. Similar efficacy data were recently reported with the pan-PI3K inhibitor copanlisib with a 40% ORR in follicular lymphoma patients, including 13.3% (2/15) complete responses.

Efficacy was limited in aggressive lymphoma disease (MCL, DLBCL) and CLL/SLL groups. Across all groups, the ORR was 18.3% (complete response 4.9%), consistent with the efficacy observed in a previous phase I expansion cohort in 12 patients with lymphoma, in which one complete response (transformed lymphoma) and two partial responses (MCL and DLBCL) were reported. Efficacy reported for copanlisib in aggressive lymphoma diseases was also limited (27.1% ORR with 4.2% complete response). Perhaps most surprising, in comparison with idelalisib, was the limited activity in CLL/SLL. Although a partial response with lymphocytosis category was not defined in this study, this did not significantly impact the reported activity, as only six CLL/SLL patients had nodal response, with four achieving objective response. Similarly, voxtalisib showed no pharmacodynamic impact on cytokine/chemokine levels in patients with CLL/SLL, even though this has been consistently observed with the PI3Kδ inhibitor idelalisib and was also recently reported for the pan-PI3K inhibitor pilaralisib. In MCL, idelalisib induces responses but they are very short-lived, and reported activity of idelalisib in DLBCL is limited. Thus, the results in these two disease groups are not as surprising, although the pan-PI3K inhibition of voxtalisib had the theoretical potential for improving response. In MCL cell lines and primary tumour samples, concurrent inhibition of PI3Kα and PI3Kδ is required to abolish constitutive PI3K activation, and is more effective than PI3Kδ inhibition alone, especially in tumour samples taken at relapse.
Exposure *in vivo* may have been insufficient to result in marked inhibition of PI3K\(\delta\) and therefore clinical activity in the aggressive lymphoma groups. In the phase I MTD expansion cohort study in patients with relapsed/refractory lymphoma (\(n=16\)), dosing of 50 mg voxtalisib BID led to an exposure with a fairly short plasma half-life.\(^{18}\) At the end of cycle 1, the mean terminal half-life was 4·61h and the median time to maximum concentration was 2·0h, (with a range of 0·50–4·17), without significant steady-state accumulation. Voxtalisib \(C_{\text{max}}\) at steady state was close to the cellular IC\(_{50}\) needed to induce apoptosis (0·828 \(\mu\)M).\(^{14,18}\) However, due to the short plasma half-life observed, this exposure was not maintained throughout the 12h period between two drug treatments. Therefore, these data suggest that despite its strong proapoptotic activity *in vitro*, insufficient exposure of voxtalisib may have led to limited PI3K\(\delta\) inhibition in patients with CLL, and may explain the limited antitumour activity observed in CLL patient subgroup as well as the MCL and DLBCL subgroups. This hypothesis could in principle be evaluated with more frequent dosing, which becomes challenging for patients, or alternative formulations.

The observed safety profile of voxtalisib was consistent with previous studies\(^{17,18}\) and with other pan-PI3K inhibitors,\(^{25,26}\) with gastrointestinal toxicities being most frequent. Furthermore, the safety profile of voxtalisib was also consistent with that of the PI3K\(\delta\)-specific inhibitor idelalisib, for which diarrhoea, fatigue and nausea are the most frequently reported adverse events in patients with lymphoma.\(^{11}\) Less transaminitis and colitis were seen in this study; however, this may be a consequence of the fact that PI3K\(\delta\) was not fully inhibited.

Hyperglycaemia, which is a characteristic toxicity of PI3K\(\alpha\) inhibition, was similar to previous voxtalisib studies (grade 3/4 in 6%),\(^{17,18}\) less frequent than with other pan-PI3K inhibitors,\(^{26}\) and higher than with the PI3K\(\delta\)-specific inhibitor idelalisib, which is expected given that the PI3K\(\alpha\) isoform is important for insulin signalling. Overall, the toxicity profile of voxtalisib in this study was manageable and consistent with the patient population.

Alterations in components of the mTOR/PI3K pathway in follicular lymphoma samples were infrequent (including one E545Q *PIK3CA* variant, one novel *PIK3RI* mutation of unknown impact and PTEN expression deficiency in 28%), but did include one patient with a *PIK3CA* and *RAS* mutation who had a complete response. PTEN expression deficiency did not correlate with response, consistent with previous findings with voxtalisib.\(^{17,18}\) This lack of correlation may be because many lymphomas show constitutive PI3K pathway activation, even in the absence of any activating mutations.
In summary, voxtalisib was associated with an acceptable safety profile in relapsed or refractory lymphoma and CLL/SLL, with promising efficacy demonstrated in the follicular lymphoma group. Responses were independent of PI3K/mTOR pathway alterations, likely because the pathway is typically constitutively activated in most lymphomas. Given the likely incomplete pharmacodynamic exposure, no further studies with voxtalisib in CLL are planned. Investigation of voxtalisib either alone or in combination with chemoimmunotherapy is warranted in follicular lymphoma.

Authors and contributors
JRB, MJK, LG, JL, BW, and CE designed the study. JRB, MH, JH, AJ, NWJ, OO, JA, HT, MM, FO, NG, SG, SA, SK, AAP, JD and MJK enrolled and treated patients, and collected the data. All authors analysed and interpreted the data. All authors critically revised draft versions, and approved the final manuscript.

Declaration of interests
JRB in the last 3 years has consulted for Janssen, Gilead, Celgene, Sun BioPharma, Novartis, AbbVie, Pfizer, AstraZeneca, Astellas, RedX, Pharmacyclics, Infinity, Roche/Genentech, Emergent, Onyx, Sanofi, Vertex, Ingelheim, and GlaxoSmithKline. MH has participated in a speaker’s bureau and has received research funding from Sanofi. JH is an employee of AbbVie and holds AbbVie shares. NWJ has participated in advisory boards for Pharmacyclics, Juno Therapeutics and Gilead. JA has received consulting fees from Gilead and Regeneron. HT reports grants and personal fees from Celgene, personal fees and non-financial support from Roche, and personal fees from Takeda, Janssen, Gilead, and Karyopharm. MM’s spouse was formerly employed at Sanofi, and still receives some deferred compensation. SA has received honoraria from Amgen Pharmaceuticals, Novartis Oncology, Pharmacyclics, Inc., Takeda Oncology and research support from Pharmacyclics, Inc. KA has received research support from Sanofi. LG is an employee of Sanofi. JL is an employee of Sanofi and holds stock in Sanofi. BW and CE were employees of Sanofi during the conduct of this study. MJK in the last 3 years has consulted for or received compensation for presentations from Gilead, Celgene, Novartis, Roche, Millennium/Takeda, Kite and BMS, and has received research support from Celgene, Roche, Millennium, and Sanofi. AJ, FO, NG, OO, SG, SK, JD have no conflicts to declare.
Acknowledgements

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References


<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lymphoma</th>
<th>CLL/SLL</th>
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<tr>
<td><strong>Median age, years (IQR)</strong></td>
<td>69.0 (62–78)</td>
<td>66.0 (55–70)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>33 (78.6)</td>
<td>27 (57.4)</td>
</tr>
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<td><strong>Primary location, n (%)</strong></td>
<td><strong>Lymph nodes</strong></td>
<td><strong>Spleen</strong></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>25 (59.5)</td>
<td>3 (7.1)</td>
</tr>
<tr>
<td>Spleen</td>
<td>3 (7.1)</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>6 (14.3)</td>
<td>1 (2.1)</td>
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<tr>
<td>Extra nodal</td>
<td>0</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (19.0)</td>
<td>4 (8.5)</td>
</tr>
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<td><strong>Disease/RAI stage at study entry, n (%)</strong></td>
<td><strong>1</strong></td>
<td><strong>2</strong></td>
</tr>
<tr>
<td>1</td>
<td>3 (7.1)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>2</td>
<td>4 (9.5)</td>
<td>7 (19.1)</td>
</tr>
<tr>
<td>3</td>
<td>5 (11.9)</td>
<td>15 (31.9)</td>
</tr>
<tr>
<td>4</td>
<td>29 (69.0)</td>
<td>22 (46.8)</td>
</tr>
<tr>
<td><strong>Bulky disease, n (%)</strong></td>
<td><strong>&gt;10 cm</strong></td>
<td><strong>&gt;5 cm</strong></td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>3 (7.1)</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>10 (23.8)</td>
<td>4 (8.5)</td>
</tr>
<tr>
<td><strong>ECOG performance status, n (%)</strong></td>
<td><strong>0</strong></td>
<td><strong>1</strong></td>
</tr>
<tr>
<td>0</td>
<td>17 (40.5)</td>
<td>21 (50.0)</td>
</tr>
<tr>
<td>1</td>
<td>21 (50.0)</td>
<td>4 (9.5)</td>
</tr>
<tr>
<td>2</td>
<td>4 (9.5)</td>
<td>5 (10.6)</td>
</tr>
<tr>
<td><strong>Median time since first diagnosis, years (IQR)</strong></td>
<td>5.0 (2.2–5.8)</td>
<td>5.5 (3.0–9.5)</td>
</tr>
<tr>
<td><strong>Median number of prior regimens (IQR)</strong></td>
<td>3.0 (2–4)</td>
<td>3.0 (2–3)</td>
</tr>
<tr>
<td><strong>Refractory to last prior therapy, n (%)</strong></td>
<td>25 (59.5)</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td><strong>Prior anticancer therapy, n (%)</strong></td>
<td><strong>Rituximab</strong></td>
<td><strong>Bortezomib</strong></td>
</tr>
<tr>
<td>Rituximab</td>
<td>41 (97.6)</td>
<td>12 (28.6)</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>46 (97.9)</td>
<td>0</td>
</tr>
<tr>
<td>Kinase inhibitor&lt;sup&gt;4&lt;/sup&gt;</td>
<td>0</td>
<td>0</td>
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<td><strong>Prior SCT, n (%)</strong></td>
<td><strong>Autologous</strong></td>
<td><strong>Allogeneic</strong></td>
</tr>
<tr>
<td>Autologous</td>
<td>1 (2.4)</td>
<td>10 (23.8)</td>
</tr>
<tr>
<td>Allogeneic</td>
<td>0</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td><strong>DLBCL cell of origin, n (%)</strong></td>
<td><strong>Activated B-cell like</strong></td>
<td><strong>Germinal centre</strong></td>
</tr>
<tr>
<td>Activated B-cell like</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Germinal centre</td>
<td>–</td>
<td>8 (19.0)</td>
</tr>
<tr>
<td>NOS</td>
<td>–</td>
<td>14 (33.3)</td>
</tr>
<tr>
<td><strong>IGHV status, n (%)&lt;sup&gt;5&lt;/sup&gt;</strong></td>
<td><strong>Mutated</strong></td>
<td><strong>Non-mutated</strong></td>
</tr>
<tr>
<td>Mutated</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Non-mutated</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>NA</td>
<td>–</td>
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</table>

<sup>1</sup> Data are expressed as n (percentage).<br> <sup>2</sup> Data are expressed as n (%).<br> <sup>3</sup> Data are expressed as n (%).<br> <sup>4</sup> Data are expressed as n (%).<br> <sup>5</sup> Data are expressed as n (%).<br> <sup>6</sup> Data are expressed as n (%).
<table>
<thead>
<tr>
<th>+12</th>
<th>–</th>
<th>–</th>
<th>–</th>
<th>–</th>
<th>4 (12·9)</th>
<th>–</th>
<th>–</th>
</tr>
</thead>
<tbody>
<tr>
<td>del (11q)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10 (32·3)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>del (13q)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11 (35·5)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>del (17p)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>6 (19·4)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*n=41 for DLBCL and n=130 for all lymphoma; †n=41 for MCL, n=41 for DLBCL, n=129 for all lymphoma, n=28 for CLL and n=33 for all CLL/SLL; disease stage listed for lymphoma, RAI stage listed for CLL/SLL; ‡n=41 for MCL, n=45 for follicular lymphoma and n=128 for all lymphoma; n = 28 for CLL, and n=33 for all CLL/SLL; §n=41 for DLBCL and n=130 for all lymphoma; ¶one patient received a BTK inhibitor, the other received an investigational kinase inhibitor; ¶¶IGHV data were only available for a subset of the CLL/SLL patients.

BTK=Bruton’s tyrosine kinase. CLL=chronic lymphocytic leukaemia. DLBCL=diffuse large B-cell lymphoma. ECOG=Eastern Cooperative Oncology Group. IGHV= immunoglobulin heavy-chain variable region. MCL=mantle cell lymphoma. NA=not available. NOS=not otherwise specified. SCT=stem cell transplant. SLL=small lymphocytic lymphoma.
Table 2: Summary of efficacy results with voxtalisib

<table>
<thead>
<tr>
<th></th>
<th>MCL (n=42)</th>
<th>Follicular lymphoma (n=46)</th>
<th>DLBCL (n=41)</th>
<th>CLL/SLL (n=35)</th>
<th>All (N=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, n (%) (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (11-9) (4-0--25-6)</td>
<td>19 (41-3) (27-0--56-8)</td>
<td>2 (4-9) (0-6--16-5)</td>
<td>4 (11-4) (3-2--26-7)</td>
<td>30 (18-3) (12-7--25-1)</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>3 (7-1)</td>
<td>5 (10-9)</td>
<td>0</td>
<td>0</td>
<td>8 (4-9)</td>
</tr>
<tr>
<td>Partial response</td>
<td>2 (4-8)</td>
<td>14 (30-4)</td>
<td>2 (4-9)</td>
<td>4 (11-4)</td>
<td>22 (13-4)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>14 (33-3)</td>
<td>14 (30-4)</td>
<td>4 (9-8)</td>
<td>23 (65-7)</td>
<td>55 (33-5)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>15 (35-7)</td>
<td>10 (21-7)</td>
<td>29 (70-7)</td>
<td>5 (14-3)</td>
<td>59 (36-0)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>8 (19-0)</td>
<td>3 (6-5)</td>
<td>6 (14-6)</td>
<td>3 (8-6)</td>
<td>20 (12-2)</td>
</tr>
<tr>
<td><strong>PFS &gt;24 weeks</strong></td>
<td>9 (21-4)</td>
<td>25 (54-3)</td>
<td>3 (7-3)</td>
<td>16 (45-7)</td>
<td>53 (32-3)</td>
</tr>
<tr>
<td><strong>Median PFS, † weeks</strong></td>
<td>8-9 (7-86-12-86)</td>
<td>58-0 (26-00-not calculated)</td>
<td>7-1 (5-14-8-14)</td>
<td>24-1 (16-57--31-57)</td>
<td>14-4 (9-00--19-43)</td>
</tr>
</tbody>
</table>

Estimated by Clopper–Pearson Exact method; † Kaplan–Meier estimates.

CLL=chronic lymphocytic leukaemia. DLBCL=diffuse large B-cell lymphoma. MCL=mantle cell lymphoma.

ORR=overall response rate. PFS=progression-free survival. SLL=small lymphocytic lymphoma.
Table 3: Adverse events occurring in ≥ 10% of patients with voxtalisib treatment

<table>
<thead>
<tr>
<th>Event</th>
<th>All grades</th>
<th>Grade 1-2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
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<tr>
<td>Any event</td>
<td>160 (95.8%)</td>
<td>156 (93.4%)</td>
<td>113 (67.7%)</td>
<td>38 (22.8%)</td>
<td>20 (12.0%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>59 (35.3%)</td>
<td>56 (33.5%)</td>
<td>5 (3.0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>53 (31.7%)</td>
<td>45 (26.9%)</td>
<td>10 (6.0%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>45 (26.9%)</td>
<td>44 (26.3%)</td>
<td>2 (1.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>44 (26.3%)</td>
<td>41 (24.6%)</td>
<td>5 (3.0%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Cough</td>
<td>40 (24.0%)</td>
<td>40 (24.0%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>35 (21.0%)</td>
<td>33 (19.8%)</td>
<td>4 (2.4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>32 (19.2%)</td>
<td>31 (18.6%)</td>
<td>2 (1.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>31 (18.6%)</td>
<td>28 (16.8%)</td>
<td>3 (1.8%)</td>
<td>1 (0.6%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>30 (18.0%)</td>
<td>20 (12.0%)</td>
<td>20 (12.0%)</td>
<td>1 (0.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>27 (16.2%)</td>
<td>27 (16.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>24 (14.4%)</td>
<td>23 (13.8%)</td>
<td>1 (0.6%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Thrombocytopenia</td>
<td>23 (13.8%)</td>
<td>13 (7.8%)</td>
<td>9 (5.4%)</td>
<td>11 (6.6%)</td>
<td>0</td>
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<tr>
<td>Alanine aminotransferase increased</td>
<td>22 (13.2%)</td>
<td>20 (12.0%)</td>
<td>6 (3.6%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Pneumonia</td>
<td>20 (12.0%)</td>
<td>9 (5.4%)</td>
<td>12 (7.2%)</td>
<td>2 (1.2%)</td>
<td>1 (0.6%)</td>
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<tr>
<td>Asthena</td>
<td>19 (11.4%)</td>
<td>18 (10.8%)</td>
<td>5 (3.0%)</td>
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<tr>
<td>Weight decreased</td>
<td>19 (11.4%)</td>
<td>18 (10.8%)</td>
<td>1 (0.6%)</td>
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<td>0</td>
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<td>Bronchitis</td>
<td>18 (10.8%)</td>
<td>16 (9.6%)</td>
<td>4 (2.4%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Neutropenia</td>
<td>18 (10.8%)</td>
<td>8 (4.8%)</td>
<td>7 (4.2%)</td>
<td>6 (3.6%)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>17 (10.2%)</td>
<td>16 (9.6%)</td>
<td>1 (0.6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>17 (10.2%)</td>
<td>17 (10.2%)</td>
<td>3 (1.8%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General physical health deterioration</td>
<td>17 (10.2%)</td>
<td>10 (6.0%)</td>
<td>8 (4.8%)</td>
<td>1 (0.6%)</td>
<td>5 (3.0%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>17 (10.2%)</td>
<td>17 (10.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are n (%). Adverse events (preferred terms) occurring in at least 10% of patients in the safety population, regardless of causality, are listed. All grade 3 or higher adverse events not shown here are reported in the appendix (p x).
Figure legends

Figure 1: Trial profile

Figure 2: Best nodal response to voxtalisib in evaluable patients with A) mantle cell lymphoma, B) follicular lymphoma and C) diffuse large B-cell lymphoma

Figure 3: Kaplan–Meier plot of progression-free survival with voxtalisib in patients with follicular lymphoma (FL), chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), or diffuse large B-cell lymphoma (DLBCL)
Figure 1: Trial profile

167 pts included

42 with MCL 47 with FL 42 with DLBL 36 with CLL/SL

Voxtalisib therapy

42 discontinued from study treatment
- 0 adverse event
- 1 disease progression
- 31 poor protocol compliance
- 2 roll-over to extension study
- 0 other

47 discontinued from study treatment
- 11 adverse event
- 0 disease progression
- 20 poor protocol compliance
- 12 roll-over to extension study
- 4 other

42 discontinued from study treatment
- 5 adverse event
- 0 disease progression
- 32 poor protocol compliance
- 3 roll-over to extension study
- 2 other

36 discontinued from study treatment
- 9 adverse event
- 0 disease progression
- 24 poor protocol compliance
- 1 roll-over to extension study
- 2 other

18 deaths
- 13 disease progression
- 3 adverse event
- 2 other

6 deaths
- 4 disease progression
- 2 adverse event
- 0 other

14 deaths
- 13 disease progression
- 1 adverse event
- 0 other

15 deaths
- 13 disease progression
- 2 adverse event
- 0 other

42 analysed for efficacy
48 analysed for efficacy
41 analysed for efficacy
35 analysed for efficacy

42 analysed for safety
47 analysed for safety
42 analysed for safety
36 analysed for safety
Supplementary tables and figure legends

Supplementary Table 1: PTEN immunohistochemical data summary

Supplementary Table 2: Effect of voxtalisib 50 mg twice daily on the plasma concentration of chemokines involved in B-cell trafficking in patients with CLL

Supplementary Figure 1: Best nodal response to voxtalisib in evaluable patients with A) mantle cell lymphoma, B) follicular lymphoma and C) diffuse large B-cell lymphoma

Supplementary Figure 2: Molecular profiling of mantle cell lymphoma tissue
Columns in the table denote tumour samples and rows denote protein and genes. Red shading represents deleterious gene alterations (mutation, ins/del, nonsense mutation as described in methods), green represents gene amplification, purple for gene loss, light blue for no alteration detected and white for unknown status. Number in cells indicates the number of alterations in a given gene. Loss of PTEN protein expression is shown in black. Samples were collected from patients without objective response from voxtalisib treatment, and from patients achieving partial response (PR) or complete response (CR). Cell of origin data was collected from tumour samples from 22 out of the 42 DLBCL patients enrolled (ABC type n=9; GCB type n=13).

Supplementary Figure 3: Molecular profiling of chronic lymphocytic leukaemia samples
Columns in the table denote genes and rows tumour samples. Red shading represents deleterious gene alterations. The number of mutations in individual CLL driver genes is marked in red boxes. Right panel: each row represents the total number of mutations in driver and non-driver genes per patient.

Supplementary Figure 4: Effect of voxtalisib 50 mg twice daily on the plasma concentration of chemokines involved in B-cell trafficking in patients with CLL
Samples were collected from 14 patients at baseline and post-dose (cycle 3 day 1 or later time points), and analysed using the Myriad RBM Human Discovery MAP panel.
Supplementary methods

Study population

Patients with MCL had histologically and phenotypically confirmed MCL that had relapsed or been refractory to \( \geq 2 \) and \( \leq 4 \) prior antineoplastic therapies. Patients with follicular lymphoma had histologically or cytologically confirmed grade 1, 2, or 3a follicular lymphoma that had relapsed or been refractory to \( \geq 2 \) and \( \leq 6 \) prior antineoplastic therapies. Patients with DLBCL had histologically or cytologically confirmed de novo DLBCL or transformed DLBCL from a prior indolent B-cell lymphoma that had relapsed or been refractory to \( \geq 1 \) prior systemic therapy that included an anthracycline (unless contraindicated) and rituximab. Patients with CLL or SLL had histologically or cytologically confirmed CLL or SLL that had relapsed or been refractory to \( \geq 2 \) and \( \leq 6 \) prior antineoplastic therapies and required treatment according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria. Patients with MCL, follicular lymphoma or DLBCL were required to have \( \geq 1 \) evaluable target lesion (\( \geq 1.5 \) cm in the longest transverse diameter). The trial required refractory disease, which is defined by unresponsive to a standard regimen or progressing within 6 months of completing a standard regimen. Progression is defined by the modified International Working Group Response Criteria for malignant lymphoma (IWRC; Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; 25:579–86.) and modified IWCLL guidelines (Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* 2008; 111: 5446–56).

Efficacy assessments

Patients were assessed for response after two 28-day cycles of study treatment, and then every three cycles for a period of 2 years, or until disease progression or withdrawal from study. If there was clinical suspicion of progression, disease assessment could be performed at any time. Patients were defined as not assessable for efficacy if they did not have a post-baseline assessment.

Statistical methodology and sample size determination

For patients with MCL, if nine or more patients achieved an objective response among the first 41 evaluable patients, the null hypothesis (ORR \( \leq 12\% \)) was to be rejected in favour of the alternative hypothesis (ORR \( \geq 30\% \)). For patients with follicular lymphoma, if 14 or more patients achieved an objective response among the first 45 evaluable patients, the null hypothesis (ORR \( \leq 20\% \)) was to be rejected in favour of the alternative hypothesis (ORR \( \geq 40\% \)). For patients with DLBCL, if ten or more patients achieved an objective response among the first 38 evaluable patients, the null hypothesis (ORR \( \leq 15\% \)) was to be rejected in favour of the alternative hypothesis (ORR \( \geq 35\% \)). For patients with CLL/SLL, if ten or more patients achieved an objective response among the first 38 evaluable patients, the null hypothesis (ORR \( \leq 15\% \)) was to be rejected in favour of the alternative hypothesis (ORR \( \geq 35\% \)).

Safety assessments

Safety assessments included adverse events, physical examination, laboratory data and electrocardiograms. Adverse event seriousness, severity grade and relationship to voxtalisib were assessed by the investigator. Adverse event severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4·03. The study protocol specified continuous monitoring of safety parameters, starting at the time of informed consent, and performed at every site visit while on study treatment and 30 days after the end of study treatment, with telephone safety assessments performed at specified intervals between site visits.
Criteria for dose and schedule modification

Patients experiencing 1 or more grade $\geq 2$ adverse events regardless of causality may require dose modifications. Dose reduction levels for voxtalisib were 30 mg and 20 mg q12hr. If the dose of voxtalisib must be held for a grade $\geq 2$ adverse event, it should not be resumed until recovery of the adverse event to grade $\leq 1$ or baseline. If there is no recovery after a 21-day treatment delay, the patient should be withdrawn from the study. Doses omitted during treatment delay will not be made up. Dose reductions for grade 2 adverse events will be at the discretion of the investigator. If a patient experiences a grade $\geq 3$ voxtalisib-related adverse event, the dose for that patient must be reduced by 1 dose level. Only 2 dose level reductions will be permitted. Dose reductions are not required for any grade tumour lysis syndrome occurring in Cycle 1 of treatment. Once a patient’s dose has been reduced, the dose may be re-escalated 1 dose level, if the toxicity that led to the dose reduction was grade $\leq 3$ and does not reoccur after 1 cycle of treatment at the reduced dose level. Dose re-escalation is not allowed for patients remaining on study after experiencing a grade 4 adverse event, regardless of causality, or for patients requiring a dose reduction for grade $\geq 2$ transaminase elevations.

Management criteria for non-haematological adverse events

<table>
<thead>
<tr>
<th>CTCAE v4.03 Grade</th>
<th>Guidelines/intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>No dose adjustments.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Continue voxtalisib at the current dose levels. If the dose is not reduced after the first occurrence, a dose reduction must be implemented after a second recurrence. All voxtalisib-related transaminase elevations require dose reduction.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Interrupt voxtalisib until the adverse event resolves to grade $\leq 1$ or baseline. Upon recovery, resume voxtalisib at the same dose or at a reduced dose as clinically indicated. If the dose is not reduced after the first occurrence, a dose reduction must be implemented after a second recurrence.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue voxtalisib permanently unless determined by the Investigator and agreed to by the Sponsor that the patient is deriving clinical benefit. In this case, the patient may be re-treated at a reduced dose that is agreed upon by the Investigator and the Sponsor once the AE resolves to grade $\leq 1$.</td>
</tr>
</tbody>
</table>

CTCAE=Common Terminology Criteria for Adverse Events.

Laboratory monitoring

Clinical laboratory data consist of blood analysis (including haematology, clinical chemistry, coagulation) and urinalysis. Clinical laboratory parameters are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Samples for haematology and serum chemistry are collected every 2 weeks in the first 3 cycles, and every 4 weeks after cycle 3. Additional samples may be collected for clinically significant adverse events which require additional follow up.

Pharmacodynamic and molecular profiling analyses

Genetic alterations were documented in follicular lymphoma, MCL and DLBCL samples using the Foundation One solid tumour T5 assay (296 cancer-related genes) at Foundation Medicine, Inc. and in CLL buffy coat samples using the Ion AmpliSeq™ Comprehensive Cancer gene panel (Life Technologies, 409 genes) at Sanofi. The tumour tissue samples were sequenced to an average depth of $>500X$. Samples were evaluated for deleterious alterations including (i) known or likely activating oncogenic mutations, (ii) indel or nonsense mutations, (iii) large deletions of multiple exons of tumour-suppressor proteins leading to truncation and loss of function and (iv) copy number alterations (amplifications and homozygous deletions). No process-matched normal control samples were available.
PTEN immunohistochemical analysis

PTEN expression status was evaluated in samples collected from patients with follicular lymphoma (n=37), DLBCL (n=29), and MCL (n=34). PTEN status in CLL samples was not investigated due to prior reports showing that PTEN is not altered in CLL. PTEN expression was evaluated by immunohistochemistry in formalin fixed, paraffin-embedded tissue sections (5 µm) with anti-PTEN antibody on the archival diagnostic tumour tissue samples collected from patients. Haematoxylin and Eosin (H&E) stains were performed on tissue sections to examine specimen quality and appropriateness. The PTEN analyses were carried out using Ventana’s Benchmark® XT staining platform. Antigen recovery was conducted under “standard” conditions with Cell Conditioner 1 buffer (VMSI, Catalog No. 950-124). Slides were incubated with a 1/80 dilution of the stock concentration of the primary antibody anti-PTEN antibody (Cell Signalling Technology Catalog # 9188) in Catalog No. S3022 (DAKO) for 60 minutes at 37°C. As a negative control, specimens were incubated with antibody diluent under the same conditions. The antibody staining was detected using the OmniMap anti-Rb HRP (Catalog No. 760-4311). Enzymatic detection of anti-PTEN antibody was accomplished with a horseradish peroxidase conjugate, followed by reaction with hydrogen peroxide in the presence of diaminobenzidine and copper sulphate. The secondary antibody and all chromogen reagents were applied at the instrument’s default times. Each batch analysis contained positive and negative tumour samples. Both nuclear and cytoplasmic PTEN staining in tumour and non-tumour tissues was observed and quantified. Tumour cells were scored manually for PTEN immunoreactivity based on cytoplasmic and nuclear staining intensity and percentage of tumour cells showing staining (using a standardized scoring scale of 0=negative, 1=weak, 2=moderate, 3=strong) followed by calculating an H-Score for each sample applying the following formula: H-Score=1 x (% weak nuclear staining) + 2 x (% moderate nuclear staining) + 3 x (% strong nuclear staining). PTEN staining in the non-neoplastic normal vascular endothelium and extratumoural stromal cells served as the internal positive control for each patient. Tumours were scored as PTEN-negative when complete absence of nuclear or cytoplasmic staining in the tumour cells was observed with positive staining in normal cells present in the same section.