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Ublituximab (TG-1101), a novel glycoengineered anti-CD20 antibody, in combination with ibrutinib is safe and highly active in patients with relapsed and/or refractory chronic lymphocytic leukaemia: results of a phase 2 trial

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Summary

Ibrutinib is effective in patients with chronic lymphocytic leukaemia (CLL); however, treatment resistance remains a problem. Ublituximab is a novel, glycoengineered anti-CD20 monoclonal antibody with single-agent activity in relapsed CLL. We report the results of a phase 2 study evaluating combination therapy with ibrutinib and ublituximab in patients with relapsed or refractory CLL. Patients received ibrutinib 420 mg once daily. Ublituximab was administered on days 1, 8 and 15 of cycle 1 followed by day 1 of cycles 2–6. Response assessments were completed at cycles 3 and 6; patients then continued on ibrutinib monotherapy per standard of care. Forty-one of 45 enrolled patients were evaluable for efficacy. Safety was consistent with prior experience for each drug, with infusion reactions the most prevalent adverse event. Combination therapy resulted in an overall response rate (ORR) of 88% at 6 months. In the 20 patients with high-risk features (17p or 11q deletions or *TP53* mutation) and evaluable for efficacy, the ORR was 95%, with three patients (15%) achieving negative minimal residual disease. Median time to response was 8 weeks. Ublituximab in combination with ibrutinib resulted in rapid and high response rates. The long-term clinical benefit of ublituximab will be defined by an ongoing phase 3 trial (NCT 02301156).

Keywords: ublituximab, ibrutinib, chronic lymphocytic leukaemia, high-risk, 17-p deletion.

Management of chronic lymphocytic leukaemia (CLL) has evolved from single-agent chemotherapy, such as chlorambucil or fludarabine, to combination regimens, such as fludarabine and cyclophosphamide. The addition of the anti-CD20 monoclonal antibody (mAb) rituximab to fludarabine and cyclophosphamide improved overall survival (OS) in CLL (Hallek *et al*, 2010), and long-term follow-up of this regimen has even raised the question of whether some patients with CLL can be cured of their disease with intensive chemoimmunotherapy (Fischer *et al*, 2016; Thompson *et al*, 2016).

More recently, novel B-cell receptor (BCR)-signalling inhibitors, such as the Bruton tyrosine kinase (BTK) inhibitor ibrutinib and the phosphoinositide-3-kinase (PI3K) delta inhibitor idelalisib, have transformed the management of patients with CLL and demonstrated further improvements in OS (Byrd *et al*, 2013, 2014; Furman *et al*, 2014; O'Brien

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et al, 2014; Burger *et al*, 2015). Ibrutinib has demonstrated remarkable single-agent activity in both the relapsed and refractory settings (Byrd *et al*, 2013), as well as in treatment-naïve CLL (O'Brien *et al*, 2014). In randomized studies, ibrutinib has improved OS compared to ofatumumab (Byrd *et al*, 2014) and chlorambucil (Burger *et al*, 2015), and has improved progression-free survival (PFS) when administered in combination with bendamustine and rituximab (Chanan-Khan *et al*, 2015).

Recent studies have suggested that ibrutinib monotherapy may result in incomplete inhibition of BCR signalling, even at approved dose levels (Poggesi *et al*, 2015), and that dose reductions or interruptions are associated with higher rates of progression (Barr *et al*, 2015). The depth of disease control in patients treated with ibrutinib monotherapy is not yet fully understood, with complete responses (CR) and minimal residual disease (MRD) negativity rare (Byrd *et al*, 2014). In addition, patients with adverse cytogenetic features may experience less durable disease control with ibrutinib compared with patients who lack such adverse features (Byrd *et al*, 2013). Further, mutations in *BTK* or the downstream-signalling protein phospholipase C gamma (*PLCG2*) have been shown to confer ibrutinib resistance (Woyach *et al*, 2014a), and survival following discontinuation of ibrutinib can be very short (Jain *et al*, 2015; Maddocks *et al*, 2015). For these reasons, combination regimens that include ibrutinib have the potential to enhance patient outcomes *versus* those seen with ibrutinib monotherapy. Both rituximab and ofatumumab have been added to ibrutinib in separate studies, with both showing more rapid response rates and higher overall response rates (ORRs) compared to historic controls (Burger *et al*, 2014; Jaglowski *et al*, 2015). Multiple studies are also evaluating the addition of the glycoengineered anti-CD20 mAb, obinutuzumab, to ibrutinib, including a randomized, multicentre, open-label phase 3 study of ibrutinib in combination with obinutuzumab *versus* chlorambucil in combination with obinutuzumab in patients with treatment-naïve CLL (Flinn *et al*, 2015).

Ublituximab is a novel, type 1, anti-CD20 mAb that binds to a unique epitope on the CD20 antigen, distinct from rituximab, ofatumumab and obinutuzumab, and has been glycoengineered to exhibit a low-fucose fragment crystallizable (Fc) region, thereby demonstrating enhanced antibody-dependent cellular cytotoxicity (ADCC). In *in vitro* studies, ublituximab demonstrated 100 times greater natural killer (NK)-cell-mediated ADCC than rituximab in patient-donor CLL cells (Le Garff-Tavernier *et al*, 2011). In a first-in-human study in patients with relapsed CLL, ublituximab demonstrated marked and durable B-cell depletion when administered as a single agent, resulting in a 45% ORR with a favourable toxicity profile (Cazin *et al*, 2011). We hypothesized that the addition of ublituximab to ibrutinib would result in quicker time to response and a greater depth of response for patients with relapsed and refractory CLL compared with ibrutinib alone.

Methods

Subjects

This was a multicentre, phase 2 study evaluating the efficacy and safety of ublituximab in combination with ibrutinib in patients with select B-cell malignancies. Adult subjects ≥18 years of age with a confirmed diagnosis of mantle cell lymphoma, CLL, or small lymphocytic lymphoma (SLL) were enrolled in the trial. The demographics and outcomes for the CLL cohort only are reported herein. CLL subjects were required to have an indication for treatment according to the 2008 International Workshop on CLL (iwCLL) criteria (Hallek *et al*, 2008) and to have received at least one prior standard treatment regimen. Subjects were required to have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 with adequate organ function, defined as an absolute neutrophil count (ANC) $\geq 1 \times 10^9$/l and platelet count $\geq 50 \times 10^9$/l for the dose confirmation period and an ANC $\geq 0{\cdot}75 \times 10^9$/l and platelet count $\geq 30 \times 10^9$/l for phase 2. Prior treatment with a BTK inhibitor and/or a PI3K inhibitor was permitted.

Subjects were excluded if they had received cancer therapy within 3 weeks of cycle 1/day 1; had received an autologous haematological stem cell transplant within 3 months of study entry or any prior allogeneic haematological stem-cell transplant; or had Richter transformation, prolymphocytic leukaemia, primary central nervous system lymphoma or the presence of any other active cancers. All subjects gave written informed consent according to International Review Board guidelines. This study was conducted in accordance with the Declaration of Helsinki and was registered at Clinicaltrials.gov [National Clinical Trial (NCT) Identifier: 02013128].

Study design

This study consisted of a dose-confirmation safety run-in period followed by an open enrolment into phase 2. The dose-confirmation safety assessment enrolled six patients with CLL into each of two cohorts: Cohort 1 received ibrutinib 420 mg daily and ublituximab 600 mg on days 1, 8 and 15 of cycle 1. Safety data were reviewed after all subjects had completed Cohort 1 therapy. If ≤1 dose-limiting toxicity (DLT) occurred in Cohort 1, the dose escalation proceeded to Cohort 2 (ibrutinib 420 mg daily; ublituximab dose increased to 900 mg on days 1, 8 and 15 of cycle 1). If ≥2 or more DLTs occurred in Cohort 1, Cohort −1 was initiated (ibrutinib 420 mg daily; ublituximab dose decreased to 450 mg on days 1, 8 and 15 of cycle 1). If ≤1 DLT was reported in Cohort 2, the dose was considered safe for phase 2.

Once the dose was confirmed, subjects were enrolled into the open phase 2 part of the study, in which they received six cycles of ublituximab 900 mg and ibrutinib according to the schedule shown in Fig 1. After cycle 6, ibrutinib was administered off study per standard of care.

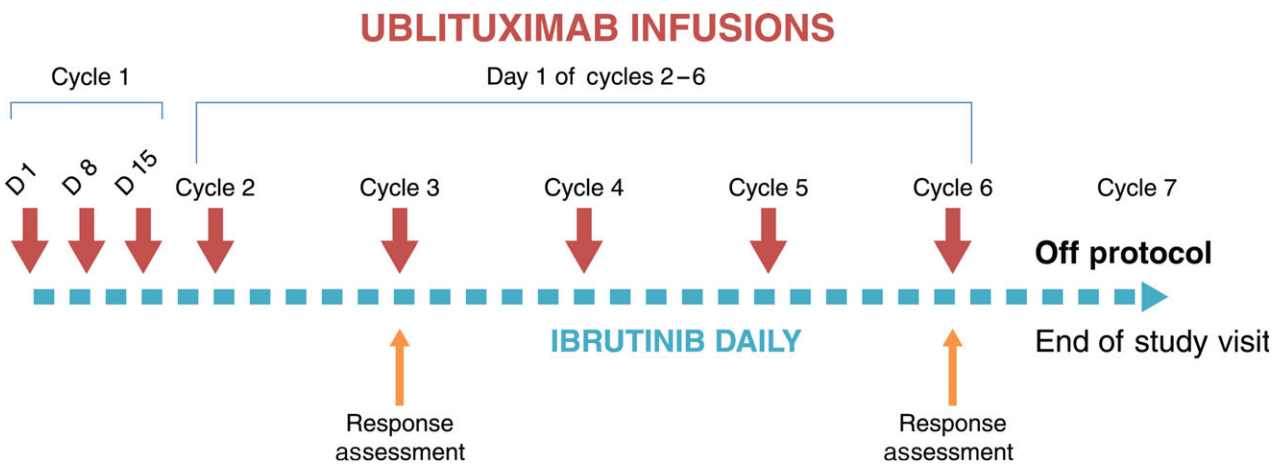

Fig 1. Study design and treatment schema. Patients received ibrutinib daily beginning on day 1 of cycle 1. Ublituximab infusions were given on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6. Patients were assessed for response after months 2 and 5. Each cycle is 28 days.

Ublituximab was administered as an intravenous infusion. Subjects received premedication with an antihistamine (diphenhydramine 50 mg or equivalent) and a corticosteroid (dexamethasone 12 mg or equivalent) approximately 30 min prior to each ublituximab infusion. Oral acetaminophen 650 mg was permitted in subjects who experienced fever or pyrexia after the first-week dose or as clinically indicated. Concurrent glucocorticoid therapy was permitted if started at least 7 days prior to study entry (≤10 mg/day prednisone or equivalent) if clinically warranted. The day 1 infusion of ublituximab in cycle 1 was split between day 1 and day 2, with up to 150 mg administered on day 1 and the remainder of the dosage on day 2 to minimize infusion-related reactions (IRRs). Prophylactic allopurinol was permitted for subjects at risk for tumour lysis syndrome.

Assessments and endpoints

The primary objective of the safety run-in was to evaluate the safety of ublituximab in combination with ibrutinib for the doses given. The primary objective of the phase 2 study was to determine the ORR, defined as the rate of CR plus the rate of partial response (PR) of the combination. Patients who met the criteria for a CR but lacked bone marrow confirmation were considered to have a PR. Secondary objectives included safety, CR rate and the rate of MRD negativity.

Efficacy was assessed by a computed tomography (CT) scan at the start of cycle 3 and then again at approximately cycle 6. All efficacy assessments had a ±7-day window. Responses were assessed per iwCLL criteria (Hallek *et al*, 2008), and PR with lymphocytosis (PR-L) was also assessed per the suggested modification of the iwCLL guidelines (Cheson *et al*, 2012). Physical examinations, vital signs, haematology and serum chemistry were performed on all ublituximab dosing days, as well as an additional assessment on day 22 of cycle 1. Adverse events (AEs) were assessed by the Common Terminology Criteria for AEs (CTCAE), version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

Statistical analysis

All statistical analyses were performed using a one-sided hypothesis test at the overall 5% level of significance. Descriptive statistics were used for all variables. The primary efficacy variable (ORR) and the 90% one-sided confidence interval of the rate were estimated. Per the statistical design, up to 50 patients with CLL were to be enrolled, assuming a 10% screen fail or non-evaluable rate. If the response rate was no more than 60%, the study would be determined a failure; if a >20% increase in ORR *versus* the 58% ORR reported for ibrutinib (https://www.janssenmd.com/pdf/imbruvica/PI-Imbruvica.pdf) was achieved, the study would be considered to have a positive result. MRD was evaluated from peripheral blood samples in local laboratories using a minimum of four-colour flow cytometry with a lower limit of detection of 0·01% (one malignant cell in 10 000 white blood cells). MRD analysis was completed at the start of cycles 3 and 6 following the patients' CT scan results.

This study employed a modified intent-to-treat (ITT) design. The modified ITT population consisted of all enrolled patients who had at least one post-baseline efficacy measurement, and the primary efficacy analyses were performed based on the modified ITT population. The safety population included all enrolled patients who received at least one dose of the study drug. All safety assessments including toxicity were performed on the safety population.

Results

Patients

A total of 45 subjects with CLL were enrolled in the study, including patients in the safety run-in and open enrolment

components; all subjects were evaluable for safety, while 41 were evaluable for efficacy. Of the four subjects not evaluable for efficacy, two subjects were lost to follow-up (one patient withdrew consent after one infusion, and one patient entered hospice after the second infusion), and two subjects discontinued the study prior to the first disease assessment due to an AE. Of the two subjects who discontinued, one was due to diarrhoea, assessed by the treating investigator as related to ibrutinib; and one was due to AEs of pneumonia and pleural effusion, which were not attributed to study drug treatment by the treating investigator (Table I). Of the 45 patients, 47% (21 of 45) were classified as 'high risk', exhibiting one or more of the following cytogenetic abnormalities: del 17p ($n = 12$), del 11q ($n = 12$), and/or a *TP53* ($n = 2$) mutation, with five having both del 17p and 11q. Prior treatment included purine analogues (22/44), bendamustine (21/44), idelalisib (2/44), a spleen-tyrosine kinase inhibitor (2/44) and the BTK inhibitor CC-292 (1/44). Of the evaluable patients, 29% were considered anti-CD20-refractory, progressing on or within 6 months of an anti-CD20-based regimen where prior anti-CD20 therapy included rituximab, ofatumumab and/or obinutuzumab.

Safety outcomes

Overall, the combination of ublituximab and ibrutinib was well tolerated. No DLTs were seen in the six patients treated in the safety run-in cohort. The most common AEs were IRRs, diarrhoea, fatigue, nausea and rash (Table II). The most common (≥5%) grades 3/4 AEs were anaemia, neutropenia, IRRs and thrombocytopenia. All rash and grades 3/4 diarrhoea events were deemed related to ibrutinib per investigator assessment. All IRRs were related to ublituximab, with dose interruptions as the most common intervention; 21 of 45 patients (47%) had dose interruptions due to IRR, and one patient was dose-reduced to 600 mg due to IRR. Other ublituximab-related dose interruptions were due to neutropenia (two patients) and elevated aspartate aminotransferase (two patients). For ibrutinib, two patients had their dose reduced (one for diarrhoea, one for dizziness) and 10 of 45 (22%) had their dose interrupted (three for rash, two for neutropenia, one for anaemia, one for thrombocytopenia, one for nausea, one for hypercalcaemia and one for dehydration).

Four subjects (9%) discontinued study participation due to an AE: one was due to grade 3 diarrhoea, and three were discontinued for AEs considered unrelated to study treatment per the treating investigator. Aside from IRRs, the addition of ublituximab to ibrutinib did not appear to alter the safety and tolerability profile historically seen with ibrutinib monotherapy.

Efficacy outcomes

All evaluable patients ($n = 41$) achieved some reduction in disease burden (Fig 2). The primary endpoint of ORR within 6 months by iwCLL criteria (Hallek *et al*, 2008) was met at 88%; two subjects (5%) achieved a CR and 34 subjects (83%) had a PR. One subject (2%) achieved a PR-L; inclusion of this subject results in an ORR of 90%, according to the 2012 suggested modification of the iwCLL guidelines (Cheson *et al*, 2012). The four subjects who did not achieve a response included three who had stable disease and one who, although exhibiting a >70% nodal reduction, met the iwCLL criteria for disease progression with the appearance of a new lesion on CT scan. Notably, the high-risk subgroup of

Table I. Demographics.

$N = 45$	
Median age, years (range)	71 (39–86)
Male/female	23/22
ECOG score, median	1
Prior regimens, median (range)	2 (1–7)
≥3 prior regimens	16 (36%)
Refractory to prior therapy	12 (27%)
Prior anti-CD20 (rituximab, ofatumumab, obinutuzumab)	42 (93%)
Refractory to anti-CD20	13 (29%)
Prior alkylating agent	29 (64%)
Prior purine analogue	22 (49%)
High-risk (17p or 11q deletion, *TP53* mutation)	21 (47%)

ECOG, Eastern Cooperative Oncology Group performance status.

Table II. All causality adverse events in >10% of patients ($n = 45$).

Adverse event	All grades *n* (%)	Grade 3/4 *n* (%)
Infusion-related reaction	24 (53)	3 (7)
Diarrhoea	18 (40)	2 (4)
Fatigue	15 (33)	
Cough	12 (27)	
Rash	12 (27)	
Nausea	11 (24)	
Arthralgia	8 (18)	1 (2)
Upper respiratory tract infection	8 (18)	
Anaemia	7 (16)	5 (11)
Thrombocytopenia	7 (16)	3 (7)
Constipation	7 (16)	
Muscle spasms	7 (16)	
Pyrexia	7 (16)	
Abdominal pain	6 (13)	
Chills	6 (13)	
Contusion	6 (13)	
Dizziness	6 (13)	
Insomnia	6 (13)	
Myalgia	6 (13)	
Oedema, peripheral	6 (13)	
Stomatitis	6 (13)	
Neutropenia	5 (11)	5 (11)
Headache	5 (11)	

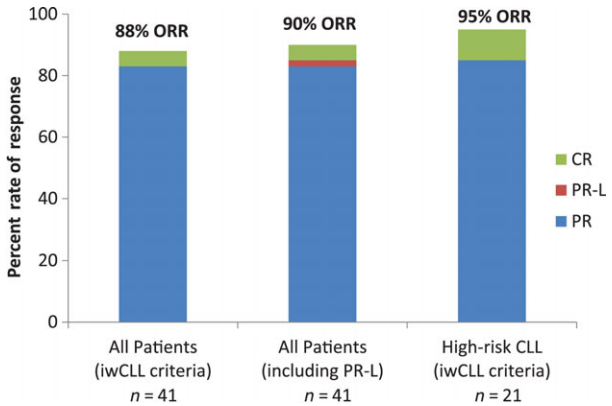

Fig 2. Best ORR. Forty-one patients were evaluable for efficacy. Per iwCLL criteria (Hallek *et al*, 2008), the ORR within 6 months was 88% with 5% CR and 83% PR. When PR-L is included, the ORR is 90%. In the high-risk CLL population (n = 20), the ORR per iwCLL criteria was 95%, with 10% CR and 85% PR. CLL, chronic lymphocytic leukaemia; CR, complete response; iwCLL, International Workshop for Chronic Lymphocytic Leukaemia; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis.

CLL subjects exhibited an ORR of 95% (10% CR and 85% PR) with 15% of the high-risk patients (one CR and two PR) achieving MRD negativity by four-colour flow cytometry within 6 months of therapy. Of the subjects who achieved a CR or PR, all but two of the responses occurred by week 8.

All 41 subjects had nodal reduction ranging from 20% to 100%, with 93% (38 of 41) of subjects achieving a >50% nodal reduction by month 6 (Fig 3). A median nodal reduction of 62% was observed at week 8 and 77% at week 20 for all CLL subjects; while among the high-risk subset, median nodal reductions of 64% and 85% were observed at weeks 8 and 20, respectively.

Absolute lymphocyte count (ALC) decreased significantly in the first month of treatment in most patients in the CLL group and continued to decrease over time (Fig 4). Addition of ublituximab to the treatment regimen appeared to reduce ibrutinib-related lymphocytosis, with a median 75% decrease in ALC from baseline by the end of cycle 3. More than 70% of CLL subjects had lymphocyte counts in the normal range (<4 × 10^9/l) within 6 cycles of therapy. Marked B-cell depletion and abrogation of lymphocytosis was also observed in the subset of patients who were refractory to prior anti-CD20 therapy (Fig S1).

Discussion

It is not yet known whether the kinetics of ibrutinib responses impact the durability of disease control. Early analyses of studies conducted with ibrutinib to date suggest that patients achieving PR-L on ibrutinib monotherapy exhibit similar outcomes to patients who achieved a true PR on ibrutinib (Woyach *et al*, 2014b), although long-term follow-up is not available in this selected clinical trial population. In the single-arm, phase 2 study that led to accelerated approval of ibrutinib (Byrd *et al*, 2013), the ORR by iwCLL 2008 criteria (Hallek *et al*, 2008) at 2 and 5 months were reported as 21% and 39%, respectively; however, an additional 52% and 46% of patients at 2 and 5 months, respectively, achieved PR-Ls, which, if included in the ORR assessment as per the suggested updates to the iwCLL criteria for response (Cheson *et al*, 2012), bring response rates at 2 and 5 months to 73% and 85%, respectively (Byrd *et al*, 2013). In a randomized, phase 3 study comparing ibrutinib to ofatumumab, the best response to ibrutinib was 43% PR, with an additional 20% demonstrating PR-L; CR was not observed (Byrd *et al*, 2014).

Initiation of ibrutinib often causes a transient lymphocytosis. Much of the initial clinical activity of ibrutinib may result from a demargination phenomenon, whereby disruption of the supportive microenvironment results in CLL cell migration from the lymph nodes into the peripheral circulation, rather than from direct cytotoxicity (de Rooij *et al*, 2012).

In this study, we observed that ublituximab abrogated the lymphocytosis commonly associated with ibrutinib. The ORRs by iwCLL 2008 criteria at 2 and 6 months were 83% and 88%, respectively, excluding those patients with PR-L. Further, within 6 months of initiating therapy, MRD-negative status

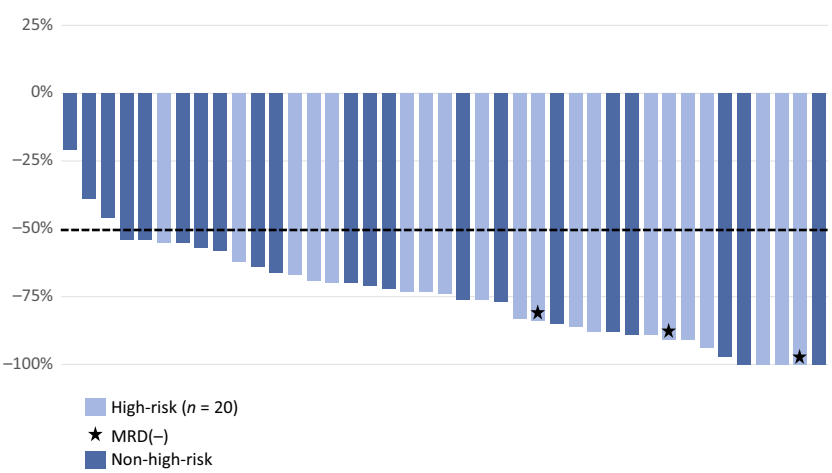

Fig 3. Best per cent change from baseline in nodal size: efficacy assessed at weeks 8 and 20. Thirty-eight of the 41 evaluable subjects, including all subjects with high-risk CLL (n = 41), achieved a ≥50% reduction in nodal size from baseline. Three subjects with high-risk CLL achieved MRD(−) status. CLL, chronic lymphocytic leukaemia; MRD(−), negative status for minimal residual disease.

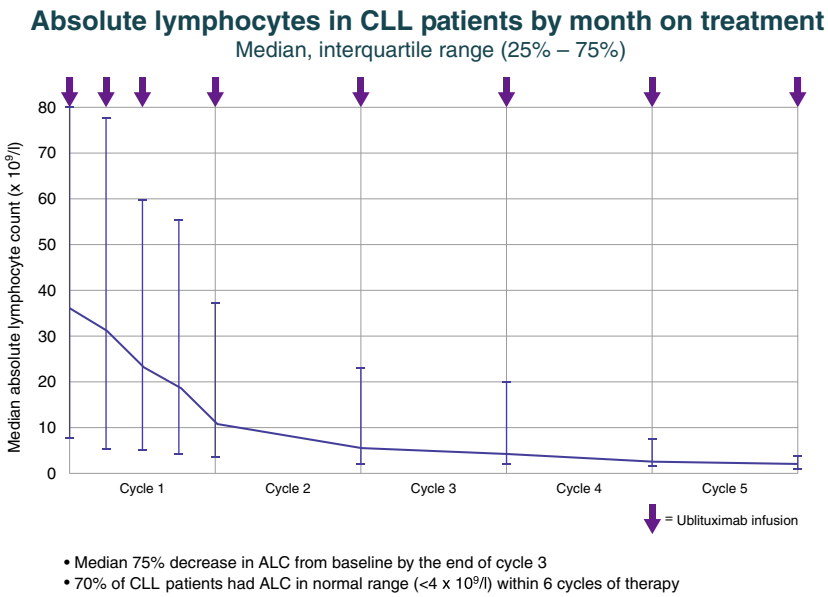

Fig 4. ALC by month on treatment. ALC decreased by a median of 75% from baseline by the end of cycle 3. Within 6 cycles of therapy, 70% of subjects had an ALC in the normal range ($<4 \times 10^9$/l). Vertical bars indicate the interquartile range. ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukaemia.

was achieved in 7% of patients, including 15% (3 of 20) with high-risk markers (17p or 11q deletions or a *TP53* mutation). In light of the recent observations that ibrutinib does not completely suppress BCR signalling in many patients and resistance is partly mediated through acquisition of *BTK*/*PLCG2* mutations (Jain *et al*, 2015; Maddocks *et al*, 2015; Poggesi *et al*, 2015), we hypothesize that the addition of anti-CD20 antibodies may protect against acquisition of resistance by providing alternative mechanisms of cytotoxicity. This study, however, does not provide confirmation of that hypothesis and will be addressed in multiple ongoing phase three studies, including: (i) ibrutinib monotherapy *versus* ublituximab plus ibrutinib in patients with previously treated high-risk CLL (NCT02301156); (ii) ibrutinib monotherapy, ibrutinib plus rituximab, or bendamustine plus rituximab in older patients with previously untreated CLL (NCT01886872); and (iii) ibrutinib plus obinutuzumab *versus* chlorambucil plus obinutuzumab in patients with previously untreated CLL (NCT02264574).

Two previous reports have characterized the addition of a CD20 antibody to ibrutinib (Burger *et al*, 2014; Jaglowski *et al*, 2015). The addition of rituximab to ibrutinib in high-risk CLL (either relapsed/refractory or treatment-naïve) resulted in an ORR of 95% by iwCLL 2008 criteria, including 8% CR as best overall response (Burger *et al*, 2014). In a separate study in which ofatumumab was added to ibrutinib, the ORR in CLL/SLL patients was 83·3%, with a single patient (1·5%) achieving a CR (Jaglowski *et al*, 2015). These two reports approximate the experience reported herein – however, several significant differences between trials are notable. The rituximab-plus-ibrutinib study included treatment-naïve patients (10% of study subjects) (Burger *et al*, 2014). Differences in response kinetics were also observed. In our study, the addition of ublituximab to ibrutinib caused the median lymphocyte count at 1 week to decrease. In contrast, neither rituximab nor ofatumumab therapy abrogated the lymphocytosis to the degree seen with ublituximab. In addition, 29% of enrolled subjects treated with ublituximab were deemed anti-CD20 refractory by standard definitions (progressing on or within 6 months of an anti-CD20-containing regimen). Additionally, age has emerged as an important predictor of ibrutinib tolerance, with older patients less able to tolerate ibrutinib therapy (Maddocks *et al*, 2015). Both the rituximab and ofatumumab studies included younger patient populations (median age 63 vs. 64 vs. 71 years for rituximab, ofatumumab and ublituximab, respectively). Whether rituximab, ofatumumab, obinutuzumab or ublituximab represents the optimal partner with ibrutinib cannot be determined from these comparisons; rather, these comparisons reinforce the faster and higher response rates observed when an anti-CD20 antibody is added.

There are concerns that ibrutinib could interfere with the activity of anti-CD20 antibodies. Ibrutinib binds interleukin-2 inducible tyrosine kinase (ITK) (Dubovsky *et al*, 2013). In NK cells stimulated by Fc receptor, ITK expression leads to calcium mobilization, granule release, and cytotoxicity (Khurana *et al*, 2007). Blocking of ITK by ibrutinib could, in theory, reduce the efficacy of anti-CD20 antibodies, and such antagonism has indeed been demonstrated *in vitro* (Kohrt *et al*, 2014; Da Roit *et al*, 2015). However, based on the robust lymphocyte depletion demonstrated by ublituximab in the presence of ibrutinib co-administration, no clinically meaningful evidence of such antagonism was observed in this study. In this context, the enhanced ADCC properties of ublituximab could provide an explanation for overcoming the antagonism demonstrated *in vitro* between rituximab and ibrutinib.

One important limitation of the current study is that it was not designed to evaluate PFS and OS. At the time this study was initiated, there were no reports of the clinical efficacy of BTK inhibitors given in combination with anti-CD20 antibodies. This study was designed primarily to evaluate

whether response rates, and particularly depth of response, were qualitatively different from those seen in the historic controls of ibrutinib monotherapy. An ongoing study using a randomized phase 3 design will determine the impact of the addition of ublituximab to ibrutinib on PFS and ORR in patients with high-risk CLL (NCT Identifier 02301156).

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Daruka Mahadevan: Conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript, provision of study material or patients.

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Disclosures of conflicts of interest

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Stock or Other Ownership: Celgene, Gilead, TG Pharma, Genmab.
Speakers' Bureau: Celgene, Takeda.

Leonard Klein
None.

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Consulting or Advisory Role: Celgene, Phmacyclics, Genentech.
Speakers' Bureau: Genentech.

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Leadership: TG Therapeutics.
Stock or Other Ownership: TG Therapeutics.

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Stock or Other Ownership: TG Therapeutics.

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Stock or Other Ownership: TG Therapeutics, Fortress Biotech.
Other Relationship: Opus Point Partners.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig S1. ALC by month in rituximab-refractory patients on treatment.

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