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A Phase I/Ib study of tolerability and activity of the chemotherapy-free triplet combination of ublituximab, umbralisib, and ibrutinib in patients with chronic lymphocytic leukaemia and non-Hodgkin lymphoma

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Summary

Background—Therapeutic approaches for B-cell malignancies continue to evolve, especially with regard to combination approaches. Ublituximab is a novel glycoengineered monoclonal antibody targeting a unique CD20 epitope. Umbralisib is a next-generation phosphoinositide 3-kinase delta (PI3Kδ) and casein kinase-1ε (CK1ε) inhibitor. Ibrutinib is a Bruton tyrosine kinase (BTK) inhibitor. This phase 1 trial evaluated the safety and efficacy of the chemotherapy-free triplet ublituximab, umbralisib, and ibrutinib in advanced B-cell malignancies.

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AUTHOR CONTRIBUTIONS

All authors were in charge of trial conception and design. LJN, MAL, JMV, MTS, TS, CRF, JBC, JAB, WGW, SO, PS, HPM, MAP, MSW, and NHF provided study materials and/or patients. Collection and assembly of data was conducted by LJN, PS, HPM, and MAP, while the data analysis and interpretation was performed by the sponsor with data access given to all authors for their review. LJN drafted the first draft of the manuscript with co-author input. Subsequent drafts were prepared and reviewed by all authors with the decision to submit the manuscript for publication, and attest to adherence to the study protocol and accuracy of data reported. The sponsor provided support in the form of a medical writer for formatting, revisions, and manuscript submission.

DATA SHARING STATEMENT

Data will be shared upon request.

DECLARATION OF INTERESTS

The other authors declared no conflict of interest.

Methods—Eligible patients in this intent-to-treat analysis had chronic lymphocytic leukaemia or relapsed/refractory B-cell non-Hodgkin lymphoma without a limit to the number of prior therapies, including prior PI3Kδ or BTK inhibitors. Escalating doses of umbralisib (400, 600, or 800 mg) were combined with fixed doses of ublituximab (900 mg) and ibrutinib (420 mg for chronic lymphocytic leukaemia/560 mg for B-cell non-Hodgkin lymphoma) in 28-day cycles until disease progression or intolerance. The primary endpoints were safety, DLTs, and MTDs. This trial is still ongoing, though no longer recruiting (NCT02006485).

Findings—Forty-six patients were enrolled [chronic lymphocytic leukaemia/small lymphocytic lymphoma (n=23); diffuse large B-cell (n=6), follicular (n=8), mantle cell (n=6), and marginal zone lymphoma (n=3)] in this phase 1/1b multi-centre, open-label, dose-escalation study. The maximum-tolerated dose was not reached. The most common adverse events (AEs) were diarrhoea (27/46, 59%), fatigue (23/46, 50%), infusion-related reaction (20/46, 43%), dizziness (17/46, 37%), nausea (17/46, 37%), and cough (16/46, 35%). Grade 3/4 AEs were infrequent with the most common being neutropenia (10/46, 22%); serious AEs included: rash (n=2), pneumonia (n=2), and atrial fibrillation (n=2).

Interpretation—The combination of ublituximab, umbralisib, and ibrutinib appears tolerable and is associated with favourable efficacy in advanced chronic lymphocytic leukaemia and B-cell non-Hodgkin lymphoma. This triplet combination will continue to be explored in future studies, which will improve understanding of the optimal role for this novel, chemotherapy-free triplet combination in the management these cancers.

Funding: TG Therapeutics

Keywords

ublituximab; umbralisib; ibrutinib; CLL; NHL

Introduction

Recent insights into the pathogenesis of mature B-cell malignancies have led to the development of therapies that target aberrant intracellular signalling of the B-cell receptor (BCR) pathway. Malignant B-cells often manipulate normal B-cell signalling to engage downstream pathways pivotal to proliferation and survival. This may be accomplished in various ways, either through gain-of-function mutations that activate signalling effectors, loss-of-function mutations that inactivate negative regulators, or autocrine receptor activation.[1–3] BCR pathway activation can be triggered by exogenous antigen, such as microbial or autoantigens, or by recognition of epitopes within the BCR itself (autonomous signalling),[4,5] although the contribution of these of these BCR activation mechanism is not fully elucidated.[3] Though there remains much to be learned about pathway addiction in B-cell lymphomas, targeting BCR signalling is an attractive therapeutic approach. Indeed, a number of BCR-associated tyrosine kinase inhibitors exist that have proven efficacy across a variety of B-cell lymphomas.[6]

Combining targeted, non-chemotherapeutic therapies to improve the durability and depth of response in chronic lymphocytic leukaemia and non-Hodgkin lymphoma is an attractive goal. Ublituximab is a novel third-generation type I chimeric anti-CD20 monoclonal

antibody bioengineered for enhanced antibody-dependent cytotoxicity (ADCC). This compound has demonstrated efficacy in relapsed or refractory chronic lymphocytic leukaemia and non-Hodgkin lymphoma patients who have been previously treated with rituximab.[7] Ublituximab depletes B-cells through complement-dependent cytotoxicity, programmed cell death, and ADCC. Combining ublituximab with ibrutinib is safe and associated with excellent activity in relapsed/refractory chronic lymphocytic leukaemia, with an ORR of 80% for ublituximab plus ibrutinib vs. 47% for ibrutinib alone in a recent study.[8]

Umbralisib is a next-generation phosphoinositide 3-kinase delta (PI3Kδ) and casein kinase-1ε (CK1ε) inhibitor.[9] It has a unique structure and activity profile that is distinct from that of other PI3Kδ inhibitors in development, including greater selectivity toward the δ isoform of PI3K and a prolonged half-life that enables once-daily dosing. In addition, umbralisib appears to have a differentiated safety profile compared with that of other PI3Kδ inhibitors, particularly with regard to hepatic toxicity and colitis.[9] Umbralisib has been safely combined with ublituximab with encouraging efficacy in preliminary reports (ORR of 57%) of patients with relapsed/refractory non-Hodgkin lymphoma and chronic lymphocytic leukaemia.[10]

Ibrutinib is a first-in-class inhibitor of Bruton tyrosine kinase (BTK) with single-agent activity in R/R chronic lymphocytic leukaemia and other B-cell malignancies.[2,11–15] New approaches are needed, however, for patients who develop ibrutinib resistance, as post-ibrutinib outcomes can prove poor.[16,17] Combining targeted agents with varying mechanisms of action appears promising with regard to synergism and overcoming resistance, however, the safety of some of the combinations explored in recent studies can present specific challenges.[18,19] Indeed, umbralisib and ublituximab have displayed synergistic activity in pre-clinical studies.[20] Various combinations of umbralisib, ublituximab, and ibrutinib are under evaluation in clinical studies. In preliminary analyses, umbralisib plus ublituximab (NCT02006485), umbralisib plus ibrutinib (NCT02268851), and ublituximab plus ibrutinib (NCT02301156) have all resulted in ORRs above 80% in patients with chronic lymphocytic leukaemia.[21–23] Thus, we conducted a phase 1/1b dose-escalation study to assess the safety of the combination of ublituximab, umbralisib, and ibrutinib in chronic lymphocytic leukaemia /small lymphocytic lymphoma and relapsed/refractory B-cell non-Hodgkin lymphoma.

Material and Methods

Study design and participants

In this phase 1/1b open-label, multi-centre, dose-escalation study, eligible patients were adults (≥18 years) with histologically confirmed B-cell non-Hodgkin lymphoma or chronic lymphocytic leukaemia / small lymphocytic lymphoma who had measurable disease, adequate organ function (absolute neutrophil count [ANC] ≥0·75 × 10^9/L, platelets ≥50 × 10^9/L, total bilirubin ≤1·5 × the upper limit of normal [ULN], alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2·5 × the ULN if no liver involvement or ≤5 × the ULN if known liver involvement and creatinine levels ≤2·0 mg/dL or clearance rate ≥50 mL/min as calculated by the Cockcroft-Gault method), and Eastern Cooperative Group (ECOG) performance status (PS) of ≤2. Patients in the B-cell non-Hodgkin lymphoma

cohort were refractory to or relapsed after at least one prior treatment regimen. Patients in the chronic lymphocytic leukaemia / small lymphocytic lymphoma cohorts initially had relapsed or refractory disease, and then the study was expanded to include patients who were previously untreated. Patients with known CNS lymphoma, active hepatitis B or C, or known history of HIV were excluded. This study was approved by local institutional review boards, and all patients or their legal representatives provided written informed consent before enrolment. The study was designed jointly by the investigators and sponsor according to Good Clinical Practice guidelines and the Declaration of Helsinki.

Procedures

A standard 3+3 dose-escalation design was used to evaluate escalating doses of umbralisib (400 mg, 600 mg, 800 mg) with fixed doses of ublituximab (900 mg), both of which were supplied by TG Therapeutics, Inc., New York, NY, USA, and commercial ibrutinib (420 mg for chronic lymphocytic leukaemia; 560 mg for B-cell non-Hodgkin lymphoma). Ublituximab was administered by intravenous infusion on days 1, 8, and 15 of cycle 1, day 1 of cycles 2 to 6, and on day 1 of cycles 9 and 12. Umbralisib and commercial ibrutinib were administered orally daily, starting on day 1 of cycle 1, and continued until disease progression or removal from study. Dose reductions and interruptions were applied as per protocol. Based on reports of opportunistic infections in studies with other PI3kδ agents, the protocol was amended in June 2015 to allow prophylactic treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy prior to cycle 1/day 1 at the discretion of the treating investigator. As a result, 15/46 (33%) of patients received prophylaxis treatment.

Toxicity was assessed during treatment and for 30 days following discontinuation using Common Terminology Criteria for Adverse Events v4.03. Efficacy assessments were performed at week 8 and approximately every 12 weeks thereafter through month 12. After month 12, efficacy assessments occurred at least every 6 months or at the treating physician’s discretion. Response assessment was performed according to the Revised Response Criteria for Malignant Lymphoma[24] for the B-cell non-Hodgkin lymphoma cohort and the International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) guidelines[25] for the chronic lymphocytic leukaemia / small lymphocytic lymphoma cohort.

Outcomes

The primary objective of this study was to evaluate the safety of the triplet combination and determine the dose-limiting toxicities (DLT) and maximum-tolerated dose (MTD) of ublituximab, umbralisib, and ibrutinib in patients with B-cell lymphoma (Supplemental Materials, page 6). The secondary objectives were to determine the overall response rate (ORR), defined as the sum of complete responses (CRs) and partial responses (PRs), progression-free survival (PFS), and duration of response (DOR). Minimal residual disease (MRD) assessment for patients with chronic lymphocytic leukaemia was introduced as protocol amendment (January 2017) and defined by peripheral blood samples collected and analysed in both central and local laboratories using a minimum of four-color flow cytometry with a lower limit of detection of <0·01%. The data cut-off for this publication was November 2017.

Statistical analysis

Descriptive statistics were used for all variables and all data listed by appropriate group. The response rate and the 90% one-sided confidence interval of the rate were estimated. Response assessments were performed by the principal investigators, with central confirmation of CRs. DOR was defined as the time from documentation of a response to treatment to the first documentation of tumour progression or death due to any cause, whichever came first. DOR was summarised using sample size, mean, standard deviation, median, minimum, and maximum for the responders. PFS was defined as the time from study entry to the first documentation of tumour progression or death due to any cause. Time to event variables were analysed using the Kaplan-Meier method. Unless otherwise stated, all statistical analyses were performed using a two-sided hypothesis test at an overall significance level of 5%. All analyses were performed using **SAS 9.2 or higher version** (SAS Institute Inc, Cary, NC). The intent-to-treat (ITT) population consisted of all patients who were enrolled and had at least one post-treatment efficacy measurement with primary efficacy analyses performed on the ITT population. The Safety Population included all patients who were enrolled and received at least one dose of study drug. All safety assessments including toxicity were performed on the Safety Population. DLT (defined in supplemental information) evaluation was conducted within the first cycle (28 days) of treatment. The trial is registered at www.clinicaltrials.gov (NCT02006485).

Role of the funding source

The funder of the study led the study design and had a role in data analysis, data interpretation, and writing of the report. Umbralisib and ublituximab were provided by the sponsor and ibrutinib was purchased commercially. The funder of the study had no role in data collection. LJN, PS, HPM, MAP, and MSW had full access to the raw data. All authors had access to the primary clinical study data, met ICMJE criteria, reviewed and provided feedback on each manuscript version, and agreed to submit the final version for publication. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.

Results

Patient characteristics

Forty-six patients were enrolled between September 2, 2014 and November 6, 2017 (n=23 chronic lymphocytic leukaemia / small lymphocytic lymphoma; n=23 B-cell non-Hodgkin lymphoma, Figure 1). The median age was 62 years (IQR: 56–67), and a majority of patients were male (n=35). Twelve patients (26%) had an ECOG PS of 0, 33 (72%) had a PS of 1, and one (2%) had a PS of 2 (Table 1). Among the chronic lymphocytic leukaemia small lymphocytic lymphoma cohort, four patients (17%) were treatment-naïve, and nine patients (39%) had deletions of 17p and/or 11q. The median number of prior therapies for all patients was 3 (IQR: 1–4), with 27 patients (59%) having three or more prior therapies. Five patients (11%) were refractory to prior PI3K inhibitor treatment, 3 (7%) were refractory to prior BTK inhibitor, and 14 (30%) were refractory to prior CD20 antibody therapy. Among the B-cell non-Hodgkin lymphoma cohort, patients were enrolled with diffuse large B-cell lymphoma (n=6), follicular lymphoma (n=8), mantle cell lymphoma (n=6),

and marginal zone lymphoma (n=3). Two follicular lymphoma patients had prior high-dose therapy/autologous stem cell transplant (HDT/ASCT), and one patient was refractory to prior ibrutinib. Among those with diffuse large B-cell lymphoma, 4 (67%) patients had the non-germinal centre subtype. Diffuse large B-cell lymphoma patients were not eligible for HDT/ASCT and had received a median of 4 prior treatments (IQR: 3–4).

Safety and tolerability data

All 46 patients were analysed in the safety analyses. The median time on study was 16 months (IQR: 6.8 to 24.5), with the longest patient on study for 44 months. Seventy-six percent of patients received ≥6 months of therapy, and 18 (47%) are still on therapy. The MTD of umbralisib in combination with ublituximab and ibrutinib in chronic lymphocytic leukaemia / and relapsed or refractory B-cell non-Hodgkin lymphoma was not reached within the tested dose range (up to 800 mg daily). One DLT of reactivated varicella zoster was observed in the chronic lymphocytic leukaemia / cohort at dose level 1 (400 mg umbralisib, 900 mg ublituximab, and 420 mg ibrutinib). This patient fully recovered with dose interruption and was successfully rechallenged. No other DLTs were observed.

Adverse events (AEs) occurring in ≥10% of patients are summarised in Table 2. The most common AEs were diarrhoea (27/46, 59%), fatigue (23/26, 50%), infusion-related reaction (20/46 43%), dizziness and nausea (both 17/46, 37%), cough (16/46, 35%), insomnia, neutropenia, pyrexia (all 15/46, 33%), thrombocytopenia (13/46, 28%), and peripheral oedema (12/46, 26%). Grade 3/4 AEs were infrequent, with the most common being neutropenia (10/46, 22%) and cellulitis (6/46, 13%). Of the patients who experienced grade 3/4 neutropenia, only 1/10 (10%) experienced grade 3/4 febrile neutropenia. Four patients (9%) had grade 3 diarrhoea. No grade 4 diarrhoea was reported, and no cases of colitis of any grade were reported. Pneumonitis was observed in 2 patients (4%, all grade 2). Neither of the 2 patients with pneumonitis were dose reduced and both were re-challenged successfully without recurrence. Of the 27 patients with diarrhoea, 2 patents were dose reduced (600 mg) with one eventually discontinuing study drugs due to recurring diarrhoea. All other patients were rechallenged successfully after initial umbralisib interruption. Twenty serious AE’s occurred in 11 patients which were considered related to at least one of the 3 study drugs. Events occurring in 2 or more patients were as follows: rash (n=2), pneumonia (n=2), and atrial fibrillation (n=2). No deaths related to AEs have been observed, and only one study death has occurred to date—a small lymphocytic lymphoma patient who died six weeks into study from pneumonia that was determined to be unrelated to study drug.

In total, 24 patients (52%) had an ublituximab dose delay, 20 patients (43%) had an umbralisib dose delay, and 20 (43%) had an ibrutinib dose delay, with infusion-related reactions, neutropenia, and stomatitis being the most common reason for each, respectively (Suppl. Table 1, page 2). Fifteen patients (33%) had dose reductions of either umbralisib (n=6) or ibrutinib (n=9). In total, 8 patients (17%) discontinued study treatment due to AEs—2 withdrew due to umbralisib (sepsis, pulmonary oedema), 5 due to ibrutinib (atrial fibrillation/cardiac complications, sepsis and pneumonitis), and 1 withdraw due to ublituximab (sepsis).

Efficacy

In total, 44 patients were evaluable for efficacy. Two patients (1 with follicular lymphoma and 1 with small lymphocytic lymphoma) discontinued therapy before efficacy assessments for reasons unrelated to the therapy drugs. Response rates for the overall study population of evaluable patients and by histologic subtype are presented in Table 3. The ORR for all patients was 84% (37/44). The ORRs by histologic subtype were 100% (22/22) for chronic lymphocytic leukaemia / small lymphocytic lymphoma, mantle cell lymphoma, and marginal zone lymphoma, 71% (5/7) for follicular lymphoma, and 17% (1/6) for diffuse large B-cell lymphoma patients. For sensitivity, inclusion of the 2 patients who were not evaluable for efficacy analyses as non-responders would yield an ORR of 80% (37/46) for the overall population, with 22/23 (96%) patients with chronic lymphocytic leukaemia / small lymphocytic lymphoma and 5/8 (63%) patients with follicular lymphoma responding to treatment. Among 18 patients with previously treated chronic lymphocytic leukaemia, 8 (44%) achieved a CR and 10 (56%) achieved a PR. All 8 evaluable patients with 17p deletion responded to treatment, with 5/8 (63%) having a CR and 3/8 (38%) having a PR. Best response observed per patient are summarised in Figure 2. Among 9 of 22 (41%) chronic lymphocytic leukaemia patients analysed for MRD, 7/9 (78%) achieved MRD negativity, with 3/7 achieving CR and 4/7 achieving PR.

With a median follow-up of 16 months (IQR: 6.8 – 24.5), the median DOR for all patients was 21·8 months (IQR: 8.5–24.3; Figure 3). Considering the DOR by histologic subtype, the median DOR observed was 22·7 months (IQR: 8.6–25.9) in chronic lymphocytic leukaemia / small lymphocytic lymphoma, 14·6 months (IQR: 5.5–22.2) in mantle cell lymphoma, 20·0 months (IQR: 7.3–23.8) in marginal zone lymphoma, 23·4 (IQR: 13.8–24.3) months in follicular lymphoma. The median time to first response was 1·8 months (IQR: 1.7–1.9) for all patients. The Kaplan-Meier estimate of median PFS for all patients was 38·2 months (IQR: 15.5 - NE; Figure 4). Considering PFS by histologic subtype, the median PFS observed was not reached (NR) (IQR: 24.5-NE) in chronic lymphocytic leukaemia / small lymphocytic lymphoma, NR (IQR: NE-NE) in mantle cell lymphoma, NR in marginal zone lymphoma (IQR: 21.3-NE), 38·2 months in follicular lymphoma (IQR: 15.5–38.2), and 1·3 months in diffuse large B-cell lymphoma patients (IQR: 0.8–1.8).

Based on these safety and efficacy data, the recommended phase 2 dose (RP2D) for umbralisib in combination with ublituximab (900 mg) and ibrutinib (420 mg chronic lymphocytic leukaemia; 560 mg B-cell non-Hodgkin lymphoma) was determined to be 800 mg daily (continuous dosing).

Discussion

Therapeutic targeting of the BCR signalling pathway has revolutionized the management of B-cell lymphomas. Optimal combinations that will induce deeper remissions, possibly allowing for discontinuation of therapy, are needed. Ublituximab in combination with umbralisib and ibrutinib is a novel non-chemotherapy combination that has separate, non-overlapping mechanisms of action against B-lymphocytes. This phase 1/1b study demonstrated that the combination of ublituximab, umbralisib, and ibrutinib is associated with a favourable safety profile, manageable AEs, and no treatment-related deaths in heavily

pretreated B-cell non-Hodgkin lymphoma and untreated chronic lymphocytic leukaemia / small lymphocytic lymphoma patients. The MTD for this triplet combination was not reached. Additionally, the combination was associated with durable high response rates of 71% (5/7) to 100% (22/22) in follicular lymphoma, chronic lymphocytic leukaemia / small lymphocytic lymphoma, mantle cell lymphoma, and marginal zone lymphoma.

In this study, the umbralisib, ublituximab, ibrutinib combination appears to be associated with a favourable toxicity profile and no new or unexpected AEs were observed. The frequency of grade 3 or higher AEs with this combination was low (with only 6 events occurring in ≥5% of patients), and more than 76% (35/46) of patients had greater than six months of drug exposure. Although 10 patients (22%) experienced grade 3/4 neutropenia, only 1 (2%) experienced febrile neutropenia. Of particular interest, the frequencies of any grade transaminitis and pneumonitis were low, and no cases of colitis were reported. This is in contrast to the frequencies of transaminitis and colitis observed in studies with the PI3Kδ inhibitor idelalisib.[18,19,26,27] A phase 2 study of idelalisib in combination with rituximab in frontline chronic lymphocytic leukaemia reported an ORR of 97% (19% CR), but also reported a higher rate of grade 3 or higher diarrhoea/colitis (42%) and transaminitis (23%).[18] It is suspected that impaired regulatory T-cell function through inhibition of PI3Kδ in a more immune competent host contributed to the higher rate of toxicity in this study. In our study, albeit with a smaller number of patients, we have observed toxicity profiles that are comparable to single-agent reports, suggesting that combination treatment may not increase toxicity concerns. Additionally, the use of prophylactic treatment with pneumocystis jiroveci pneumonia (PCP) and antiviral therapy at investigator's discretion was permitted in this study, which may help account for the lower rate of infections. Four patients with treatment-naïve chronic lymphocytic leukaemia / small lymphocytic lymphoma were included in this study, with rates of AEs that were comparable to rates for the entire study group.

Adherence to therapy is associated with improved patient outcomes. For example, a recent study reported that patients who experienced ibrutinib interruptions of less than 8 days had fewer PFS events.[28] The favourable toxicity profile observed with ibrutinib in combination with ublituximab and umbralisib may explain the infrequent discontinuations as a result of AEs and the large portion of patients remaining on study drug for more than 6 months. Manageable toxicity with either drug interruption or dose modification may have contributed to the observed efficacy in this study.

The optimal duration of therapy with targeted agents remains unclear. In this study, umbralisib and ibrutinib were continued daily until disease progression or intolerance. We have observed high response rates and meaningful PFS with such ongoing therapy. Although only small numbers of patients have been studied to date, we observed CRs across the indolent lymphoma subtypes as well as mantle cell lymphoma. Although this study was not designed to answer whether discontinuing therapy at MRD or CR would impact efficacy, this concept is appropriate for future exploration.

The diffuse large B-cell lymphoma patients in this study were heavily pretreated with a high tumour volume and failed to achieve meaningful responses with this combination, suggesting the highly proliferative nature of their tumour may not be able to be overcome

with this chemotherapy-free approach. With only six diffuse large B-cell lymphoma patients included in this study, however, caution should be applied when drawing any conclusions regarding efficacy in this population. The combination of umbralisib, ublituximab, plus bendamustine in relapsed or refractory diffuse large B-cell lymphoma and follicular lymphoma is currently under investigation; the cytotoxic activity of bendamustine may provide the necessary disease control when combined with targeted therapy in diffuse large B-cell lymphoma.

One limitation of this study is the lack of correlative comparisons to examine potential synergism or mechanisms of resistance. The emergence of increasing numbers of therapeutic agents with promising efficacy, such as immune modulators, BCL-2 inhibitors, and BCR-targeting agents, is rapidly expanding the treatment landscape; however, few biomarkers are available to guide treatment decisions. Future studies are needed to identify appropriate biomarkers to improve prognostic abilities and guide treatment decisions. Additional limitations to this study include the inclusion of a heterogenous patient population that resulted in small numbers of patients in each lymphoma subgroup.

In summary, the findings of this study establish the tolerable safety profile of the ublituximab, umbralisib, and ibrutinib regimen in chronic lymphocytic leukaemia / small lymphocytic lymphoma and relapsed/refractory B-cell non-Hodgkin lymphoma. This triplet combination is expected to be explored further in future clinical trials in various patient populations. Additionally, various doublet combinations, such as ibrutinib + umbralisib, are currently being examined in patients with relapsed/refractory chronic lymphocytic leukaemia and mantle cell lymphoma (NCT02268851). Additional follow-up from the expansion phase of this study will improve understanding of the optimal role for this novel, chemotherapy-free triplet combination in the management of chronic lymphocytic leukaemia / small lymphocytic lymphoma, follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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RESEARCH IN CONTEXT

Evidence before this study

There is an unmet need for new therapies which aim to improve the efficacy, durability, and tolerability for patients with advanced chronic lymphocytic leukaemia and non-Hodgkin lymphoma. The importance of targeting B-cell receptor signalling in B-cell malignancies has been well established in the literature over the last decade. Ibrutinib is a Bruton tyrosine kinase inhibitor with single-agent activity in B-cell malignancies, however, patients who develop resistance to ibrutinib often face poor outcomes. Ublituximab is a novel third generation type I chimeric anti-CD20 monoclonal antibody bioengineered for enhanced antibody-dependent cytotoxicity, while umbralisib is a next-generation PI3K delta and CK1 epsilon inhibitor. Ublituximab in combination with umbralisib and ibrutinib represents a novel approach which has the advantage of targeting malignant B-lymphocytes via separate, non-overlapping mechanisms of action. Combining targeted, non-chemotherapeutic therapies to improve durability and depth of response in advanced chronic lymphocytic leukaemia and non-Hodgkin lymphoma is an attractive goal and provided the rationale to assess this combination of ublituximab, umbralisib, and ibrutinib in chronic lymphocytic leukaemia and R/R B-cell non-Hodgkin lymphoma.

Added value of this study

This study demonstrates that ublituximab, umbralisib, and ibrutinib can be safely combined with no new or unexpected AEs and yields a response rate of 100% in chronic lymphocytic leukaemia, mantle cell lymphoma, and marginal zone lymphoma and 71% in follicular lymphoma. Unfortunately, diffuse large B-cell lymphoma patients in this study failed to achieve meaningful responses, suggesting the highly proliferative nature of their tumours may not be able to be overcome with a chemotherapy-free approach. Median duration of response was 22·7 months for chronic lymphocytic leukaemia patients, 14·6 months for mantle cell lymphoma, 20·0 months for marginal zone lymphoma, and 23·4 months for follicular lymphoma patients. Additionally, the median PFS has not been reached in chronic lymphocytic leukaemia, mantle cell lymphoma, or marginal zone lymphoma.

Implications of all the available evidence

To our knowledge, this is the first study to combine ublituximab, umbralisib, and ibrutinib has demonstrated that this regimen in safe. The high overall response rate and durability of responses suggests that combining agents that target B-lymphocytes with non-overlapping mechanisms of action may represent a useful addition to the management strategies for patients with chronic lymphocytic leukaemia and relapsed/refractory non-Hodgkin lymphoma. The expansion phase of this study is ongoing, and further study of this triplet combination, as well as doublet combinations, will be explored in future clinical trials.

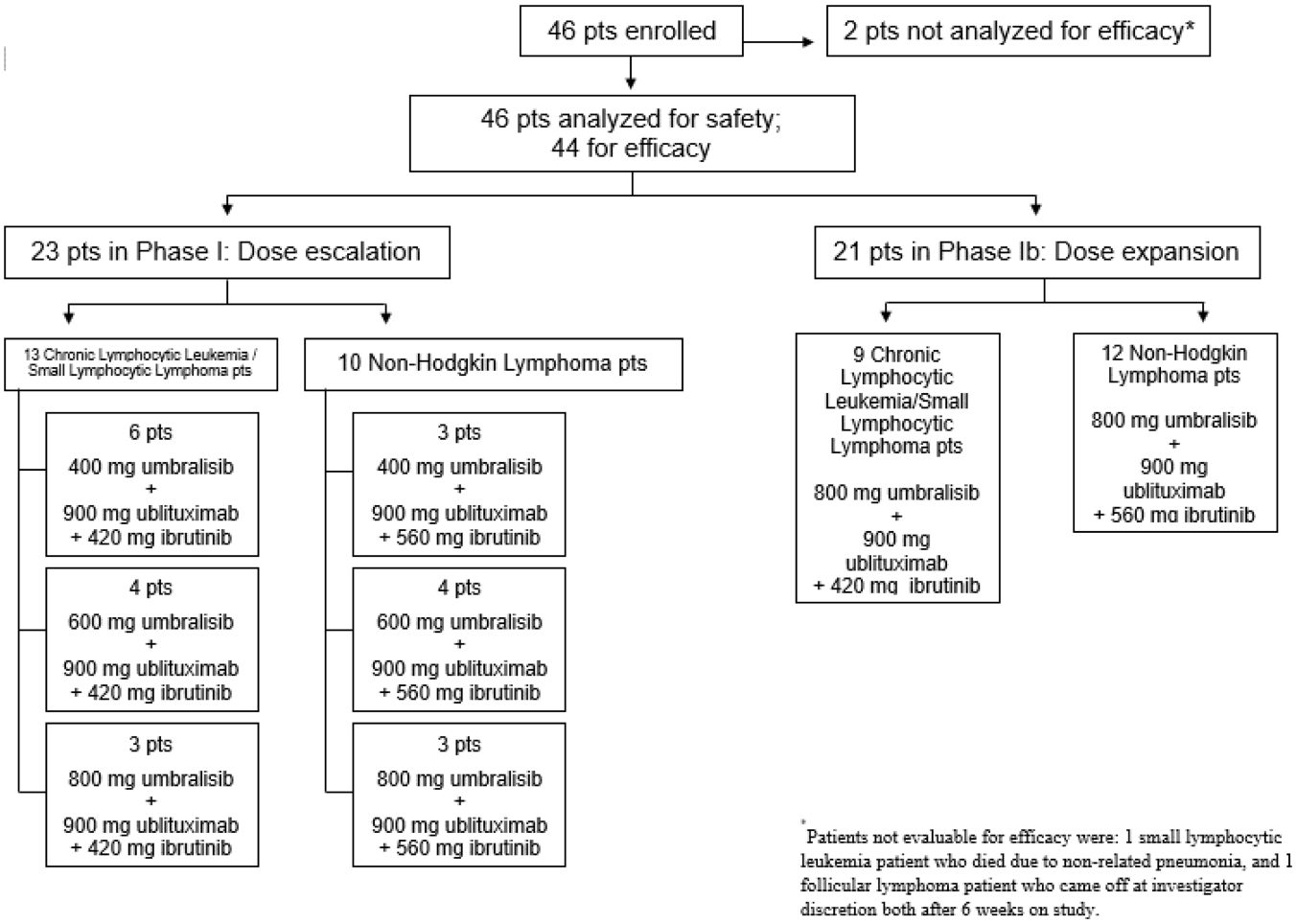


Figure 1. Trial Profile.

23 patients were included in the Phase I dose escalation portion of the study, while 21 were included in the Phase Ib dose expansion cohorts.

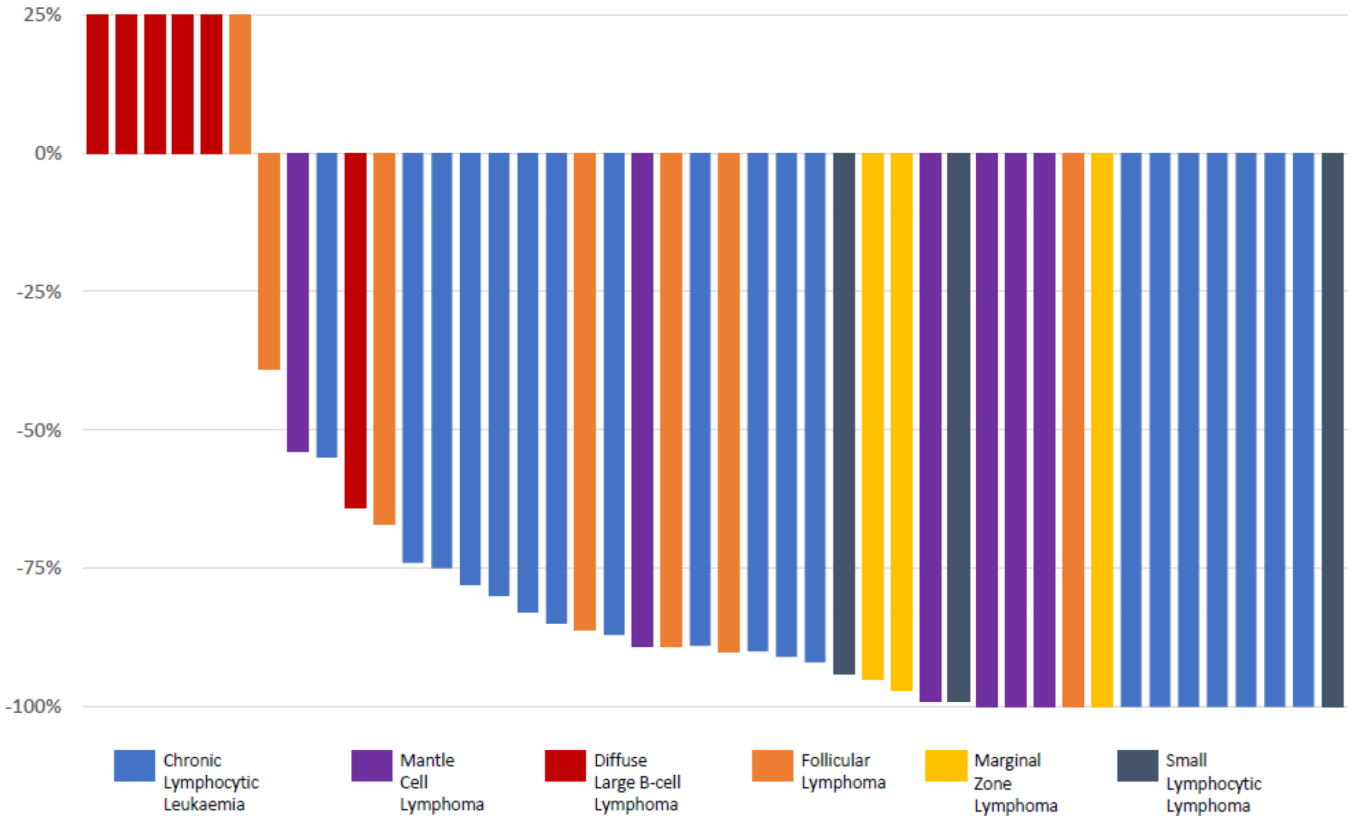


Figure 2. Best percentage change from baseline in disease burden.

The best percentage change in tumour size for 44 patients eligible for efficacy analysis was determined by principal investigators. Each bar represents an individual patient. Patients are grouped according to histology.

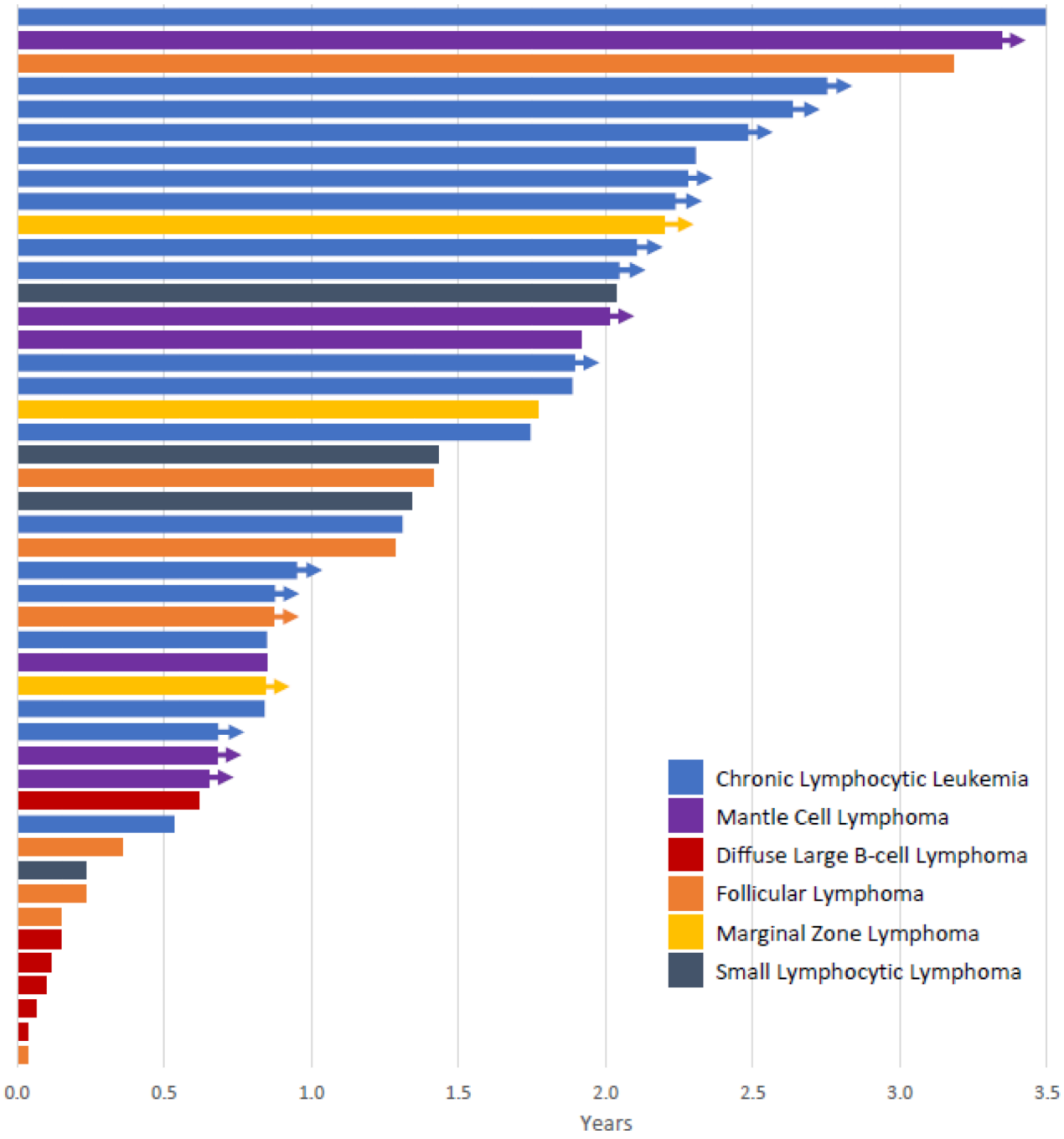
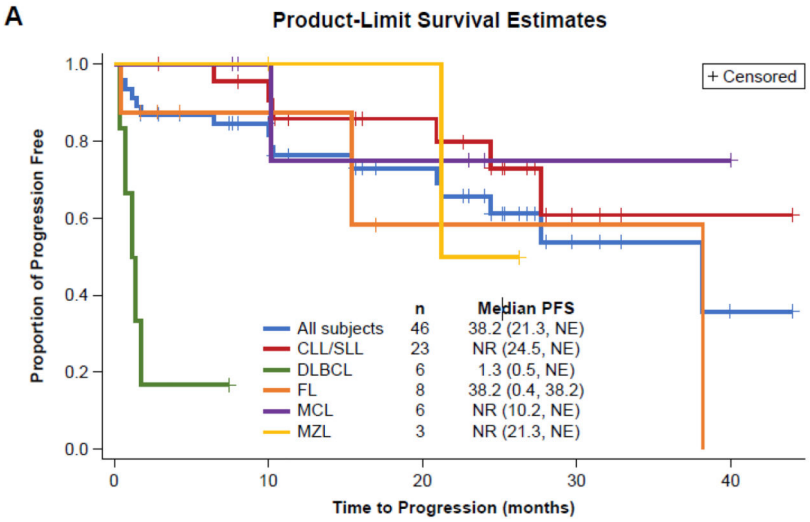


Figure 3. Duration of response for individual patients.

The duration of response for 44 patients eligible for efficacy analysis. Each bar represents an individual patient. Patients are grouped according to histology.

(A) PFS by histologic subtype



(B) PFS for Chronic lymphocytic leukaemia / small lymphocytic lymphoma patients by key baseline patient characteristics

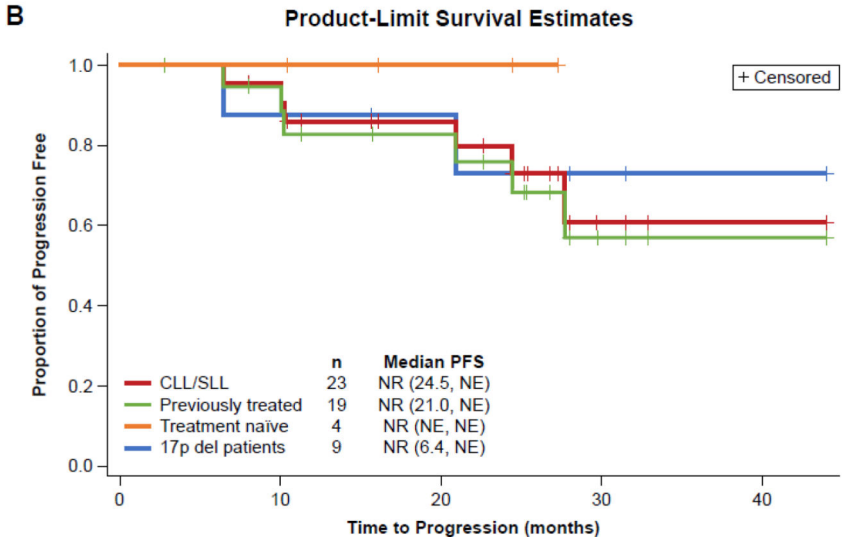


Figure 4. Kaplan-Meyer curves for progression-free survival.

(A). PFS by histologic subtype. DLBCL=diffuse large B-cell lymphoma. FL=follicular lymphoma. MZL=marginal zone lymphoma. CLL=chronic lymphocytic leukaemia. SLL=small lymphocytic lymphoma. MCL=mantle cell lymphoma. **(B).** PFS for chronic lymphocytic leukaemia / small lymphocytic lymphoma patients (n=23) by key baseline patient characteristics. CLL=chronic lymphocytic leukaemia. SLL=small lymphocytic lymphoma.

Table 1.

Patient baseline characteristics

Evaluable for safety, n	46
Evaluable for efficacy [†], n	44
Age, years, median (range)	62 (32 to 85)
Sex, n	
Male	35
Female	11
Histology, n	
Chronic lymphocytic leukaemia/small lymphocytic lymphoma	23
Treatment-naïve chronic lymphocytic leukaemia	4
Previously-treated chronic lymphocytic leukaemia	19
17p deletion	9
Diffuse large B-cell lymphoma	6
Follicular lymphoma	8
Mantle cell lymphoma	6
Marginal zone lymphoma	3
ECOG performance status, n	
0	12
1	33
2	1
Prior therapy regimens, median (IQR)	3 (1 to 4)
Patients with ≥3 prior therapies n (%)	27 (59)
Prior PI3K, n (%)	6 (13)
Refractory to prior PI3K	5 (11)
Prior BTK, n (%)	6 (13)
Refractory to prior BTK	3 (7)
Prior CD20, n (%)	42 (91)
Refractory to prior CD20[§]	14 (30)
Refractory to prior therapy, n (%)	16 (35)
Prior SCT	8 (17)

ECOG=Eastern Cooperative Oncology Group.

[†]Patients who were not evaluable for efficacy were: 1 small lymphocytic lymphoma patient who died due to non-related pneumonia after 6 weeks on study, and 1 follicular lymphoma patient who came off for investigator discretion after 6 weeks on study.

[§]Patients progressing on or within 6 months of a rituximab-based regimen were considered refractory to prior CD20; this did not include those threated with a lower dose of rituximab as maintenance therapy.

Table 2.

Adverse events occurring in >10% of patients, N=46

Adverse Event	All Grades, n (%)	Grade 3/4, n (%)
Diarrhoea	27 (59)	4 (9)
Fatigue	23 (50)	0
Infusion-related reaction	20 (43)	0
Dizziness	17 (37)	1 (2)
Nausea	17 (37)	1 (2)
Cough	16 (35)	0
Insomnia	15 (33)	0
Neutropenia	15 (33)	10 (22)
Pyrexia	15 (33)	2 (4)
Thrombocytopenia	13 (28)	3 (7)
Oedema peripheral	12 (26)	0
Stomatitis	11 (24)	3 (7)
Vomiting	11 (24)	2 (4)
Anaemia	10 (22)	1 (2)
Rash	10 (22)	1 (2)
Back pain	9 (20)	0
Headache	9 (20)	2 (4)
Pneumonia	9 (20)	4 (9)
Blood creatinine increased	8 (17)	0
Constipation	8 (17)	0
Upper respiratory tract infection	8 (17)	0
Abdominal pain	7 (15)	1 (2)
Contusion	7 (15)	
Dyspnoea	7 (15)	1 (2)
Hyperglycaemia	7 (15)	3 (7)
Hypokalaemia	7 (15)	0
Pleural effusion	7 (15)	2 (4)
Sinusitis	7 (15)	0
Vision blurred	7 (15)	0
Vitamin D decreased	7 (15)	0
Anxiety	6 (13)	0
Cellulitis	6 (13)	6 (13)
Ecchymosis	6 (13)	0
Hypertension	6 (13)	1 (2)
Hypophosphatemia	6 (13)	2 (4)
Bronchitis	5 (11)	0
Dyspepsia	5 (11)	0

Adverse Event	All Grades, n (%)	Grade 3/4, n (%)
Hypoalbuminaemia	5 (11)	0
Hypocalcaemia	5 (11)	0
Myalgia	5 (11)	0
Neuropathy peripheral	5 (11)	0
Oropharyngeal pain	5 (11)	0

Table 3.

Overall response by histology (all doses, intent-to-treat)

Histology	Response, n (%)				
	ORR (CR + PR)	**CR**	**PR**	**SD**	**PD**
All patients (N=44)	**37 (84)**	**13 (30)**	**24 (55)**	**1 (2)**	**6 (14)**
Chronic lymphocytic leukaemia/ small lymphocytic lymphoma (n=22)	22 (100)	8 (36)	14 (64)	-	-
Treatment naïve (n=4)	*4 (100)*	-	*4 (100)*	-	-
Previously treated (n=18)	*18 (100)*	*8 (44)*	*10 (56)*	-	-
17p deletion (n=8)	*8 (100)*	*5 (63)*	*3 (38)*	-	-
Follicular lymphoma (n=7)	5 (71)	1 (14)	4 (57)	1 (14)	1 (14)
Marginal zone lymphoma (n=3)	3 (100)	1 (33)	2 (67)	-	-
Mantle cell lymphoma (n=6)	6 (100)	3 (50)	3 (50)	-	-
Diffuse large B-cell lymphoma (n=6)	1 (17)	-	1 (17)	-	5 (83)

CR=complete response. ORR=overall response rate. PD=progressive disease. PR=partial response. SD=stable disease.