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The phase 3 DUO trial: duvelisib versus ofatumumab in relapsed and refractory CLL/SLL

SHORT TITLE

Duvelisib, a dual PI3K-δ,γ inhibitor in CLL

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Abstract

Duvelisib (also known as IPI-145) is an oral, dual inhibitor of phosphoinositide 3-kinase (PI3K)-δ and -γ being developed for treatment of hematologic malignancies. PI3K-δ,γ signaling can promote B cell proliferation and survival in clonal B cell malignancies, such as chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). In a Phase 1 study, duvelisib showed clinically meaningful activity and acceptable safety in CLL/SLL patients. We report here the results of DUO™, a global Phase 3 randomized study of duvelisib versus ofatumumab monotherapy for patients with relapsed or refractory (RR) CLL/SLL. Patients were randomized 1:1 to oral duvelisib 25 mg twice daily (BID) (n = 160) or ofatumumab intravenous (IV) (n = 159). The study met the primary study endpoint by significantly improving progression-free survival (PFS) per Independent Review Committee (IRC) assessment compared to ofatumumab for all patients (median 13.3 months versus 9.9 months; hazard ratio [HR] = 0.52; $p < 0.0001$), including those with high-risk chromosome 17p13.1 deletions [del(17p)] and/or *TP53* mutations (HR = 0.40; $p = 0.0002$). The overall response rate (ORR) was significantly higher with duvelisib (74% versus 45%; $p < 0.0001$) regardless of del(17p) status. The most common adverse events (AEs) were diarrhea, neutropenia, pyrexia, nausea, anemia, and cough on the duvelisib arm, and neutropenia and infusion reactions on the ofatumumab arm. The DUO trial data support duvelisib as a potentially effective treatment option for patients with RR CLL/SLL. This trial is registered at ClinicalTrials.gov as NCT02004522.

Key Points

- Duvelisib significantly improved progression-free survival and overall response rates compared to ofatumumab in RR CLL/SLL patients.
- Duvelisib's efficacy and manageable safety profile support its consideration as a novel, oral monotherapy for RR CLL/SLL patients.

Introduction

CLL is the most common adult lymphoproliferative disorder in Western countries, with more than 20,000 estimated new cases in the United States in 2017 and over 4,600 deaths.[1] The timing and selection of therapy is largely informed by multiple clinical and biologic factors, specifically disease stage, presence of poor prognostic molecular features (eg, del(17p), *TP53* mutations) and the general status of individual patients, many of whom are elderly with comorbid conditions precluding aggressive chemoimmunotherapy.[2,3] Chemotherapy, specifically alkylating agents and purine analogs, and monoclonal CD20 antibody therapy have long represented the traditional backbone of frontline therapy.[4] The comparator agent for the DUO trial, ofatumumab, is a humanized anti-CD20 antibody with single-agent efficacy against refractory CLL and a Food and Drug Administration (FDA)-approved treatment option.[5,6] Recently approved therapies targeting key pathways of CLL cell proliferation and survival, particularly Bruton's tyrosine kinase (BTK), PI3K-δ, and BCL2, have greatly improved outcomes for CLL patients and have been integrated into the CLL treatment landscape.[7] However, except for allogeneic stem cell transplantation, there is general consensus that current therapies for CLL/SLL are not curative, and most patients will ultimately succumb to their disease.[8,9] Given the inevitable development of resistance or intolerance to available therapies, there remains an urgent need to develop novel effective and tolerable CLL/SLL treatment options.

Duvelisib is an oral dual PI3K-δ,γ inhibitor that targets key signaling pathways that promote the growth and survival of hematologic malignancies. PI3K-δ inhibition blocks the survival and proliferation of malignant B cells,[10-12] while PI3K-γ inhibition disrupts the recruitment and differentiation of T cells and macrophages within the tumor microenvironment that support

malignant B cell maintenance.[13-16] Dual PI3K-δ,γ inhibition has shown greater activity in preclinical models of CLL than blocking either isoform alone.[17-21] Accordingly, duvelisib's unique therapeutic potential offers a novel approach to treat patients with CLL/SLL.

The efficacy and safety profile of duvelisib monotherapy for the treatment of hematologic malignancies was demonstrated in a Phase 1 trial.[22,23] Clinically meaningful activity was observed in a cohort of RR CLL/SLL patients with a 56% ORR and a median PFS of 15.7 months.[22,24] Reductions in serine/threonine kinase AKT phosphorylation (p-AKT) and proliferating (Ki67+) CLL cells were seen in CLL patient samples following duvelisib administration, demonstrating pharmacodynamic evidence of PI3K inhibition. Based on the combined efficacy, safety, pharmacokinetics, and pharmacodynamic data from this Phase 1 study, duvelisib 25 mg BID was selected as a clinically active dose for a Phase 3 investigation in CLL/SLL.[22]

Building on these encouraging Phase 1 results, the global Phase 3 randomized DUO study was initiated in 2014 to fully characterize the efficacy and safety of duvelisib monotherapy in patients with RR CLL/SLL when compared to an approved standard of care, ofatumumab monotherapy. Herein are reported the final analysis results for this trial.

Methods

Study Design and Treatment

DUO is a global, multicenter, randomized, open-label, Phase 3 trial comparing the efficacy and safety of duvelisib monotherapy with ofatumumab monotherapy for RR CLL/SLL. Between January 21, 2014 and December 9, 2015, 319 patients with RR CLL/SLL were randomized 1:1 to study treatment with duvelisib (n=160) or ofatumumab (n=159) at 62 clinical study sites in 11 countries. Patients were required to have active CLL/SLL disease necessitating treatment, per the International Workshop on CLL (IWCLL)[25] criteria or Revised International Working Group (IWG)[26] criteria that had progressed during or relapsed after at least one previous CLL/SLL therapy. Radiologically measurable disease, defined as at least one lymph node or tumor mass measuring > 1.5 cm by computed tomography (CT) scan, was required. Other standard eligibility

requirements included adequate renal and hepatic function, hemoglobin ≥ 8.0 g/dL, and platelet count ≥ 10,000 μL with or without transfusion support. There was no eligibility requirement with regards to neutrophil count. Key exclusion criteria included prior treatment with BTK or PI3K-δ inhibitors; refractoriness to prior ofatumumab therapy; or a history of Richter's transformation, prolymphocytic leukemia, or allogenic stem cell transplant. *Pneumocystis jirovecii* prophylaxis concomitant with study drug treatment was required for all patients on both treatment arms. Per protocol, antiviral prophylaxis was recommended to be implemented at the discretion of the treating Investigator.

Patient stratification at randomization included the presence or absence of del(17p), Grade 4 cytopenia, and refractoriness/early relapse to purine analog based therapy (defined as progression < 12 months after fludarabine/pentostatin). Patients randomized to the duvelisib arm self-administered 25 mg capsules BID continuously in 28-day cycles except for the first cycle (21 days) to align with administration of ofatumumab infusions. Patients were allowed to take duvelisib for up to 18 cycles, until disease progression, or until unacceptable toxicity. Additional treatment with duvelisib beyond 18 cycles was allowed based on the judgement of the Investigator. Guidance for AE management was provided in the protocol and included dose modifications (interruptions and reductions) for treatment-related Grade 2 or higher pneumonitis or pneumonia, Grade 3 or higher non-hematologic AEs, febrile neutropenia, and thrombocytopenia with hemorrhage. Corticosteroids were recommended for colitis or persistent or recurrent severe diarrhea and in combination with antibiotic therapy in patients presenting with pulmonary symptoms or radiographic changes suspicious for pneumonitis.

Ofatumumab arm dosing was based on the dose and schedule outlined in the approved product labeling for monotherapy in relapsed CLL at the time the study was initiated and could not exceed the 12 doses (within 7 cycles) as described in the prescribing information.[27]

Study visits for duvelisib arm patients occurred on Cycle 1 Day 1 and 8, Cycle 2 Day 1 and 15, and Day 1 of every other cycle thereafter. Study visits for ofatumumab arm patients were similar except for additional visits on Cycle 1 Day 15, and Cycle 2 Day 8 and 22, for study drug infusions. Patients on either treatment arm that experienced radiographically confirmed progressive disease (PD) had the option to crossover to a separate extension study to receive the opposite therapy.

Study Endpoints and Assessments

The primary endpoint was PFS, defined as time from randomization to first documentation of PD as determined by an IRC or death due to any cause. Key secondary endpoints included (1) ORR, with overall response (per IRC determination) defined as the best response of complete response/remission (CR), CR with incomplete marrow recovery (CRi), partial response/remission (PR), or PR with lymphocytosis (PRwL), according to IWCLL[25,26] or IWG Response Criteria,[28] with modification for treatment-related lymphocytosis and (2) overall survival (OS). Per protocol, a response of PRwL was limited to patients with lymphadenopathy as the only abnormal baseline Group A criterion (eg, no organomegaly and normal blood lymphocyte count < 4,000/μL) who achieved a PR (≥ 50% reduction in lymphadenopathy) but had post-baseline isolated progressive lymphocytosis. Response assessments for both arms included complete blood count with differential, CT scan, disease-associated symptom review, and bone marrow biopsy (for CR confirmation only) that were performed after every 2 cycles until Cycle 7, every 4 cycles until Cycle 19, and then every 6 cycles until disease progression, start of new anticancer therapy, or subject withdrawal.

Efficacy Analysis and Statistics

PFS was compared between the duvelisib and ofatumumab treatment arms using a stratified log-rank test (one-sided) with the overall one-sided significance level controlled at 0.025. The HR for duvelisib/ofatumumab and the corresponding 2-sided 95% confidence interval (CI) was estimated using a stratified Cox proportional hazards model, and PFS for both arms were plotted using the Kaplan-Meier method. The ORR was analyzed using the Cochran-Mantel-Haenszel (CMH) test to compare treatments. OS (time from randomization to death) was compared between treatment arms using a stratified one-sided log-rank test, and the HR along with the 95% CI was estimated using a stratified Cox model. Kaplan-Meier plots for OS were generated for each treatment group. The lymph node response rates (≥ 50% reduction in target lymph nodes from baseline) between treatment arms was analyzed using the one-sided CMH test.

Safety Methods

AEs and hematology and blood chemistry laboratory values were assessed at each study visit or as clinically warranted and coded using MedDRA Version 16.1. The severity of AEs and applicable laboratory values was graded according to the NCI-CTCAE Version 4.03.

Data Sharing Statement

For original data, please contact nmirza@verastem.com

Results

Patient Baseline Characteristics and Disposition

The baseline characteristics and stratification of study patients were well balanced between the two treatment arms (Table 1). Patients were predominantly male (60%) with a median age in both arms of 69 years. Most patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, with a similar percentage of patients with an ECOG PS of 2 (duvelisib 7%; ofatumumab 10%). The median time from initial diagnosis was 7.5 years for duvelisib and 6.7 years for ofatumumab, and 56% of patients in both arms were ≥ Rai stage III at the start of therapy. Nearly half of duvelisib and ofatumumab-treated patients had bulky disease (46% and 45%, respectively), and both arms had similar median baseline lymphocyte counts (38 x 10^9/L and 35 x 10^9/L). Central laboratory determination of molecular features identified del(17p) and/or *TP53* mutation in approximately one third of patients (duvelisib 31%; ofatumumab 33%) and unmutated IGHV status in 69% and 73% of duvelisib and ofatumumab patients, respectively.

On both study arms, the median number of prior therapies was 2, with approximately one third having received ≥ 3 prior lines of therapy (Table S1). Most patients had previously received an alkylating agent (93% duvelisib; 95% ofatumumab), a monoclonal antibody (78% duvelisib; 83% ofatumumab), and purine analog (60% duvelisib; 71% ofatumumab).

Of the patients randomized into each arm, 158 and 155 patients initiated treatment with duvelisib and ofatumumab respectively (Table 2; Figure S1). As of the 19 May 2017 data cutoff date,

124 duvelisib-treated patients had discontinued treatment, with the most common reasons being AEs (35%), disease progression (22%), subject withdrawal (8%), and death (8%). All ofatumumab-treated patients had discontinued treatment; most (67%) completed treatment as per protocol, while others discontinued due to disease progression (20%), subject withdrawal (5%), and AEs (4%). At the time of disease progression, 8 (5%) duvelisib patients opted to crossover to ofatumumab therapy and 89 (57%) ofatumumab-treated patients opted to crossover to duvelisib therapy in a separate extension study. Efficacy and safety data for that study will be reported separately.

Efficacy

The primary efficacy endpoint for this study was PFS as determined by IRC, with ORR and OS as key secondary endpoints. With a median overall follow up of 22.4 months for the duvelisib and ofatumumab arms, median PFS by blinded IRC review was significantly longer for the duvelisib arm compared to the ofatumumab arm (13.3 months vs. 9.9 months, HR = 0.52, $p<0.0001$) (Figure 1A). The estimated probability of being progression-free at 6 months and 12 months was 78% and 60%, respectively, in the duvelisib arm, and 72% and 39% in the ofatumumab arm. Improvement in PFS with duvelisib compared with ofatumumab was also observed per Investigator assessment (17.6 months vs. 9.7 months, HR = 0.40; $p < 0.0001$, Figure 1B). PFS was also extended with duvelisib in multiple predefined CLL/SLL subgroups examined, including patients with high-risk cytogenetic markers (Figure 2A). In the subset of patients with del(17p)/*TP53* mutations, median PFS by IRC assessment was 12.7 months with duvelisib versus 9.0 months for ofatumumab (HR = 0.40; $p = 0.0002$), with an estimated probability of being progression-free at 6 months and 12 months of 73% and 55% with duvelisib, and 63% and 30% with ofatumumab (Figure 2B). By Investigator assessment, median PFS in patients with del(17p)/*TP53* mutations was 13.8 months with duvelisib and 9.5 months with ofatumumab (HR = 0.41; $p = 0.0003$) with an estimated probability of being progression-free at 6 months and 12 months of 77% and 66% with duvelisib, and 53% and 33% with ofatumumab (Figure 2C). Duvelisib maintained a favorable odds ratio relative to ofatumumab for all subgroups analyzed, including refractory/early relapse (HR = 0.51), baseline Grade 4 cytopenia (HR = 0.14), and prior anticancer therapy within the past 12 months (HR = 0.40).

The ORR per IRC response assessment for duvelisib was also significantly higher compared to ofatumumab (73.8% versus 45.3%; $p < 0.0001$) (Figure 3). In the duvelisib arm, nearly all responses were PR (72.5%) with the exception of 2 patients; 1 patient achieving a CR (0.6%), and 1 patient achieving a PRwL (0.6%). Responses on the ofatumumab arm were also predominantly PRs (44.7%) with a CR (0.6%) in 1 patient (Table S2). Duvelisib treatment was particularly effective in targeting the lymph node disease compartment, with a lymph node response by IRC assessment of 85.0% (95% CI: 79.5, 90.5) compared to 15.7% (95% CI: 10.1, 21.4) in the ofatumumab arm ($p < 0.0001$; Figure 3). Median OS was not reached on either treatment arm with a 12-month probability of survival of 86% (HR = 0.99; CI: 0.65 , 1.50) for both treatments (Figure S2).

Safety

AEs were assessed during the treatment periods of each arm. Median treatment exposure was approximately twice as long among duvelisib-treated patients (median duration 50 weeks) compared to ofatumumab-treated patients (median duration 23 weeks). Per protocol, ofatumumab treatment did not exceed the 12 doses (approximately 6 months) specified in the ofatumumab prescribing information. As of the data cut-off, 49% of duvelisib-treated patients had received more than a year of treatment, with 31% and 12% having received 1.5 years and 2 years of treatment, respectively. AEs that occurred in ≥ 10% patients during these respective AE reporting periods (ie, not exposure matched) are presented in Table 3. Nearly all patients in both arms experienced an AE. The most common hematologic AEs with duvelisib and ofatumumab were neutropenia (33% and 21%), anemia (23% and 10%) and thrombocytopenia (15% and 6%), respectively. The nonhematologic AEs most commonly reported with duvelisib were diarrhea (51%), pyrexia (29%), nausea (23%), and cough (21%). Colitis, as a distinct event from diarrhea, was reported in 13% with 8% of patients having diarrhea directly preceding and/or overlapping with the colitis event. Median time to first event of diarrhea or colitis was approximately 4 months and 7 months, respectively. With ofatumumab, infusion-related reaction (19%), cough (14%), and diarrhea, rash, and fatigue (12% each) were the most common nonhematologic AEs.

AEs ≥ Grade 3 occurred in 87% of duvelisib arm patients and 48% of ofatumumab arm patients. In the duvelisib arm, the most common severe events were neutropenia (30%), diarrhea (15%), pneumonia (14%) and anemia (13%). On the ofatumumab arm, only neutropenia (17%) occurred

in ≥ 10% of patients. As previously observed in the Phase 1 study,[22,24] severe immune-related toxicities (≥ Grade 3) were noted in duvelisib-treated patients. In this Phase 3 study, the occurrence of severe immune-related toxicities included colitis (12%) and pneumonitis, alanine transaminase (ALT) or aspartate transaminase (AST) increase (3% each). While these events were primarily managed with dose interruptions, 60% of patients with pneumonitis or colitis received steroid therapy with resolution reported in nearly all patients at the time of data cut-off. None of these events were fatal.

Infectious AEs were more frequently reported in the duvelisib arm (69% vs. 43%) with pneumonia (18%) and upper respiratory tract infection (URTI, 16%) representing the most common events. *Pneumocystis jirovecii* pneumonia occurred in 3 duvelisib-treated patients and 1 ofatumumab-treated patient, 3 of whom were not receiving prophylaxis at the time of their infections despite being required per protocol and 1 duvelisib-treated patient who discontinued prophylaxis due to intolerance. Of the duvelisib-treated patients who discontinued treatment due to AEs, colitis and diarrhea were the only AEs occurring in ≥ 5% of patients (both 5%). Treatment discontinuations from the other immune-related toxicities of pneumonitis (2%), and elevated AST levels (1%) were infrequent.

Serious AEs (SAEs) are summarized in Table S3. Pneumonia was the most frequently reported SAE in both treatment arms (duvelisib 15%; ofatumumab 3%). There were 19 fatal AEs on the duvelisib arm (Table S4), 4 of which were assessed by Investigators as related to study drug; staphylococcal pneumonia (n = 2), and sepsis and general health deterioration (n = 1 each). On the ofatumumab arm, 7 patients had fatal AEs although none were attributed to ofatumumab treatment.

Pharmacodynamic Measurements

Twenty-four chemokines and cytokines were measured in patient serum samples, and the median percent change from baseline to Cycle 2 Day 1 was determined to assess treatment-related effects associated with the targeting of leukemia cells and the tumor microenvironment,[29,30] as described in the Supplemental Methods section. Sixteen chemokines were significantly reduced from baseline in duvelisib-treated patients ($p < 0.05$; Figure 4). Ofatumumab-treated patients had levels that were not statistically decreased from baseline, whereas the duvelisib-treated patients had decreased levels that were highly significant: CCL1 ($p < 0.0001$), CCL17 ($p < 0.0001$),

CXCL10 ($p < 0.0002$), CXCL11 ($p < 0.0009$), CXCL9 ($p < 0.0001$), and IL10 ($p < 0.0001$). In total, 10 chemokines showed greater than 50% median decreases in duvelisib-treated patients.

Discussion

In this pivotal Phase 3 DUO study, duvelisib monotherapy resulted in statistically significant improvement in PFS and ORR compared to ofatumumab in patients with RR CLL/SLL, including those with del(17p)/*TP53* mutations. This improvement was consistently observed across all sensitivity and subgroup analyses for both efficacy endpoints. In the duvelisib arm, the median PFS as determined using Investigator response assessments was notably longer than IRC-assessed PFS (17.6 months vs. 13.3 months). This difference likely reflects inherent differences in methodologies used to derive responses and determine progression between the two evaluator groups. With the IRC PFS largely based upon radiologic data, the Investigator-derived PFS, incorporating both radiological and real-time clinical assessments, as would be applied in the standard oncology care setting, likely represents a more clinically relevant PFS. Clinically meaningful reductions in target lymph nodes were observed in most patients treated with duvelisib (85%), representing a statistically significant treatment effect over ofatumumab (16%) ($p < 0.0001$). Median OS was similar between the 2 treatment arms, which may be explained by the availability of multiple CLL therapies to rescue patients on either arm following disease progression, including administration of duvelisib in a separate, optional extension study to 89 patients who had confirmed progressive disease on ofatumumab in the DUO study.

Based on the study design, the treatment period for duvelisib was longer than ofatumumab (median exposure 50 weeks versus 23 weeks), which resulted in a longer AE reporting period for duvelisib compared to ofatumumab. Of the patients treated with duvelisib, 49%, 31%, and 12% received more than a year, 18 months, and 2 years of treatment, respectively. The duvelisib AE profile observed in this trial was consistent with the drug safety profile to date,[22,24] with the majority of AEs presenting as Grade 1 or 2 events. Many of the more common AEs, such as cytopenias and constitutional symptoms, are also well-recognized complications of CLL/SLL. Similar to other B-cell receptor pathway inhibitors, infections (particularly pneumonias and URTIs)[31,32] were frequently observed on duvelisib, representing the most common severe and

serious AEs; 3 patients died due to treatment-related infections. Although a well-recognized major cause of morbidity and mortality in CLL given the humoral immunodepression inherent to the disease[33,34] and therapy-induced immunosuppression, infections remain an important risk with duvelisib treatment. The protocol requirement for *Pneumocystis jirovecii* pneumonia prophylaxis may have mitigated against the risks of these opportunistic infections, which have been reported with other B cell receptor inhibitors.[35-39] Of interest, the 3 duvelisib-treated patients who experienced *Pneumocystis jirovecii* infections during the study were not receiving prophylaxis due to protocol deviations or medication intolerance.

Several prespecified AEs of interest relating to possible immunomodulatory effects of PI3K-δ/γ inhibition[40-45] were closely monitored in this study. Incidences of neutropenia, diarrhea, colitis, transaminase elevations, pneumonitis, and rash with duvelisib therapy were moderate and manageable with early intervention and dose modification as required per protocol. Of these, colitis was the most commonly observed severe (≥ Grade 3) event, reported in 12% of duvelisib treated patients, while severe cases of pneumonitis, transaminase elevations, and toxic skin eruption/rash were reported in < 3%. None of these events were fatal. These potential immune-mediated toxicities, identified in clinical studies with the PI3K-δ specific inhibitor idelalisib, infrequently led to discontinuations of duvelisib therapy.

Malignant B cell proliferation and survival in CLL/SLL is promoted by PI3K.[10-12] The PI3K-δ/γ isoforms are also expressed in cells comprising the tumor microenvironment where they provide supportive signaling.[13-16] As a dual PI3K-δ/γ inhibitor, duvelisib has the potential to target cell autonomous mitogenic and survival signaling as well as the supportive tumor microenvironment that further enables CLL proliferation.[30,46] An analysis of patient blood protein profiles showed significant reductions in the levels of serum chemokines and cytokines associated with malignant B cells, consistent with decreases in CLL viability and proliferation, as previously reported.[24] Considering the dual inhibitor action of duvelisib, the pattern of chemokine change may reflect the inhibition of both PI3K-δ and PI3K-γ signaling within the tumor microenvironment.

This report of the DUO study data represents the second Phase 3 randomized trial to investigate the safety and efficacy of an oral PI3K inhibitor in relapsed CLL patients. In a prior study, idelalisib, an oral inhibitor of the PI3K-δ isoform, in combination with rituximab showed improved PFS compared with rituximab monotherapy (not reached versus 5.5 months) and

response rate (81% versus 13%) in patients with relapsed CLL who have clinically significant coexisting medical conditions.[47] The incidence of the more common AEs in the idelalisib + rituximab arm, such as cytopenias, constitutional symptoms, and diarrhea, occurred at similar rates in the duvelisib arm of the DUO trial. However, at the time of the idelalisib trial analysis, patients in the idelalisib + rituximab arm had only received study drug for a median of 3.8 months compared with the much longer exposure of duvelisib of nearly a year in the DUO trial. This large difference in drug exposure and observation periods makes it difficult to compare incidences across trials. Additionally, the timing of some immune-mediated toxicities, such as colitis and pneumonitis, which tend to emerge with longer drug exposure, may be more accurately represented in this study with a longer duration of assessment. Interestingly, however, the incidence of high grade transaminitis AEs with duvelisib was low in this study. The AE profile with duvelisib monotherapy remains consistent across studies[22,23] and manageable with appropriate intervention via dose modifications, routine medical care, and prophylactic measures. Additional characterization of key safety events associated with the use of idelalisib[40] and PI3K inhibitors as a whole[41] has greatly informed the guidance for maximizing safe administration of drugs in this class.

The anti-CD20 monoclonal antibody ofatumumab is approved as monotherapy for the treatment of relapsed CLL and represented an accepted and appropriate standard of care agent for comparing to duvelisib monotherapy at the time of study initiation. However, the use of single-agent ofatumumab for the treatment of relapsed CLL has diminished in recent years, being supplanted by newer agents that target the B-cell receptor pathway. In addition to idelalisib in combination with rituximab, ibrutinib, an oral BTK inhibitor, received full approval in 2014 based on a Phase 3 randomized study demonstrating significantly improved PFS compared to ofatumumab (median PFS not reached versus 8.1 months [HR = 0.22]).[7] Treatment indications have since expanded to include ibrutinib use as a frontline CLL therapy. Despite advantages of being an effective and well-tolerated therapy, it is not curative, and treatment discontinuations due to disease progression and drug intolerance have been described in published reports.[48-50] Given the unfortunate reality that many patients have or acquire resistance or intolerance to currently-available, targeted therapies, or have comorbidities that may preclude their safe use, there remains a critical medical need for additional, novel, targeted therapies for patients with RR CLL/SLL, especially those with del(17p)/*TP53* mutations. These combined safety and

efficacy results suggest that duvelisib monotherapy may offer an effective treatment for CLL/SLL patients in need of additional therapeutic options.

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Authorship

I.W.F. provided primary authorship, trial design input, and data interpretation; I.W.F., P.H., M.M., Z.N., A.I., G.E., J.D., B.J.K., C.S.T., Z.G., F.O., S.L., F.B., M.S.D., N.L., U.J., P.G., F.C., C.A.P., A.P.S., A.F.C., and S.S. enrolled patients, performed the research and contributed to/edited the manuscript; V.M.K. analyzed data and wrote and/or edited the manuscript; B.T. provided statistical outputs; and D.T.W. performed pharmacodynamic analysis and data interpretation.

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Oncology; V.M.K. was formerly an employee of Infinity Pharmaceuticals and is a consultant for Verastem Oncology; B.T. was a consultant to Verastem Oncology when the analyses were performed. The remaining authors have declared no competing financial interests.

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Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Duvelisib (n = 160)	Ofatumumab (n = 159)
Median age (range), years	69 (39-90)	69 (39-89)
Male, %	60	60
ECOG PS 2, %	7	10
CLL/SLL, %	97 / 5	99 / 2
Median time from initial diagnosis, years	7.5	6.7
Rai stage ≥ III / Binet Stage C, %	56 / 41	56 / 34
Bulky disease (≥ 5 cm target lesion), %	46	45
Enlarged liver[a], %	18	18
Enlarged spleen[a], %	38	32
Baseline lymphocytes (x 10^9/L), median	38	35
Grade 4 Cytopenia[b], %	11	11
Refractory/Early relapse to purine therapy[c]	31	30
Molecular features (per central laboratory), %		
17p deletion	21	28
TP53 mutation	20	18
17p deletion and/or *TP53* mutation	31	33
Unmutated IGHV	69	73
CD38 Positive	43	44
ZAP70 Positive (> 19%)	54	52

Abbreviations: 17p deletion = deletion of the 17p13 chromosomal region; CLL = chronic lymphocytic leukemia; ECOG = Eastern Cooperative Oncology Group; IGHV = immunoglobin heavy chain variable; PS = performance status; SLL = small lymphatic lymphoma.

[a] As assessed by study Investigators during screening.

[b] Thrombocytopenia and/or neutropenia.

[c] Progression < 12 months after fludarabine/pentostatin.

Table 2. Patient Disposition

Characteristic	Duvelisib	Ofatumumab
Randomized, n	160	159
Treated, n	158	155
Median exposure (weeks)	50	23
Discontinued Treatment, n (%)	124 (79)	155 (100)
AE	55 (35)	6 (4)
Disease progression	35 (22)	31 (20)
Subject withdrawal	13 (8)	7 (5)
Death	12 (8)	3 (2)
Investigator decision	3 (2)	4 (3)
Completed treatment per protocol	1 (1)[a]	103 (67)[a]
Other	5 (3)	1 (1)
On Treatment, n (%)	34 (22)	0
Crossed over to Study IPI-145-12 to receive opposite treatment, n (%)	8 (5)	89 (57)

Abbreviations: AE = adverse event.

[a] Completed treatment for ofatumumab = 7 cycles and for duvelisib = 18 cycles (duvelisib-treated patients permitted to receive duvelisib ≥ 18 cycles).

Table 3. Adverse Events in ≥ 10% of Duvelisib-treated Patients

Adverse Event	All Grades		Grade 3 and above	
	Duvelisib	Ofatumumab	Duvelisib	Ofatumumab
	n (%)	n (%)	n (%)	n (%)
Any AE	156 (99)	144 (93)	138 (87)	75 (48)
Hematologic AEs				
Neutropenia	52 (33)	32 (21)	48 (30)	27 (17)
Anemia	36 (23)	16 (10)	20 (13)	8 (5)
Thrombocytopenia	23 (15)	9 (6)	12 (8)	3 (2)
Nonhematologic AEs				
Diarrhea	80 (51)	19 (12)	23 (15)	2 (1)
Pyrexia	45 (29)	16 (10)	4 (3)	1 (1)
Nausea	37 (23)	17 (11)	0	0
Cough	33 (21)	22 (14)	2 (1)	0
Pneumonia	29 (18)	9 (6)	22 (14)	2 (1)
Constipation	26 (17)	13 (8)	1 (1)	0
URTI	25 (16)	12 (8)	0	0
Vomiting	23 (15)	10 (7)	0	0
Bronchitis	21 (13)	13 (8)	5 (3)	1 (1)
Colitis	21 (13)	2 (1)	19 (12)	1 (1)
Fatigue	20 (13)	19 (12)	2 (1)	2 (1)
Decreased appetite	20 (13)	5 (3)	0	1 (1)
Weight decreased	18 (11)	3 (2)	0	0
Asthenia	18 (11)	17 (11)	3 (2)	4 (3)
Abdominal pain	16 (10)	3 (2)	3 (2)	0
Dyspnea	16 (10)	9 (6)	4 (3)	0
Rash	16 (10)	18 (12)	3 (2)	1 (1)

Abbreviations: AE = adverse event; URTI = upper respiratory tract infection.

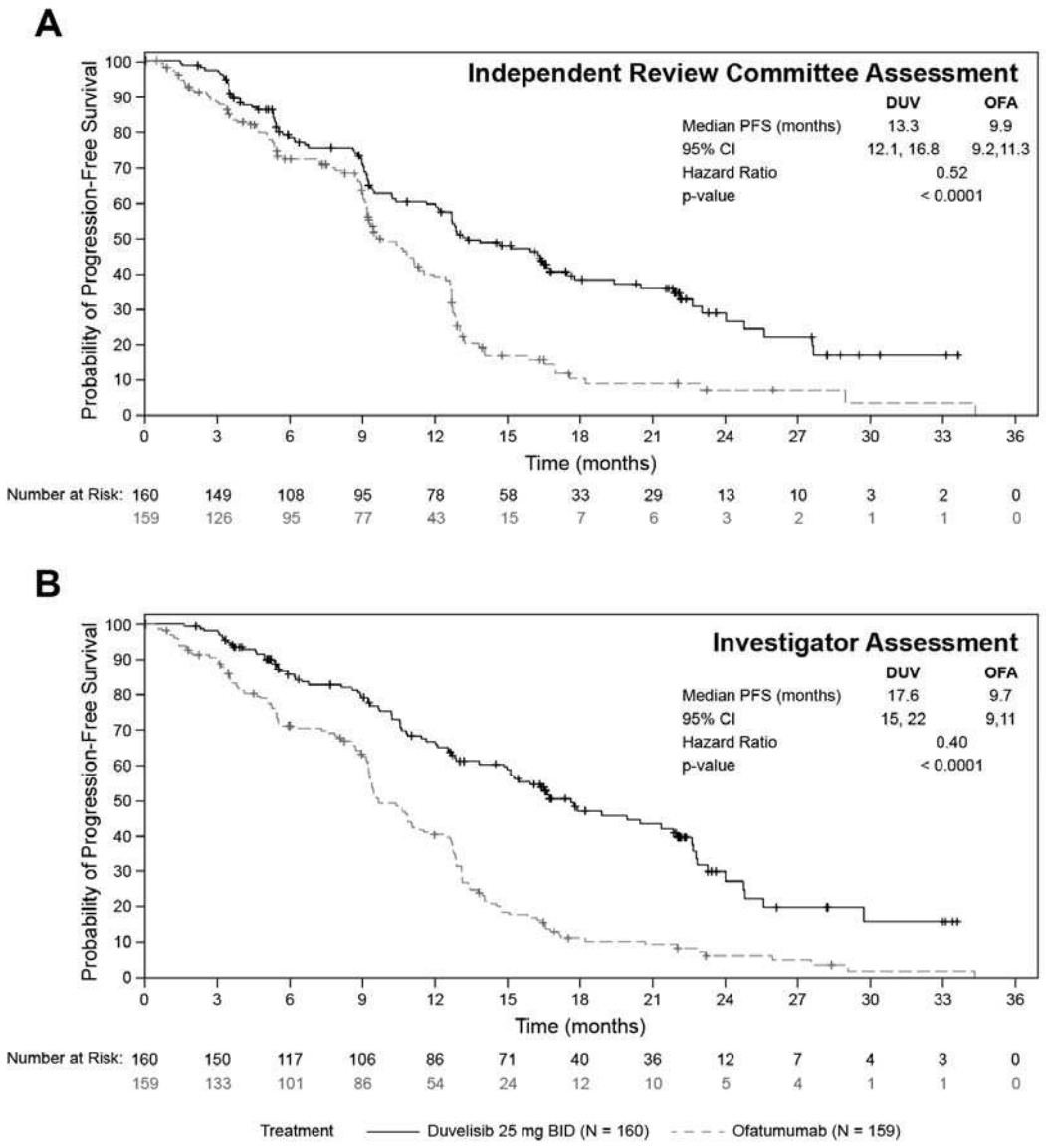

Figure 1. Progression-free survival in the study population. Kaplan-Meier curves of PFS assessments in CLL/SLL patients treated with monotherapy duvelisib or ofatumumab. PFS was significantly longer for duvelisib-treated patients compared to ofatumumab-treated patients by assessments of (**A**) blinded IRC (13.3 months vs. 9.9 months, HR = 0.52, $p < 0.0001$) and (**B**) Investigators (17.6 months vs. 9.7 months, HR = 0.40; $p < 0.0001$). Abbreviations: BID = twice daily; CI= confidence interval; DUV = duvelisib; PFS = progression-free survival; OFA = ofatumumab.

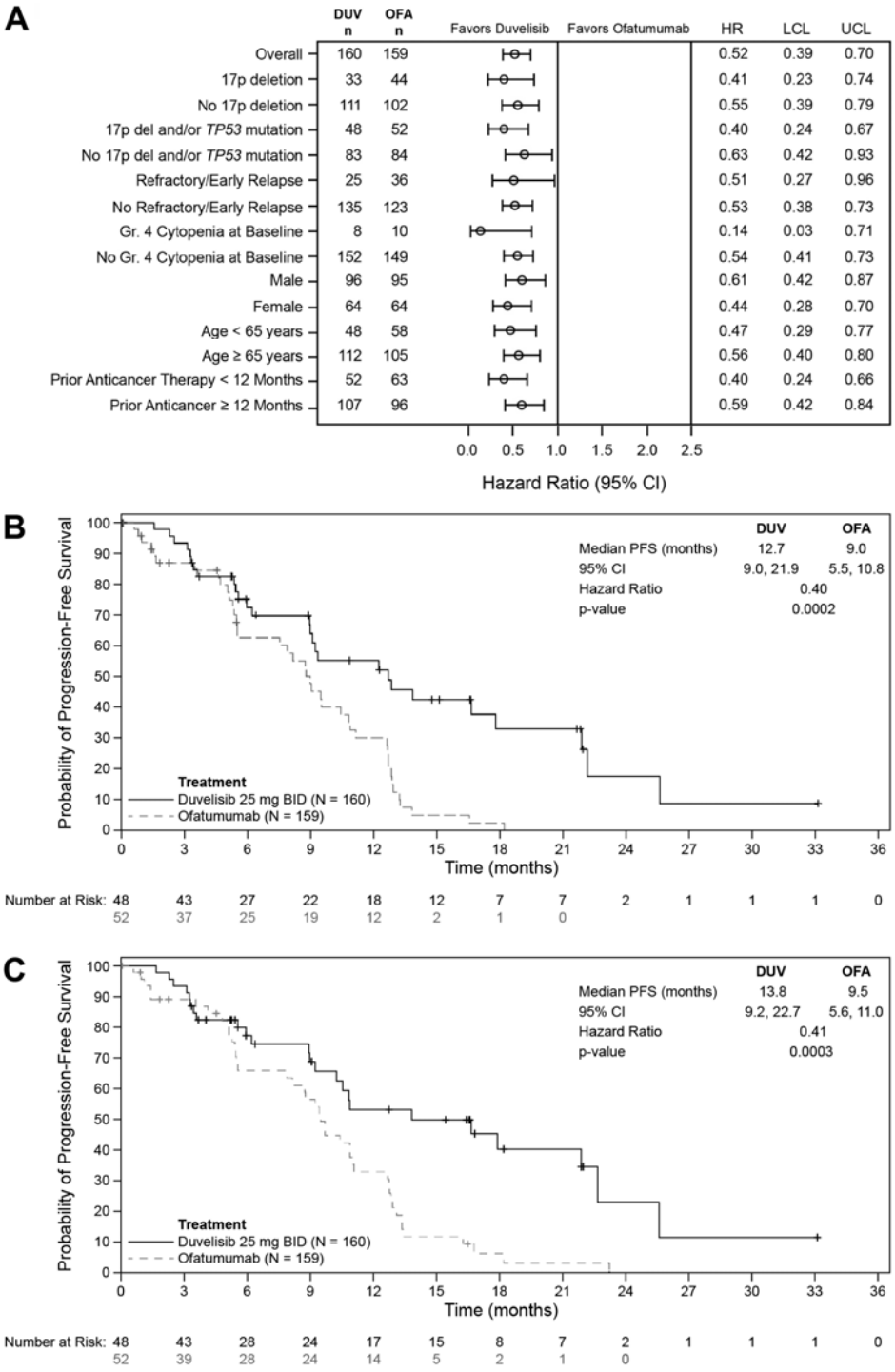

Figure 2. Progression-free survival in selected study subgroups. (**A**). Forest plot and hazard ratios for PFS per IRC assessment on duvelisib or ofatumumab monotherapy for predefined subgroups within the total study population. Kaplan-Meier curves of progression-free survival per IRC assessment (**B**) and Investigator assessment (**C**) in the subgroup of patients with

del(17p)/*TP53* mutation. In this high-risk subgroup, median PFS was 12.7 months and 9.0 months (HR = 0.40, p = 0.0002) by IRC assessment and 13.8 months and 9.5 months (HR = 0.41, p = 0.0003) by Investigator assessment for duvelisib and ofatumumab, respectively.

Abbreviations: BID = twice daily; CI = confidence interval; DUV = duvelisib; OFA = ofatumumab; Refractory/Early Relapse = Refractory/Early Relapse to Purine Analog-Based Therapy; Prior Anticancer Therapy = Most Recent Prior Anticancer Therapy from Randomization; HR = Hazard Ratio; LCL = Lower Confidence Limit; UCL = Upper Confidence Limit.

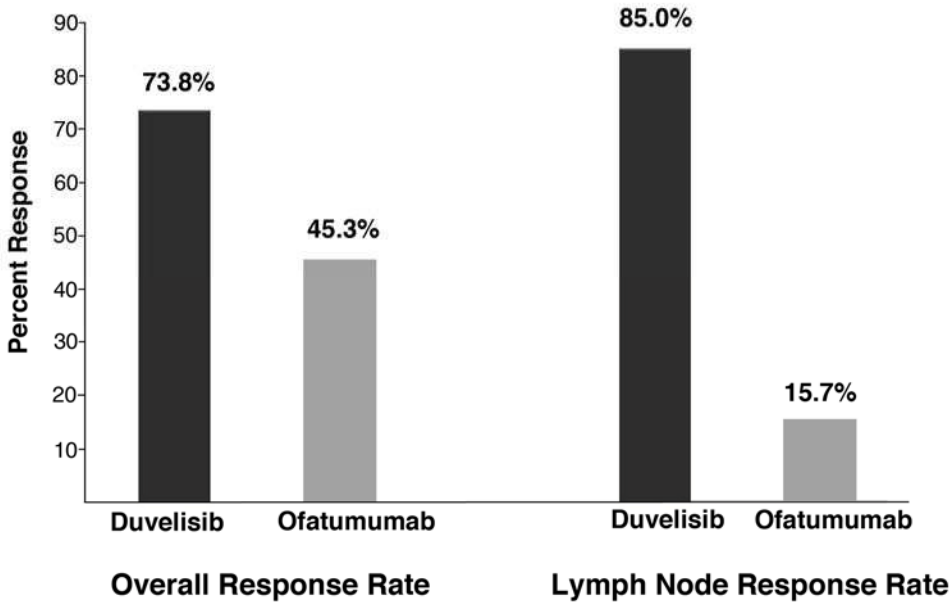

Figure 3. ORR per IRC assessment and lymph node response rate for the total CLL/SLL study population for duvelisib versus ofatumumab monotherapy. Lymph node response was defined as ≥ 50% decrease in the sum of the products of target lymph nodes. Both the ORR ($p < 0.0001$) and the lymph node response rate ($p < 0.0001$) were significantly higher in duvelisib-treated patients. Abbreviations: CLL = chronic lymphocytic leukemia; IRC = independent review committee; ORR = overall response rate; SLL = small lymphatic lymphoma.

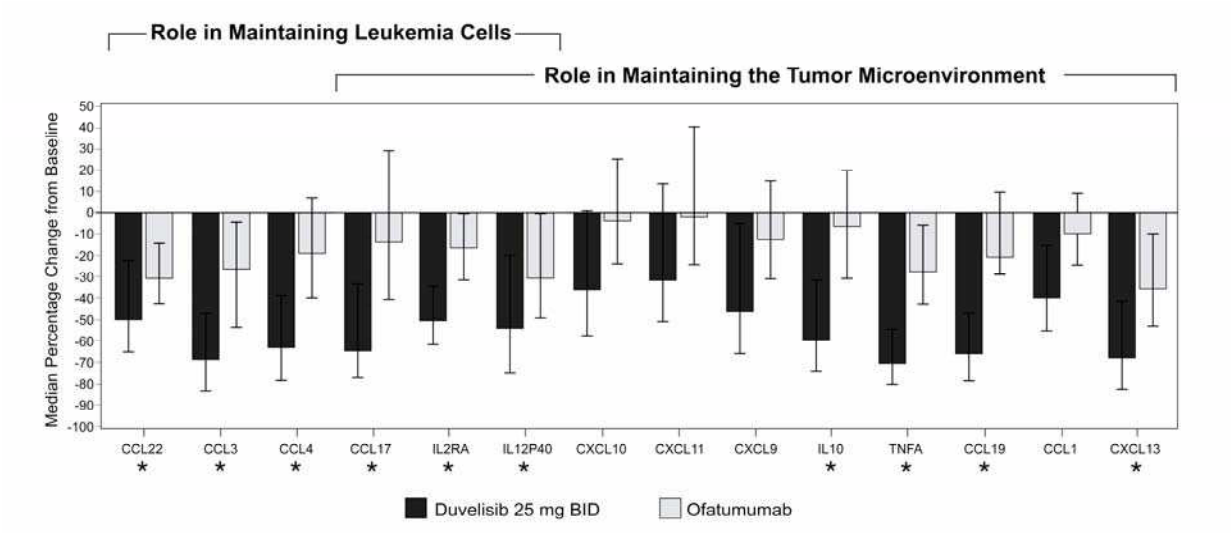

Figure 4. Cytokine and chemokine changes in CLL/SLL patients treated with duvelisib or ofatumumab. The median percent change from Baseline to Cycle 2 Day 1 is depicted. The 10 cytokines and chemokines that showed greater than 50% median reductions in duvelisib patients from baseline are denoted with an asterisk. Abbreviations: BID = twice daily; CLL = chronic lymphocytic leukemia; SLL = small lymphatic lymphoma.

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The phase 3 DUO trial: duvelisib versus ofatumumab in relapsed and refractory CLL/SLL

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