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Duvelisib, an oral dual PI3K-δ,γ inhibitor, shows clinical and pharmacodynamic activity in chronic lymphocytic leukemia and small lymphocytic lymphoma in a phase 1 study

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Abstract

Duvelisib (IPI-145), an oral, dual inhibitor of phosphoinositide-3-kinase (PI3K)-δ and -γ, was evaluated in a Phase 1 study in advanced hematologic malignancies, which included expansion cohorts in relapsed/refractory (RR) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) and treatment-naïve (TN) CLL. Per protocol, TN patients were at least 65 years old or had a del(17p)/*TP53* mutation. Duvelisib was administered twice daily (BID) in 28-day cycles at doses of 8–75 mg in RR patients ($n = 55$) and 25 mg in TN patients ($n = 18$.) Diarrhea was the most common nonhematologic AE (TN 78%, RR 47%); transaminase elevations the most frequent lab-abnormality AE (TN 33.3%, RR 30.9%); and neutropenia the most common ≥grade 3 AE (RR 44%, TN 33%). The overall response rates were 56.4% for RR patients (1.8% CR, 54.5% PR) and 83.3% for TN patients (all PRs); median response duration was 21.0 months in RR patients but was not reached for TN patients. Based upon phase 1 efficacy, pharmacodynamics,

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AUTHOR CONTRIBUTIONS

Contributions: S.O., M.P., B.K., S.H, F.F., P.P., J.J., J.B., N.J., K.A., K.F., M.D., H.M.S., J.S., P.K., V.K., and I.F. all contributed to the paper.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

CONFLICT OF INTERESTS

S.O., M.P., B.K., S.H, F.F., P.P., J.J., J.B., N.J., and I.F. declare no competing financial interests. Authors K.A., K.F., M.D., H.M.S., J.S., P.K., and V.K. were employees of Infinity Pharmaceuticals at the time of study conduct.

and safety, duvelisib 25 mg BID was selected for further investigation in a phase 3 study in RR CLL/SLL.

1 | INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the US, accounting for 30% of all leukemias.[1] An estimated 20 110 new CLL cases and 4660 CLL deaths will occur in the US in 2017.[2]

Novel targeted agents such as anti-CD20 antibodies (ofatumumab and obinutuzumab) in combination with chemotherapy, kinase inhibitors (ibrutinib and idelalisib), and the BCL-2 inhibitor venetoclax have expanded therapeutic options in CLL/SLL.[3] Despite these advances and the widespread use of chemoimmunotherapy, many patients with CLL eventually relapse.[4] The deletion of chromosome 17p (17p deletion) and/or a mutation in *TP53* confer a poorer prognosis, with a predicted survival of only 2–3 years.[5] Thus, novel and effective oral treatments with acceptable safety profiles are needed.

Duvelisib (also known as IPI-145)[6] is an oral, dual inhibitor of PI3K-δ, and PI3K-γ. PI3K-δ is constitutively expressed in hematologic malignancies, and its inhibition reduces the proliferation of various hematologic tumor cells while allowing normal immune cells to survive.[7–12] PI3K-γ plays an important role in the differentiation and migration of myeloid cells and T cells in the tumor microenvironment, while PI3K-δ blocks signals from the microenvironment sustaining leukemia and lymphoma cells in a protective niche.[13] Administration of duvelisib to mice engrafted with a peripheral T-cell lymphoma patient-derived xenograft resulted in a shift among tumor-associated macrophages from the immunosuppressive M2-like phenotype to the inflammatory, antitumor M1-like phenotype.[14] Thus, there are at least three different mechanisms through which dual inhibition of PI3K-δ and -γ isoforms could be active against lymphoid malignancies, including CLL: blockade of cell autonomous mitogenic and survival signaling, disruption of supportive tumor microenvironment juxtacrine interactions, and activation of anti-lymphoma immune responses. Accordingly, duvelisib may provide greater benefit through its dual inhibition of PI3K-δ and -γ than one PI3K isoform alone.[15]

Dose escalation, maximum tolerated dose (MTD) determination, and safety for the entire enrolled phase 1 study population are described in a separate publication.[16] Here we report on the efficacy, safety, and pharmacodynamics of duvelisib in patients with relapsed/refractory (RR) CLL/SLL and treatment-naïve (TN) CLL enrolled in expansion cohorts of the first clinical study of duvelisib in hematologic malignancies. These data support the ongoing investigation of duvelisib for CLL/SLL in a phase 3 trial.

1.1 | Patients and methods

1.1.1 | Study design and treatment—Study IPI-145–02 was a phase 1, open-label, dose-escalation and cohort expansion study in 210 patients with advanced hematologic malignancies.[15] Duvelisib was administered as oral capsules twice daily (BID), continuously in 28-day cycles until disease progression or unacceptable toxicity. Dose interruptions and

reductions (up to 2) were allowed. Clinic visits occurred weekly during the first three cycles, biweekly during cycles 4 (C4) and C5, monthly during C6–19, and every three cycles thereafter. Within the broader phase 1 study population, two CLL populations were examined in expansion cohorts: 55 patients with RR CLL/SLL were enrolled during dose escalation or sequentially (nonrandomized) into duvelisib 25 or 75 mg BID expansion cohorts depending upon cohort availability, and 18 patients with TN CLL received 25 mg BID. Peripheral blood and bone marrow samples were submitted at screening for central laboratory biomarker analysis, including del17p, *TP53* mutation, and IGHV mutational status.

All patients provided signed informed consent. The protocol was approved by site Institutional Review Boards, and the study was conducted according to local and federal regulations and the Declaration of Helsinki.

1.1.2 | Key enrollment criteria—Eligible patients were required to have a life expectancy >3 months, an ECOG score of 0–2, adequate hepatic (aspartate aminotransferase [AST] and/or alanine aminotransferase [ALT] ≤ 2.5 × upper limit of normal [ULN]; direct bilirubin ≤1.5 × ULN) and renal function (serum creatinine ≤1.5 × ULN). Baseline cytopenias were permitted, as was prior therapy with PI3K or BTK inhibitors. Key exclusions were HIV infection; history of alcohol abuse, chronic hepatitis, or other chronic liver disease; and pregnancy. In addition, TN patients had to be either ≥65 years old or had a documented *TP53* mutation or 17p deletion by local laboratory determination prior to or during screening. The protocol was amended in March 2013 to require concomitant *Pneumocystis* prophylaxis.

1.1.3 | Efficacy methods—Response was assessed by the investigator on day 1 of cycles 3, 5, and 7, every third cycle from C10–19, and every sixth cycle thereafter, using computed tomography (CT) scans and other relevant clinical data. The International Workshop on CLL (iwCLL) criteria 2008[17] were utilized for definitions of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). PR with lymphocytosis was not defined as a response. Bone marrow biopsy and/or aspiration was performed to confirm a CR.

Efficacy was assessed by overall response rate (ORR; CR + PR), time to response, lesion response (≥50% decrease from baseline in the sum of the product of diameters), duration of response (DOR; months from first response to progressive disease or death), progression-free survival (PFS; months from first dose to either progressive disease or death), and overall survival (OS; months from first dose to death).

1.1.4 | Safety methods—Adverse events (AEs), blood chemistry, and hematology laboratory parameters were monitored at all clinic visits and summarized for all patients who received at least one dose of duvelisib. AE severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

1.1.5 | Pharmacodynamic methods—Using serum collected from iNHL or CLL patients, multiplex panels of cytokines, chemokines, and matrix metalloproteinases (74 total

analytes) associated with the B-cell malignancy tumor microenvironment were evaluated using Luminex xMAP technology (Luminex, Austin, TX). The PD analysis set consisted of patients with iNHL and CLL with a C1D1 predose sample and at least one other sample (C1D8, C2D1, C3D1, or C5D1).

2 | RESULTS

2.1 | Demographic and baseline characteristics, disposition, and treatment

Fifty-five (55) RR patients initiated treatment with duvelisib BID at 8 mg (n = 1), 15 mg (n = 2), 25 mg (n = 28), or 75 mg (n = 24). Eighteen (18) TN patients were treated with duvelisib 25 mg BID. Most TN CLL patients were enrolled in 2013, with the last patient enrolled in January 2014.

The median age of RR patients was 66 years (range 42–82); most were male (76%), white (89%), and had a diagnosis of CLL (91%). Nearly all had an ECOG performance status of 0 (24%) or 1 (71%) (Table 1). Over a third (38%) had a grade 3 or 4 cytopenia at baseline. RR patients had a median of four prior systemic therapies, and 78% had stage ≥3 disease at study entry. Prior anticancer therapies were typical of a relapsed population with CLL. Six patients (11%) had previously received a Bruton's tyrosine kinase inhibitor (BTKi) and one patient had prior idelalisib plus rituximab therapy. The majority of RR patients had high-risk features, including unmutated *IGHV* status (86%) and *TP53* mutation and/or 17p deletion (56%).

The median age of TN patients was 74 years (range 49–83); 72% were male, and all 18 were white. At baseline, all TN patients had an ECOG performance status of 0 (44%) or 1 (56%), and four (22%) presented with grade 3/4 cytopenia. Similar to RR CLL, unmutated *IGHV* status and *TP53* mutation and/or 17p deletion was reported in the majority of TN patients (82% and 55%, respectively).

Among RR patients, median duration of duvelisib treatment was 24 weeks (range 3–167) and was similar between the 25-mg (25 weeks) and 75-mg (24 weeks) dose cohorts. As of data cutoff, most of the 49 RR patients who discontinued treatment did so due to an AE (n = 20) or progressive disease (n = 19).

Among TN patients, median duration of treatment was 62.3 weeks (range 3–90). As of data cutoff, 10 TN patients (56%) remained on duvelisib, with AEs (n = 6) the most common reason for discontinuation. Of the 18 TN patients, 11 had received greater than 1 year of duvelisib and 7 received greater than 18 months of duvelisib, all of whom were still on treatment as of the data cutoff.

2.2 | Safety

2.2.1 | Relapsed/refractory CLL/SLL—Treatment-emergent AEs and investigation abnormalities were generally similar across doses (Table 2A). Most AEs were grade 1–2. Several common AEs (eg, fatigue, pyrexia, cytopenias, pneumonia) are frequently associated with CLL. The most frequent severe (≥grade 3) Aes were neutropenia (43.6%) and thrombocytopenia (18.1%) and did not result in treatment discontinuation. Diarrhea (47.3%)

was the most frequent nonhematologic AE, but resulted in only two treatment discontinuations. Severe diarrhea (9.1%) and colitis (5.5%) were reported less frequently, and some cases overlapped. These events were managed by dose interruptions and standard-of-care interventions including antidiarrheal medications and enteric-acting steroids (ie, budesonide). Dose reduction and budesonide treatment were reported for three patients. Median time to onset of diarrhea was 2.6 months (any grade) and 5 months (grade 3); no grade 4 diarrhea occurred. Transaminase increases were the most frequent nonhematologic laboratory abnormality (30.9%), with a median time to onset of approximately 2 months. All six patients with dose interruptions for grade 3/4 transaminase elevations resumed treatment: two at the same dose and four at a reduced dose. Pneumonitis was reported in 5 (9.1%) patients with no relationship to dose. Otherwise, grade 3/4 nonhematologic and investigation AEs were uncommon.

As typically observed in heavily pretreated CLL, infections of all grades were frequently reported (72.7%), with pneumonias (combined terms) (38.2%) and upper respiratory tract infection (URTI) (27.3%) the most common infectious AEs. One patient who enrolled prior to the protocol amendment requiring *Pneumocystis* prophylaxis experienced *Pneumocystis* pneumonia and recovered with antimicrobial therapy. A grade 3 cytomegalovirus infection occurred in one patient and one patient had a grade 1 herpes zoster event (ie, shingles).

Twenty patients discontinued duvelisib due to AEs. Pneumonitis (4 patients), pneumonia, stomatitis, diarrhea, and colitis (all 2 patients) were the only AEs that led to treatment discontinuation in more than one patient. Fatal AEs occurred in nine patients. Four were due to disease progression and three were AEs considered unrelated to study treatment: one each due to pneumonia *Pseudomonas aeruginosa* sepsis, cardiac arrest/respiratory failure, and sepsis. Two deaths were considered related to treatment by the investigator. One patient receiving 25 mg BID discontinued duvelisib after 158 days due to disease progression and died 21 days later due to respiratory syncytial viral pneumonia. Another patient receiving 75 mg BID died due to metabolic acidosis in the setting of sepsis and renal failure after 70 days of duvelisib.

2.2.2 | Treatment-naïve CLL—The most frequent treatment-emergent AEs were similar to those observed in RR patients (Table 2B). Neutropenia was the most common ≥ grade 3 AE (6, 33.4%). The incidences of all-grade (14, 77.8%) and severe diarrhea events (4, 22.2%) were higher in TN patients, but manageable with dose modifications and resulted in only one treatment discontinuation. Median times to any-grade or severe diarrhea (grade 3, no grade 4) events were 2.6 and 9.7 months, respectively. AST/ALT elevations occurred in 6 (33.3%) patients, three of whom experienced grade-3 events, resulting in one treatment discontinuation. Similar to the RR population, the most common infectious AEs in TN patients were pneumonia and URTI, in 4 (22.2%) patients each. Other than oral *Candida* and a Grade 1 herpes zoster event in one subject each, no opportunistic infections were reported. Colitis was reported in three patients, with onset at 7.2, 12.4, and 17 months; two of these patients had grade 3 events and discontinued treatment. Two patients experienced pneumonitis, both grade 3. One patient discontinued treatment and recovered; the other recovered following treatment interruption and was still receiving duvelisib 13 months later at the time of data cutoff. Six TN patients discontinued duvelisib due to AEs, with colitis

being the only AE resulting in treatment discontinuation in more than one patient. No TN patients experienced fatal AEs.

2.3 | Efficacy

2.3.1 | Relapsed/refractory CLL/SLL—The ORR for all RR patients was 56.4% (31/55), including 1 (1.8%) CR and 30 (54.5%) PRs and was similar between the 25 and 75-mg cohorts (Table 3). Nodal response (≥50% reduction in adenopathy) occurred in 83.3% (40/48) of patients with radiologically assessed baseline disease across dose groups (Supporting Information Figure 1 A). The median time to response was 1.87 months (range 1.6–16.6). A nondose–dependent lymphocytosis following duvelisib initiation was noted in 75% of patients with absolute lymphocyte counts (ALC) returning to baseline around C5D1 (Supporting Information Figure 2 A). Stable disease (SD) was the best response in 19 (34.5%) patients, 6 of whom (32%) achieved a nodal response and met at least one group B criterion but had persistent treatment-related lymphocytosis; 2 (3.6%) patients did not achieve any response. In patients with *TP53* mutation or 17p deletion, the ORR was 46.4% (13/28), including one (3.6%) CR. The ORR in patients with unmutated *IGHV* was 51.4% (18/35) and included the aforementioned CR. One patient who had received idelalisib and rituximab as a prior therapy achieved PR with duvelisib. Among the six patients with disease progression on prior BTKi therapy, one patient achieved a PR with a response duration of approximately 6.5 months, and another patient maintained SD for approximately 16.5 months. One subject had SD at the time of treatment discontinuation (day 117) due to physician's decision. The three remaining patients discontinued duvelisib for progressive disease at 2, 3, and 4 months, respectively.

The median DOR in responders ($n = 31$) was 21.0 months. The estimated probability of remaining in response at 6, 12, and 24 months was 73.3%, 62.4%, and 31.2%, respectively. Among patients with *TP53* mutation or 17p deletion receiving duvelisib 25 mg BID, median DOR was 23.2 months, with a 71.4% estimated probability of remaining in response at 12 months and 18 months.

Across all doses, median PFS was 15.7 months (Figure 1). PFS events included 23 disease progressions and three deaths. The estimated probability of being progression-free at 6, 12, and 18 months was 67.7%, 57.1%, and 44.5%, respectively. Among patients with TP53 mutation and/or 17p deletion who received duvelisib 25 mg BID, median PFS was 27.9 months, with an estimated 65.7% and 52.5% probability of being progression free at 12 and 24 months, respectively.

The median OS for RR patients was not reached, and the estimated probability of survival at 6, 12, and 18 months was 81.8%, 65.5%, and 63.6%, respectively (Figure 1). The estimated median OS for RR patients with *TP53* mutation and/or 17p deletion who received duvelisib 25 mg BID was 21.3 months.

2.3.2 | Treatment-naïve CLL—The ORR was 83.3% (15/18) including all PRs and was similar among patients with *TP53* mutation or 17p deletion (80.0% [8/10]) and unmutated *IGHV* (85.7% [12/14]) (Table 3). The absence of a postbaseline assessment precluded response determination in one patient, and the remaining two patients (11.1%) had SD as

their best response. The median time to response was 3.71 months (range 1.7–8.3). Nodal response (≥50% reduction in adenopathy) occurred in 87.5% (14/16) of patients with radiologically assessed baseline disease (Supporting Information Figure 1B). Similar to RR CLL/SLL, lymphocytosis was observed shortly after duvelisib initiation in 70.6% of TN patients, with return to baseline ALC for the population occurring around C3D1 (Supporting Information Figure 2B).

The median DOR was not reached, with estimated 6- and 12-month probabilities of remaining in response of 100% and 87.5%, respectively. The median PFS and OS were also not reached, with estimated probabilities of remaining progression-free and surviving at 12 months of 94% and 100%, respectively.

2.4 | Duvelisib pharmacodynamics in CLL

Chemokines, cytokines, and serum factors reflective of CLL tumor cells, the immune system, and the tumor microenvironment were evaluated in an exploratory analysis by collecting blood samples at baseline and at various timepoints during cycles 1–3. Supporting Information Table 1 lists all of the chemokines, cytokines, and serum factors evaluated; 13 of the 74 analytes tested decreased significantly from baseline at cycle 1 Day 8 (C1D8) and displayed ≥50% median change: CCL1, CCL3, CCL4, CCL17, CCL22, CXCL10, CXCL13, IL-6, IL-10, IL-12p40, MMP-9, MMP-12, and TNFα (Supporting Information Figure 3A) with P value <.0018 after Bonferroni correction for the 74 multiple comparisons. All 13 analytes were elevated at baseline in the serum from RR patients compared to healthy donors ($n = 33$). All but IL-6 were statistically significantly decreased at C2D1 and C3D1 compared to baseline. After 8 days of duvelisib, seven of these analytes were no longer significantly higher than healthy donor samples (data not shown).

Pharmacodynamic data were collected from 17 TN patients (94%); 10 of the 74 serum analytes tested had decreased significantly at C1D8 with ≥50% median change: CCL3, CCL4, CCL17, CCL22, CXCL10, CXCL13, IL-10, IL-12p40, MMP-9, and TNFα (Supporting Information Figure 3B) with P value <.0018 after Bonferroni correction for the 74 multiple comparisons. All analytes except CXCL10 also exhibited significant decreases at C2D1 and C3D1. Only IL-6 changed significantly at C2D1 or C3D1 but not at C1D8; 9 of these 10 analytes (except CXCL10) were elevated at baseline in TN serum compared with healthy donors ($n = 33$). After 8 days of duvelisib, levels of five of the analytes elevated at baseline were no longer significantly higher than healthy donor samples (data not shown).

3. | DISCUSSION

Here we present the first demonstration of the anti-leukemic activity and safety of duvelisib in patients with CLL/SLL. Data were collected within a broader phase 1 study in patients with multiple advanced hematologic malignancies, described elsewhere.[16]

Through dual PI3K-δ and PI3K-γ inhibition, duvelisib targets multiple facets of the pathogenesis and maintenance of CLL, including cell-autonomous survival signaling and growth and migration signaling through supportive cellular interactions and circulating factors provided by the tumor microenvironment.[18] Duvelisib demonstrated *in vivo*

pharmacologic activity in CLL cells through rapid, sustained, and maximal inhibition of p-AKT, a downstream marker of PI3K signaling,[19] at 25 mg BID. In addition, nearly complete inhibition of CLL cell proliferation, assessed by Ki-67 expression at C2D1, was noted in most RR patients and all TN patients. Neither p-AKT nor Ki-67 inhibition was dose-dependent, with maximal inhibition at 25 mg.[16]

Significant reductions in chemokines, cytokines, and matrix metalloproteinases expressed by malignant B cells and tumor-supporting myeloid and T cells following duvelisib treatment in RR and TN patients suggest potential CLL tumor microenvironment disruption through dual inhibition of PI3K-δ and PI3K-γ.[19–26]

The clinical benefit of duvelisib in RR and TN CLL is supported by the induction of durable disease responses. Lymphocytosis was observed in 70–75% of patients shortly after initiating duvelisib and, per recent guidance,[27] was not considered progressive disease. In RR CLL patients, ALC returned to baseline levels approximately 4 months into duvelisib treatment, which is shorter than reported for other BCR pathway inhibitors (BCRPIs)[28,29] ORRs among all RR patients and the subset with *s* mutation and/or 17p deletion, 56.4% and 46.4% respectively, were not dose dependent. While PFS appeared to differ between the RR CLL 25 mg BID and 75 mg BID cohorts, interpretation is limited by the phase 1 trial design and conduct, and further accentuated by the small patient numbers within each dose group. Per eligibility criteria, TN CLL patients represented a population for which frontline chemoimmunotherapy would be considered suboptimal. The median age was 74, much older than in most frontline clinical trials of CLL.[30] Additionally, the proportion of patients with *TP53* mutation and/or 17p deletion (56%) far exceeds the prevalence in the general untreated CLL population and typical frontline CLL therapy trials (5–10%).[30] Within this context, the ORR of 83% with 87% of responding patients maintaining response through 12 months is clinically meaningful.

Duvelisib was generally well tolerated in the RR CLL/SLL population, with some patients remaining on treatment for more than 3 years. The safety profile was consistent with the entire phase 1 patient population,[16] and characterized by potentially autoimmune toxicities similar to those observed with PI3K-δ inhibitor therapy.[31] While there were numerical differences in some individual AE incidences between the 25 mg BID and 75 mg BID dose cohorts, there did not appear to be a definitive dose effect of duvelisib on the overall safety profile in the RR CLL population. Diarrhea (47%) was the most frequently reported nonhematologic event but was managed with dose modifications and supportive-care interventions (eg, antidiarrheals) and rarely resulted in treatment discontinuation. In this report, the incidences of severe diarrhea (9.1%) and colitis (5.5%) are derived from the AE terms reported by investigators and in some cases these events overlapped. Colonoscopy data were not formally collected. Transaminase elevations (25–27%) were mostly low-grade, reversible upon dosing interruptions, and rarely resulted in treatment discontinuation. Hematologic AEs, including grade 3 and 4 events, were also common but expected given baseline cytopenia (grade ≥ 3) in over a third of patients and not preclusive of maintaining therapy.

Infectious complications are a well-recognized major cause of morbidity and mortality in CLL, given the humoral immunodepression inherent to the disease and therapy-induced immunosuppression.[32,33] Similar to other BCRPIs, infections, particularly pneumonias and URTIs, were frequently observed and remain an important risk.[34,35] Fatal infections were reported in four patients, two of whom previously experienced disease progression. The requirement for prophylaxis added to this study was intended to mitigate the risk for *Pneumocystis* pneumonia and continues to be implemented in duvelisib clinical trials.

The AE profile in TN was generally similar to RR, although incidences of diarrhea and transaminase elevations were higher. As noted previously, treatment with idelalisib and rituximab resulted in a high incidence of presumed immune-mediated side effects in patients with previously untreated CLL, and was higher in younger patients.[36,37] The disruption of Treg signaling via PI3K-δ inhibition and the resultant emergence of a cytotoxic effector T-cell population may account for the autoimmune toxicities with the higher incidence in previously untreated and/or younger patients attributed to a better-preserved population of T cells.[37]

While differences in study design and treatment exposure preclude direct cross-study comparisons of autoimmune toxicity risk, preclinical data support the rationale that concomitant inhibition of PI3K-γ by duvelisib may mitigate autoimmune complications through maintenance of a safe balance between regulatory and effector T-cell activity. It has been shown that inactivation of PI3K-γ, either through mutations or inhibition by small molecules, impairs the migration of leukocytes from the bloodstream to sites of injury or inflammation; in addition, PI3K-γ is required for optimal T-cell activation and differentiation.[38,39] In mouse models of multiple chronic inflammatory diseases, PI3K-γ inhibition or absence abrogated disease activity.[38,40–44] While the data from this small cohort suggest a predictable and manageable safety profile in TN patients, additional investigation to elucidate the pharmacologic and clinical sequelae of PI3K-γ inhibition by duvelisib would be informative.

Overall, the clinical and pharmacodynamic activity and manageable safety profile in these heavily pretreated, RR CLL/SLL, and high-risk TN CLL patients highlight the potential of duvelisib as an effective new therapy. These data, together with the data from the overall phase 1 study population, support the selection of 25 mg BID for further clinical development.[18] A phase 3 clinical trial (DUO) is ongoing to assess duvelisib as a monotherapy in patients with RR CLL/SLL (NCT02004522).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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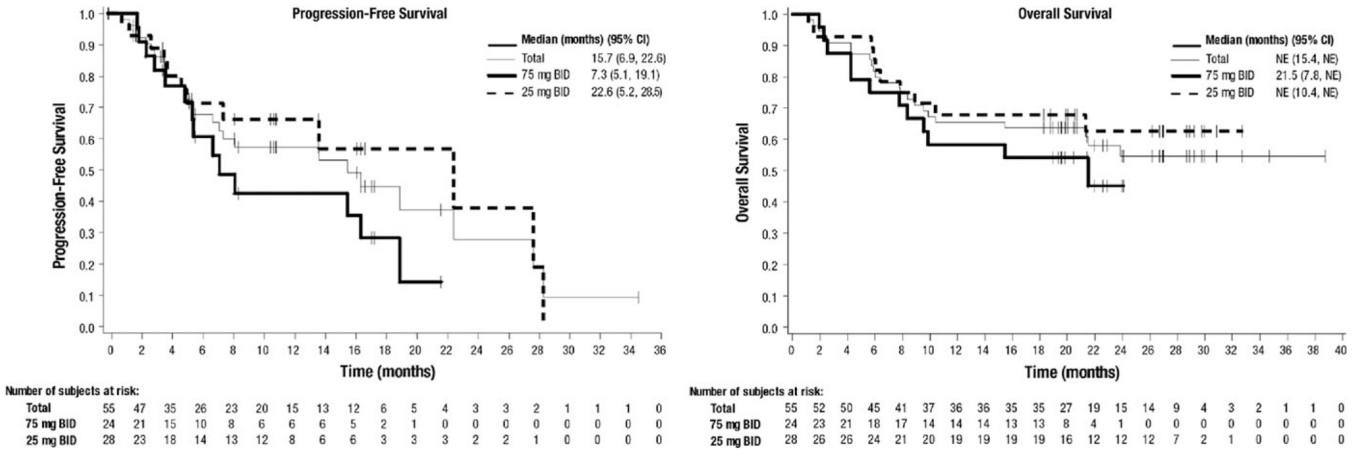

FIGURE 1.

Progression-free survival and overall survival in patients with relapsed/refractory CLL/SLL

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TABLE 1

Patient demographics and baseline characteristics of patients with CLL

	Relapsed/refractory			Treatment-naïve
Demographics and baseline characteristics	**25 mg BID *n* = 28**	**75 mg BID *n* = 24**	**All doses *n* = 55**	**25 mg BID *n* = 18**
Demographics				
Age (years), median (range)	66 (42–82)	66 (51–79)	66 (42–82)	74 (49–83)
Race, white, *n* (%)	24 (85.7)	22 (91.7)	49 (89.1)	18 (100)
Sex, male, *n* (%)	25 (89.3)	15 (62.5)	42 (76.4)	13 (72.2)
Baseline disease status				
Diagnosis, *n* (%)				
CLL	24 (85.7)	23 (95.8)	50 (90.9)	18 (100)
SLL	4 (14.3)	1 (4.2)	5 (9.1)	NA
Years from initial diagnosis, median (range)	9.25 (1.4–20.9)	7.15 (0.7–17.8)	8.50 (0.7–20.9)	2.90 (0.1–9.4)
Baseline disease istage 3, *n* (%)	23 (85.2)[a]	17 (70.1)	42 (77.8)	6 (33)
Bulky disease (>5 cm lesion)	13 (46.4)	13 (65.0)[b]	26 (50.9)[b]	5(29)
Splenomegaly, *n* (%)	6 (21.4)	6 (25.0)	14 (25.5)	8 (44.4)
ECOG score, 0/1/2, %	28.6/64.3/7.1	16.7/79.2/4.2	23.6/70.9/5.5	44.4/55.6/0
Cytopenias at baseline				
Grade 3, *n* (%)	8 (28.6)	5 (20.8)	13 (23.6)	2 (11.1)
Grade 4, *n* (%)	3 (10.7)	5 (20.8)	8 (14.5)	2 (11.1)
Previous anticancer therapies				
No. prior systemic therapies, median (range)	5.0(1–11)	4.0 (1–11)	4.0 (1–11)	NA
<6 mo. from last systemic therapy, *n* (%)	16 (57.1)	19 (79.2)	35 (63.6)	NA
Alkylating agent, *n* (%)	27 (96.4)	23 (95.8)	53 (96.4)	NA
Rituximab, *n* (%)	27 (96.4)	23 (95.8)	52 (94.5)	NA
Purine analog, *n* (%)	20 (71.4)	22 (91.7)	43 (78.2)	NA
Anthracycline, *n* (%)	7 (25.0)	3 (12.5)	12 (21.8)	NA
BTKi, *n* (%)	2 (7.1)	4 (16.7)	6 (10.9)	NA
High-risk mutation status				
TP53 mutation/17p-deletion, *n* (%)[c]	14 (53.8)	14 (58.3)	28 (56.0)	10 (55.5)

	Relapsed/refractory			Treatment-naïve
Demographics and baseline characteristics	**25 mg BID *n* = 28**	**75 mg BID *n* = 24**	**All doses *n* = 55**	**25 mg BID *n* = 18**
Unmutated IGHV[d]	21 (84.0)	14 (87.5)	38 (86.4)	14 (82.4)
Del11q, *n* (%)[e]	6 (31.6)	8 (57.14)	14 (40.0)	6 (37.5)

Abbreviations: BID, twice daily; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy chain variable; NA, not applicable; RR, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naïve.

[a]Baseline disease stage not reported for 1 patient on duvelisib 25 mg BID; the incidence is based upon patients with available data.

[b]Bulky disease information at baseline not reported for 4 patients at 75 mg BID, and 4 patients across all doses for RR; the incidence is based upon patients with available data.

[c]Baseline mutation status not reported for 2 patients at 25 mg BID, 3 patients at 75 mg BID, and 5 patients across all doses for RR. For TN, 1 patient had no mutation status reported at baseline. The incidence is based upon patients with available data.

[d]Baseline *IGHV* mutation status was not available for 3 patients at 25 mg BID, 8 patients at 75 mg BID, and 11 patients across all doses for RR-CLL/SLL, nor for 1 patient with TN-CLL. The incidence is based upon patients with available data

[e]Baseline mutation status was not available for 9 patients at 25 mg BID, 10 patients at 75 mg BID, and 20 patients across all doses for RR-CLL/SLL, nor for 2 patients with TN-CLL. The incidence is based upon patients with available data.

TABLE 2A

Incidence of adverse events in patients with relapsed/refractory CLL/SLL (>15% of patients overall)

	Duvelisib 25 mg BID			**Duvelisib 75 mg BID**			**All Duvelisib doses**		
	(*n* = 28)			**(*n* = 24)**			**(*n* = 55)**		
AE	***n* (%)**			***n* (%)**			***n* (%)**		
Grade[a], *n* (%)	**Any**	**Grade 3**	**Grade 4**	**Any**	**Grade 3**	**Grade 4**	**Any**	**Grade 3**	**Grade 4**
Hematologic									
Neutropenia	19 (67.9)	5 (17.9)	10 (35.7)	10 (41.7)	2 (8.3)	5 (20.8)	31 (56.4)	7(12.7)	17 (30.9)
Anemia	8 (28.6)	5 (17.9)	1 (3.6)	10 (41.7)	5 (20.8)	0	19 (34.5)	11 (20.0)	1 (1.8)
Thrombocytopenia	6 (21.4)	2 (7.1)	3 (10.7)	6 (25.0)	0	5 (20.8)	13 (23.6)	2 (3.6)	8 (14.5)
Febrile neutropenia	4 (14.3)	4 (14.3)	0	4 (16.7)	5 (16.7)	0	9 (16.4)	9 (16.4)	0
Nonhematologic									
Diarrhea	12 (42.9)	3 (10.7)	0	13 (54.2)	1 (4.2)	0	26 (47.3)	5(9.1)	0
Fatigue	12 (42.9)	3 (10.7)	0	8 (33.3)	2 (8.3)	1 (4.2)	21 (38.2)	5(9.1)	1 (1.8)
Cough	8 (28.6)	0	0	10 (41.7)	0	0	19 (34.5)	0	0
Pyrexia	4 (14.3)	0	0	11 (45.8)	2 (8.3)	0	17 (30.9)	2 (3.6)	0
URTI	9 (32.1)	1 (3.6)	0	5 (20.8)	0	0	15 (27.3)	1 (1.8)	0
Arthralgia	7 (25.0)	0	0	6 (25.0)	0	0	14 (25.5)	0	0
Decreased appetite	8 (28.6)	1 (3.6)	0	5 (20.8)	0	0	14 (25.5)	1 (1.8)	0
Nausea	5 (17.9)	0	0	7 (29.2)	1 (4.2)	0	14 (25.5)	1 (1.8)	0
Dyspnea	6 (21.4)	1 (3.6)	0	7 (29.2)	2 (8.3)	0	13 (23.6)	3 (5.5)	0
Pneumonia[b]	9 (32.1)	4 (14.2)	1 (3.6)	12 (50.0)	8 (33.3)	0	21 (38.2)	12 (21.8)	1 (1.8)
Edema (peripheral)	2 (7.1)	0	0	7 (29.2)	0	0	10 (18.2)	0	0
Rash (maculopapular)	4 (14.3)	0	0	5 (20.8)	0	0	10 (18.2)	0	0
Sinusitis	5 (17.9)	0	0	4 (16.7)	0	0	10 (18.2)	0	0
Stomatitis	5 (17.9)	2 (7.1)	0	5 (20.8)	1 (4.2)	0	10 (18.2)	3(5.5)	0
Vomiting	2 (7.1)	0	0	7 (29.2)	1 (4.2)	0	10 (18.2)	1 (1.8)	0
Investigations									
AST/ALT increased	9 (32.1)	3 (10.7)	0	7 (29.2)	2 (8.3)	1 (4.2)	17 (30.9)	5(9.1)	1 (1.8)

	Duvelisib 25 mg BID			Duvelisib 75 mg BID			All Duvelisib doses		
	(*n* = 28)			(*n* = 24)			(*n* = 55)		
AE	***n* (%)**			***n* (%)**			***n* (%)**		
Grade[a], *n* (%)	**Any**	**Grade 3**	**Grade 4**	**Any**	**Grade 3**	**Grade 4**	**Any**	**Grade 3**	**Grade 4**
Hypokalemia	2 (7.1)	0	0	7 (29.2)	2 (8.3)	2 (8.3)	10 (18.2)	2 (3.6)	3 (5.5)
Hypomagnesaemia	6 (21.4)	0	0	3 (12.5)	0	0	9 (16.4)	0	0
Hypophosphatemia	3 (10.7)	2 (7.1)	0	6 (25.0)	3 (12.5)	1 (4.2)	9 (16.4)	5(9.1)	1 (1.8)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; URTI, upper respiratory tract infection. Notes: Patients are counted once within each system organ class and preferred term. Percentages are based on the number of patients in each dose group for the All-Treated Analysis Set. Patients with an event in more than 1 grade are counted only once at the maximum grade within each system organ class, and within each preferred term.

[a]AEs were coded using the Medical Dictionary of Regulatory Activities (MedDRA) version 16.1, and were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

[b]Includes the preferred terns of pneumonia (*n* = 13), lung infection (*n* = 2), lung infiltration (*n* = 1), pneumonia Pseudomonas aeruginosa (*n* = 1), Bronchopulmonary aspergillosis (*n* = 1), pneumonia aspiration (*n* = 1), pneumonia Escherichia (*n* = 1), and pneumonia respiratory syncytial viral (*n* = 1).

TABLE 2B

Incidence of adverse events in patients with treatment-naïve CLL (>20% of patients)

AE	Duvelisib 25 mg BID (*n* = 18)		
Grade[a], *n* (%)	**Any**	**Grade 3**	**Grade 4**
Hematologic			
Neutropenia	8 (44.4)	1 (5.6)	5 (27.8)
Anemia	5 (27.8)	1 (5.6)	0
Thrombocytopenia	4 (22.2)	1 (5.6)	1 (5.6)
Nonhematologic			
Diarrhea	14 (77.8)	4 (22.2)	0
Cough	8 (44.4)	0	0
Peripheral edema	8 (44.4)	0	0
Fatigue	7 (38.9)	1 (5.6)	0
Nausea	7 (38.9)	1 (5.6)	0
Rash	7 (38.9)	1 (5.6)	0
Pyrexia	6 (33.3)	0	0
Dizziness	5 (27.8)	0	0
Abdominal pain	4 (22.2)	2(11.1)	0
Alopecia	4 (22.2)	0	0
Arthralgia	4 (22.2)	1 (5.6)	0
Constipation	4 (22.2)	0	0
Contusion	4 (22.2)	0	0
Decreased appetite	4 (22.2)	0	0
Headache	4 (22.2)	0	0
Insomnia	4 (22.2)	0	0
Pneumonia	4 (22.2)	1 (5.6)	0
Pollakiuria	4 (22.2)	0	0
URTI	4 (22.2)	0	0
Investigations			
AST increased	6 (33.3)	2(11.1)	0
ALT increased	6 (33.3)	3 (16.7)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; URTI, upper respiratory tract infection. Notes: Patients are counted once within each system organ class and preferred term. Percentages are based on the number of patients in each dose group for the All-Treated Analysis Set. Patients with an event in more than 1 grade are counted only once at the maximum grade within each system organ class, and within each preferred term.

[a]AEs were coded using the Medical Dictionary of Regulatory Activities (MedDRA) version 16.1, and were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03.

TABLE 3

Overall response rate in patients with CLL

	Relapsed/refractory				Treatment-naïve	
Duvelisib dose	**25 mg BID *n* = 28**	**75 mg BID *n* = 24**	**All doses *n* = 55**	***TP53* mutation/17p deletion All doses *n* = 28**	**25 mg BID *n* =18**	***TP53* mutation/17p deletion 25 mg BID *n* = 10**
Overall response rate (ORR) (CR + PR)						
ORR, *n* (%)	16(57.1)	13 (54.2)	31 (56.4)	13 (46.4)	15 (83.3)	8 (80.0)
95% confidence interval	(37.2, 75.5)	(32.8, 74.4)	(42.3, 69.7)	(27.5, 66.1)	(58.6, 96.4)	(44.4, 97.5)
Best overall response						
Complete response (CR), *n* (%)	1 (3.6)	0	1 (1.8)	1 (3.6)	0	0
Partial response (PR), *n* (%)	15 (53.6)	13 (54.2)	30 (54.5)	12 (42.9)	15 (83.3)	8 (80.0)
Stable disease[a] *n* (%)	10 (35.7)	8 (33.3)	19 (34.5)	12 (42.9)	2(11.1)	1 (10.0)
Progressive disease, *n* (%)	1 (3.6)	1 (4.2)	2 (3.6)	2 (7.1)	0	0
Unknown, *n* (%)	1 (3.6)	2 (8.3)	3 (5.5)	1 (3.6)	1 (5.6)	1 (10.0)

Abbreviations: BID, twice daily; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma. Notes: The Clopper-Pearson confidence interval is presented. Patients with no post-baseline response assessment are represented as having an 'unknown' response. Percentages are based on the number of patients in each dose group.

[a]Among RR patients with stable disease, 6/19 (32%) had a lymph node response and persistent lymphocytosis, meeting the criteria for partial response for agents causing increased peripheral blood lymphocytes {Cheson, 2012 #2743}.