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Efficacy and Safety of Duvelisib Following Disease Progression on Ofatumumab in Patients with Relapsed/Refractory CLL or SLL in the DUO Crossover Extension Study

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Abstract

Purpose: In the phase 3 DUO trial, duvelisib, an oral dual PI3K-δ,γ inhibitor, demonstrated significantly improved efficacy vs ofatumumab (median [m]PFS, 13.3 vs 9.9 months [HR, 0.52; *P* < .0001]; ORR, 74% vs 45% [*P* < .0001]), with a manageable safety profile in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL). We report results from patients with progressive disease (PD) after ofatumumab who crossed over to duvelisib in the DUO trial.

Experimental Design: Patients with radiographically confirmed PD after ofatumumab received duvelisib 25 mg twice daily in 28-day cycles until PD, intolerance, death, or study withdrawal. The primary endpoint was ORR per investigator. Secondary endpoints included duration of response (DOR), PFS, and safety.

Results: As of December 14, 2018, 90 ofatumumab-treated patients in the DUO trial prior to crossover had an ORR of 29%, mDOR of 10.4 months, and mPFS of 9.4 months. After crossover, 77% of patients (69/90) achieved a response, with an mDOR of 14.9 months and mPFS of 15.7 months. Patients with del(17p) and/or *TP53* mutations had similar outcomes (ORR, 77% [20/26]; mPFS, 14.7 months). Notably, 73% of patients (47/64) with disease previously refractory to ofatumumab achieved a response. The most frequent any-grade/grade 3/4 treatment-emergent adverse events were diarrhea (47%/23%), neutropenia (26%/23%), pyrexia (24%/4%), cutaneous reactions (23%/4%), and thrombocytopenia (10%/6%).

Conclusion: Duvelisib demonstrated high response rates with good durability and a manageable safety profile in patients with R/R CLL/SLL who progressed on ofatumumab, including patients with high-risk disease and disease previously refractory to ofatumumab.

Translational Relevance

Despite the efficacy of agents recently approved for the treatment of patients with CLL, in many patients, the disease will develop resistance and progress, resulting in an urgent need for new effective and tolerable treatment options. Duvelisib is an oral, dual PI3K-δ,γ inhibitor that recently received US Food and Drug Administration approval as monotherapy in R/R CLL/SLL. In the registrational phase 3 DUO trial, duvelisib demonstrated a significant improvement in efficacy vs ofatumumab in patients with R/R CLL/SLL. Following disease progression while receiving ofatumumab in DUO, patients could cross over to receive duvelisib in a crossover extension study. We show that duvelisib resulted in favorable outcomes and had a manageable safety profile in patients treated with duvelisib in this crossover study. These results confirm duvelisib as an effective treatment option in CLL/SLL, even in patients with high-risk features, prior refractory disease, and disease progression on ofatumumab.

Introduction

Despite recent approvals of several active novel agents for chronic lymphocytic leukemia (CLL), the disease remains incurable for most patients. Agents targeting Bruton tyrosine kinase (BTK) and BCL2 are efficacious for many patients with relapsed or refractory (R/R) CLL, yet many patients will develop resistance and progressive disease (PD) (1-5). As occurs with chemoimmunotherapy, high-risk genetic features such as 17p13.1 deletion (del(17p)) or *TP53* somatic mutations confer a poorer prognosis with BTK and BCL2 inhibitor therapy (6-8). As such, there remains an urgent need to develop new effective and tolerable CLL/small lymphocytic lymphoma (SLL) treatment options, particularly for patients with high-risk disease.

Duvelisib is an oral, dual PI3K-δ,γ inhibitor that directly targets malignant B cells and key signaling pathways in the tumor microenvironment (9-11). In preclinical studies, dual inhibition of PI3K-δ,γ with duvelisib was more effective at inhibiting CLL B cells and reducing the number of CLL-supporting cells in vivo than PI3K-δ inhibition alone (9,10).

In early-phase clinical trials, duvelisib monotherapy demonstrated a manageable safety profile and clinically meaningful activity in patients with R/R hematologic malignancies, including CLL/SLL (12). In the randomized, open-label, registrational, phase 3 DUO trial (NCT02004522), the efficacy and safety of duvelisib 25 mg twice daily (BID) was compared with the anti-CD20 monoclonal antibody ofatumumab (13) in patients with R/R CLL/SLL (14). Duvelisib demonstrated a statistically significant improvement in progression-free survival (PFS) and overall response rate (ORR) compared with ofatumumab in patients with R/R CLL/SLL (median PFS [mPFS], 13.3 vs 9.9 months [hazard ratio, 0.52; $P < .0001$]; ORR, 74% vs 45% [$P < .0001$]), with similar efficacy in patients with high-risk del(17p) or *TP53* mutation (14). Duvelisib monotherapy demonstrated a consistent safety profile in this phase 3 trial compared with earlier trials,

with the most common toxicities observed being any-grade diarrhea, neutropenia, and pyrexia. In most cases, these toxicities were manageable with appropriate intervention via dose modifications and routine medical care (12,15-17). Duvelisib monotherapy was approved by the US Food and Drug Administration in September 2018 for the treatment of patients with R/R CLL/SLL after ≥ 2 prior therapies (12).

The DUO crossover extension study (IPI-145-12; NCT02049515) is an open-label, phase 3 study that evaluated the efficacy and safety of duvelisib monotherapy in patients with R/R CLL/SLL who experienced PD while receiving ofatumumab in the DUO trial. We report the final results for this extension study.

Patients and Methods

Study design and treatment

DUO crossover is a 2-arm, open-label, nonrandomized, optional, extension study of duvelisib and ofatumumab in patients with R/R CLL/SLL who had received treatment in the parent DUO study. Patients who exhibited radiographically confirmed PD by central review in the DUO trial had the option to subsequently receive the other study treatment (duvelisib or ofatumumab).

The dose and regimen of duvelisib and ofatumumab were the same as those in the DUO trial (14). Patients receiving duvelisib were started at a dose of 25 mg BID in a 21-day treatment cycle followed by 28-day treatment cycles until PD, unacceptable toxicity, death, or study withdrawal (whichever came first). Ofatumumab was administered per the approved product label for monotherapy in relapsed CLL at the time the DUO study was initiated and could not exceed the 12 doses (within 7 cycles), as described in the prescribing information (13). *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis

concomitant with study drug treatment was required for all patients; trimethoprim/sulfamethoxazole was the most commonly used medication for PJP prophylaxis in the parent DUO study. Per protocol, antiviral prophylaxis was recommended to be implemented at the discretion of the treating investigator.

The final study protocol, and its amendments, were approved by an Institutional Review Board/Independent Ethics Committee for each clinical trial site and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

Patient eligibility

Eligible patients included all those who participated in the DUO study and experienced radiographically confirmed PD by central review prior to enrollment in the DUO crossover trial. Key inclusion and exclusion criteria were the same as those in the parent DUO study (14). Inclusion criteria included active CLL/SLL necessitating treatment per the International Workshop on CLL (iwCLL) criteria or measurable disease per the revised International Working Group (IWG), defined as ≥ 1 lymph node or tumor mass measuring > 1.5 cm by computed tomography (CT) scan; adequate renal and hepatic function; hemoglobin level ≥ 8.0 g/dL; and platelet count ≥ 10,000 μL with or without transfusion support. There was no eligibility requirement regarding neutrophil count. Exclusion criteria included prior treatment with BTK or PI3K inhibitors, refractoriness to prior ofatumumab therapy prior to enrollment in DUO, and a history of Richter transformation, prolymphocytic leukemia, or allogeneic stem cell transplant.

Study endpoints and assessments

The primary endpoint was ORR, as assessed by investigators, defined as complete response (CR), CR with incomplete marrow recovery (CRi), partial response (PR), or PR with lymphocytosis (PRwL),

according to the 2008 iwCLL (18) with modification for treatment-related lymphocytosis. Per protocol, a response of PRwL was limited to patients with lymphadenopathy as the only abnormal baseline group A criterion (no organomegaly and normal blood lymphocyte count, 4 x 10^9/L) who achieved a PR (≥ 50% reduction in lymphadenopathy) but had post-baseline isolated lymphocytosis.

Secondary efficacy endpoints were PFS, defined as time from first dose to first documentation of investigator-assessed PD per iwCLL/IWG (18,19) criteria or death resulting from any cause, and DOR, defined as time from first response to PD or death. This study was not designed to detect differences in PFS among subgroups.

Patients were followed up for overall survival (OS) for 6 years following randomization to the parent DUO study. Response assessments (including review of disease-associated symptoms) were performed every 4 cycles until cycle 12, every 6 cycles until cycle 24, and then every 6 cycles until PD, start of new anticancer therapy, or patient withdrawal.

Local laboratories assessed lymphocyte counts. Central laboratories assessed prognostic markers and cytogenetics at baseline in the DUO study and did not re-evaluate on enrollment in the DUO crossover study.

Safety was assessed at days 1 and 8 of cycle 1, days 1 and 15 of cycle 2, day 1 of cycles 3 to 7, then day 1 of every even-numbered cycle of cycles 8 to 18 and every third cycle from cycle 21 thereafter until 30 days from the last dose of study drug. Events were coded using Medical Dictionary for Regulatory Activities version 16.1. The severity of treatment-emergent adverse events (TEAEs) was assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 (20).

TEAEs were defined as any AE that emerged or worsened in the period from the first dose of study treatment through 30 days after the last dose of study treatment.

Statistical methods

ORR was analyzed as the proportion of patients achieving a best response of PR/PRwL or CR/CRi as determined by the investigator; the corresponding 95% CIs were calculated. PFS and duration of response, as determined by investigators, were estimated using Kaplan-Meier methods on all patients receiving duvelisib and all patients who achieved a response on duvelisib, respectively. OS was estimated using Kaplan-Meier methods on all patients receiving duvelisib.

Results

Patient baseline characteristics

Between September 19, 2014, and July 17, 2017, 99 patients were enrolled at 43 clinical sites in 11 countries and received duvelisib (n = 90) or ofatumumab (n = 9) within 3 months of PD in the DUO trial. This report focuses on the results in the 90 patients who crossed over from ofatumumab and received duvelisib 25 mg BID.

The baseline characteristics of these 90 patients were similar to those of the overall population of patients reported in the DUO trial (14) (**Table 1**). Patients were predominately male (63%), with a median age of 68 years. Most patients (89%) had a baseline Eastern Cooperative Oncology Group performance status of 0 to 1. The median time from initial diagnosis was 7.1 years, and more than half of the patients had bulky disease (≥ 5-cm target lesion; 52%). A total of 22% of patients (9/41) had Rai stage III/IV disease at diagnosis (vs 49% of patients [21/43] at enrollment in the parent DUO study), and 66% of patients (31/47) had Binet stage B or C disease at diagnosis (vs 100% [47/47] at enrollment in the

parent DUO study). Median baseline lymphocyte count was 14.4×10^9/L. Central laboratory determination of molecular features identified del(17p) and/or *TP53* mutations in 29% of patients (del[17p], 22% [20/90]; *TP53*, 18% [16/90]; del(17p) and *TP53*, 11% [10/90]) and unmutated *IGHV* in 72% of patients (65/90).

The median number of prior therapies was 3 (range, 2-8), including ofatumumab received in the parent DUO study (**Supplementary Table S1**). Most patients previously received a monoclonal antibody (100%), alkylating agent (96%), or purine analogue (73%). No patients received prior ibrutinib, idelalisib, or venetoclax.

Efficacy

The investigator-assessed ORR with duvelisib treatment after crossover was 77% (69/90); in the subset of patients with del(17p) and/or *TP53* mutations, the ORR was also 77% (20/26) (**Table 2**). In all patients, responses were predominantly PR (61%): 10 patients (11%) achieved a PRwL and 4 (4%) achieved a CRi. Similar outcomes were observed in patients with del(17p) and/or *TP53* mutations (PR, 58%; PRwL, 8%; CRi, 12%). The median time to response was 2.6 months (range, 1.5-10.7 months). The median duration of response was 14.9 months (95% CI, 9.0-18.6 months) for the total patient population and 11.3 months (95% CI, 5.1-21.2 months) for the subset of patients with del(17p) and/or *TP53* mutations (**Table 2**). Response rates were higher for patients after crossing over to duvelisib compared with their prior response rates to ofatumumab in the DUO trial (**Supplementary Table S2**). Similar response rates were also observed in patients with bulky disease (≥ 5 cm) and in those with del(11q): ORR (n/N; 95% CI), bulky disease: 74% (35/47; 0.6-0.86); del(11q): 80% (16/20; 0.56-0.94).

Responses to duvelisib in the crossover study were also observed in patients whose disease did not respond to ofatumumab in the DUO trial **(Table 2)**. Of 64 patients who were refractory to ofatumumab, 47 (73%) achieved a response after crossing over to duvelisib, with the majority of these responses being PRs (63%).

Reductions in lymph node tumor burden over time were generally accompanied by a decrease in absolute lymphocyte count (ALC) **(Fig. 1A**). Overall, 70 of 78 (90%) response-evaluable patients had > 50% reduction in target nodal lesions (**Fig. 1B**). Of those 70 patients with > 50% reduction, 71% had PR, 13% had PRwL, 10% had stable disease, and 6% had CRi. Additionally, 82% of patients (74/90) experienced redistribution lymphocytosis, which occurred early, with a median time to onset of 1.1 weeks (range, 0.7-89.7 weeks) and a median duration of 15.1 weeks (range, 1.1-127 weeks). The median time to resolution of first lymphocytosis (ALC less than or equal to baseline value or ALC < 5×10^9/L) was 14.6 weeks (range, 2-87.3 weeks).

Survival

With a median overall follow-up of 13.5 months, mPFS per investigator assessment was 15.7 months in all patients who received duvelisib and 14.7 months in the subset of patients with del(17p) and/or *TP53* mutations **(Fig. 2**). In all patients, the estimated probability of being progression free at 6 months and 12 months was 88% and 64%, respectively. In contrast, mPFS with ofatumumab before crossover was 9.4 months in all patients and 9.1 months in patients with del(17p) and/or *TP53* mutations (**Supplementary Fig. S1**). PFS with duvelisib after crossover was numerically longer in patients with del(11q) (vs those with no del(11q)) and in patients without trisomy 12 (vs those with trisomy 12); PFS was similar in patients with and those without bulky disease (**Supplementary Fig. S2**). All patients in the parent DUO study were followed up for survival for 6 years from randomization. In patients who received duvelisib

after crossover (n = 90), the median OS was 43 months (**Supplementary Fig. S3**), with an estimated probability of survival at 6 and 12 months of 91% and 82%, respectively.

Safety

The median duration of exposure to duvelisib was 43 weeks (range, 2-187 weeks), and 48% of patients received ≥ 12 cycles (≈ 1 year) of duvelisib, with a median of 11 cycles (range, 1-48 cycles). Hematologic TEAEs that occurred in > 5% of patients and nonhematologic TEAEs that occurred in ≥ 10% of patients are reported in **Table 3.** All patients treated with duvelisib experienced ≥ 1 TEAE. The most common any-grade hematologic TEAEs occurring in > 5% of patients were neutropenia (26%), thrombocytopenia (10%), and anemia (8%). The rate of febrile neutropenia was low (3%), and 23% of patients (21/90) received ≥ 1 administration of granulocyte colony-stimulating factor. The most common any-grade nonhematologic TEAEs occurring in ≥ 10% of patients included diarrhea (47%), pyrexia (24%), and rash (23%). Grade ≥ 3 TEAEs occurred in 89% of duvelisib-treated patients. The most common grade ≥ 3 events were neutropenia and diarrhea (23% each) and colitis and pneumonia (11% each). Three patients had grade ≥ 3 PJP (2 who had self-discontinued PJP prophylaxis and 1 who was receiving prophylaxis with Bactrim™ [trimethoprim and sulfamethoxazole] at the time of onset), and 1 patient had grade ≥ 3 cytomegaloviral pneumonia. TEAEs observed in this study were generally manageable with dose interruptions and reductions, which occurred in 65 (72%) and 18 (20%) patients, respectively. TEAEs resulting in treatment discontinuation occurred in 47 patients (52%), with colitis (n = 9), diarrhea (n = 8), pneumonia (n = 2), PJP (n = 2), and rash (n = 2) as the only TEAEs leading to discontinuation in > 1 patient.

TEAEs of special interest (AESI) related to duvelisib were defined as infections, diarrhea, colitis, neutropenia, cutaneous reactions, transaminase elevations, and pneumonitis (13). Rates of grade ≥ 3 events due to AESI are depicted in **Fig. 3.** Median time to onset of each AESI ranged from 2 to 7 months (colitis, 5.8 months; diarrhea, 5.5 months; pneumonitis, 6 months; pneumonia, 7.2 months; infections, 3.2 months; transaminitis, 2.6 months; cutaneous reactions, 3.2 months). Ten of 42 patients with diarrhea, 5 of 13 patients with colitis, 6 of 25 patients with cutaneous reactions, and 1 of 1 patient with pneumonitis received steroid therapy, with resolution reported in the majority of patients at the time of data cutoff.

Serious TEAEs are summarized in **Supplementary Table S3.** Serious hematologic TEAEs occurring in ≥ 2 patients were febrile neutropenia, neutropenia, and pancytopenia. Serious nonhematologic TEAEs not due to PD occurring in ≥ 2 patients were bronchitis, pseudomonal sepsis, urinary tract infection, acute renal failure, respiratory failure, and maculopapular rash. Twelve patients (13%) died within 30 days of the last dose (**Supplementary Table S4**).

As of the December 14, 2018, data cutoff, 79 patients (88%) had discontinued treatment with duvelisib, due to TEAEs (48%), PD (22%), death (7%), patient decision (3%), investigator decision (2%), protocol deviation (1%), or other reasons (4%) (**Supplementary Table S5**)**.** Rates of discontinuation due to AESI are depicted in **Fig. 3**.

Discussion

Duvelisib monotherapy achieved robust and durable responses in patients with R/R CLL/SLL who had radiographically confirmed PD following ofatumumab monotherapy in the phase 3 DUO study (14). Patients with del(17p) and/or *TP53* mutations and those refractory to ofatumumab had results

equivalent to those of the group as a whole. PFS with duvelisib was also favorable in light of the PFS that these same patients had while receiving ofatumumab (15.7 vs 9.4 months, respectively). In addition, the median OS and OS at 12 months were similar to those reported with duvelisib in the parent DUO study (median OS, 43 months vs not reached; 12-month OS, 82% vs 86%, respectively).

The favorable efficacy observed with duvelisib in patients previously treated with ofatumumab in this study is similar to that reported in the parent DUO clinical trial (14) and is consistent with results from the phase 1 study of duvelisib in R/R CLL/SLL, in which approximately 95% of patients received prior rituximab (16). The efficacy of duvelisib monotherapy was similar to that reported for ibrutinib in the post–anti-CD20 setting (21). Furthermore, compared with a 77% ORR and 15.7 month median PFS in the duvelisib study reported here, a previous extension study in a similar patient population with idelalisib after rituximab demonstrated a 47.6% ORR and 6.9 month median PFS (22). Thus, duvelisib has been shown to be an attractive all-oral therapy option for patients with R/R CLL/SLL, providing improved durability of benefit over that of idelalisib without the need for infusional anti-CD20 therapy.

The safety profile of duvelisib monotherapy was manageable via dose interruption or reduction in this study and was similar to that observed to date, which has not been affected by the number and type of previous therapies received (12). As typically observed with all CLL therapies, infections were relatively common with duvelisib, although the rate of febrile neutropenia was low at 3%. PJP prophylaxis is an important supportive measure for this therapy because 2 of 3 patients who had severe PJP on this study did not receive prophylaxis at the time of onset. Neutropenia and diarrhea were the most common severe (grade ≥ 3) AEs reported in 23% of duvelisib-treated patients, followed by colitis and pneumonia (11% each). Several of these prespecified AESI were known to be associated with PI3K inhibition and were observed with similar median times to onset than those reported for DUO (14,23). Occurrences of

infections, diarrhea, colitis, neutropenia, cutaneous reactions, alanine aminotransferase/aspartate aminotransferase elevations, and pneumonitis were generally manageable with early intervention, including steroids in some cases as well as dose modifications as recommended by protocol; in most cases, they did not lead to treatment discontinuation. Additionally, in the parent DUO study, dose modifications (interruptions and reductions) did not significantly impact efficacy outcomes with duvelisib in a subset of patients with demographic characteristics comparable to those of the rest of the population and allowed patients to remain on treatment (23).

Despite the availability of several novel agents that are active in CLL, additional treatment options are needed for this disease. In this study, duvelisib demonstrated effectiveness in patients who had received ≥ 1 prior therapy before being enrolled in the DUO trial and had then progressed after ofatumumab therapy. Additionally, PFS in the subgroup of patients with del(17p) and/or *TP53* mutations was similar to that for the whole population, which is in contrast to the shorter PFS outcomes reported in patients with del(17p) and/or *TP53* mutations treated with ibrutinib or venetoclax (4,24). Even among heavily pretreated patients who had received ≥ 2 lines of prior therapy, the majority responded to duvelisib (ORR, 79%), with a decreased risk of progression in nearly all high-risk patient subgroups (25).

A limitation of our study is that, compared with when the study was initiated, ofatumumab is being used less commonly as monotherapy for R/R CLL. Nonetheless, we anticipate that the results observed in the patients in our study are likely to be similar to patients who have progressed after regimens containing other anti-CD20 monoclonal antibodies, such as obinutuzumab (26). None of the patients in this study had previously received a BTK or BCL2 inhibitor, although preclinical data suggest that duvelisib has inhibitory activity in CLL cells in the presence of BTK resistance mutations (27) and efficacy in a BTK

C481S animal model of CLL (10). Therefore, further studies of duvelisib following BTK inhibitors and venetoclax therapies are warranted.

In summary, our study provides additional evidence that duvelisib is effective and tolerable in difficult-to-treat patients with R/R CLL/SLL. These results confirm duvelisib as an effective, all-oral treatment option in CLL/SLL and support the development of further prospective studies of the drug both as a single agent and in combination regimens.

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References

1. Woyach JA, Furman RR, Liu TM, Ozer HG, Zapatka M, Ruppert AS*, et al.* Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med* **2014**;370(24):2286-94.
2. Maddocks KJ, Ruppert AS, Lozanski G, Heerema NA, Zhao W, Abruzzo L*, et al.* Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol* **2015**;1(1):80-7.
3. Blombery P, Anderson MA, Gong JN, Thijssen R, Birkinshaw RW, Thompson ER*, et al.* Acquisition of the recurrent Gly101Val mutation in BCL2 confers resistance to venetoclax in patients with progressive chronic lymphocytic leukemia. *Cancer Discov* **2019**;9(3):342-53.
4. Roberts AW, Davids MS, Pagel JM, Kahl BS, Puvvada SD, Gerecitano JF*, et al.* Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med* **2016**;374(4):311-22.
5. Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T*, et al.* Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. *Lancet Oncol* **2016**;17(6):768-78.
6. Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. *Hematology Am Soc Hematol Educ Program* **2010**;2010:481-8.
7. Byrd JC, Furman RR, Coutre SE, Burger JA, Blum KA, Coleman M*, et al.* Three-year follow-up of treatment-naive and previously treated patients with CLL and SLL receiving single-agent ibrutinib. *Blood* **2015**;125(16):2497-506.
8. Tausch E, Bahlo J, Robrecht S, Schneider C, Bloehdorn J, Schrell S*, et al.* Genetic markers and outcome in the CLL14 trial of the GCLLSG comparing front line obinutuzumab plus chlorabmucil or venetoclax in patients with comorbidity. *Hematol Oncol* **2019**;37(S2):84-6.
9. Chen S-S, Ham S, Rai KR, McGovern K, Kutok JL, Chiorazzi N. Dual inhibition of PI3K-delta and gamma by duvelisib (IPI-145) impairs CLL B- and T-cell migration, survival and proliferation in a murine xenograft model using primary chronic lymphocytic leukemia cells. *Blood* **2015**;126(23):1753.
10. Chen S-S, Kutok JL, Ferrer G, Ravichandran P, Ibrahim M, Kieso Y*, et al.* Dual inhibition of PI3K-δ and PI3K-γ by duvelisib eliminates CLL B cells, impairs CLL-supporting cells, and overcomes ibrutinib resistance in a patient-derived xenograft model. *Blood* **2018**;132(Suppl 1):4420.
11. Pachter JA, Weaver DT. Effect of dual PI3K-δ,γ inhibitor duvelisib on immunosuppressive Tregs and myeloid cells to enhance efficacy of checkpoint and co-stimulatory antibodies in a B cell lymphoma model. *J Clin Oncol* **2018**;36(5_suppl):33.
12. Copiktra (duvelisib) [package insert]. Needham, MA: Verastem, Inc;. **2018**.
13. Arzerra (ofatumumab) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation;. **2018**.
14. Flinn IW, Hillmen P, Montillo M, Nagy Z, Illes A, Etienne G*, et al.* The phase 3 DUO trial: duvelisib vs ofatumumab in relapsed and refractory CLL/SLL. *Blood* **2018**;132(23):2446-55.
15. Flinn IW, O'Brien S, Kahl B, Patel M, Oki Y, Foss FF*, et al.* Duvelisib, a novel oral dual inhibitor of PI3K-δ,γ, is clinically active in advanced hematologic malignancies. *Blood* **2018**;131(8):877-87.
16. O'Brien S, Patel M, Kahl BS, Horwitz SM, Foss FM, Porcu P*, et al.* Duvelisib, an oral dual PI3K-delta,gamma inhibitor, shows clinical and pharmacodynamic activity in chronic lymphocytic leukemia and small lymphocytic lymphoma in a phase 1 study. *Am J Hematol* **2018**;93(11):1318-26.
17. Flinn I, Hillmen P, Montillo M, Nagy Z, Illés Á, Etienne G*, et al.* Results from the phase 3 DUO trial: a randomized comparison of duvelisib vs ofatumumab in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. *Blood* **2017**;130(suppl 1).

18. Hallek M, Cheson BD, Catovsky D, Caligaris-Cappio F, Dighiero G, Döhner H*, et al.* Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood* **2008**;111(12):5446-56.
19. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ*, et al.* Revised response criteria for malignant lymphoma. *J Clin Oncol* **2007**;25(5):579-86.
20. National Institutes of Health; National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 <https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. September 11, 2019.
21. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM*, et al.* Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med* **2014**;371(3):213-23.
22. Sharman JP, Coutre SE, Furman RR, Cheson BD, Pagel JM, Hillmen P*, et al.* Final Results of a Randomized, Phase III Study of Rituximab With or Without Idelalisib Followed by Open-Label Idelalisib in Patients With Relapsed Chronic Lymphocytic Leukemia. *J Clin Oncol* **2019**;37(16):1391-402.
23. Flinn I, Montillo M, Illés Á, Etienne G, Delgado J, Kuss BJ*, et al.* Effect of dose modifications on response to duvelisib in patients with relapsed/refractory (R/R) CLL/SLL in the DUO trial. *J Clin Oncol* **2019**;37(15_suppl):7523.
24. Imbruvica (ibrutinib) [package insert]. Sunnydale, CA: Pharmacyclics, LLC and Horsham, PA: Janssen Biotech;. **2019**.
25. Flinn IW, Davids MS, Hillmen P, Montillo M, Delgado J, Kuss BJ*, et al.* An improved benefit-risk profile of duvelisib in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma who received 2 or more prior therapies. *Hematol Oncol* **2019**;37(S2):213-4.
26. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM*, et al.* Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med* **2014**;370(12):1101-10.
27. Dong S, Guinn D, Dubovsky JA, Zhong Y, Lehman A, Kutok J*, et al.* IPI-145 antagonizes intrinsic and extrinsic survival signals in chronic lymphocytic leukemia cells. *Blood* **2014**;124(24):3583-6.

	Duvelisib After Crossover (n = 90)
Median age (range), years	68 (39-90)
≥ 65 years, n (%)	55 (61)
Male, n (%)	57 (63)
Race, n (%)	
White	83 (92)
Other	4 (4)
Unknown	3 (3)
ECOG PS 2, n (%)	10 (11)
Diagnosis of CLL/SLL, n (%)	89 (99)/1(1)
Median time from initial diagnosis (range), years	7.1 (0.5-22)
Median time from most recent R/R diagnosis (range), months	0.9 (0-16.6)
Molecular features, n (%)	
del(11q)	20 (22)
del(17p)	20 (22)
TP53 mutation	16 (18)
del(17p) and/or *TP53* mutations	26 (29)
del(17p) and *TP53* mutations	10 (11)
Unmutated *IGHV*	65 (72)
Bulky disease, n (%)	
≥ 5-cm target lesion	47 (52)
≥ 10-cm target lesion	15 (17)
Median baseline lymphocytes (range), $\times 10^9$/L	14.4 (0-273.2)
Median baseline hemoglobin (range), g/L	124 (67-176)
Median baseline platelets (range), $\times 10^9$/L	122 (16-272)
Rai stage: diagnosis (n = 41)/enrollment in parent DUO study (n = 43), n (%)	
0	7 (17)/0
I	14 (34)/9 (21)
II	11 (27)/13 (30)
III	1 (2)/4 (9)
IV	8 (20)/17 (40)
Binet stage: diagnosis (n = 47)/enrollment in parent DUO study (n = 47), n (%)	
A	16 (34)/0
B	26 (55)/33 (70)
C	5 (11)/14 (30)

Table 1. Patient demographics and baseline characteristics

	Duvelisib After Crossover		
	All Patients (n = 90)	del(17p) and/or *TP53* Mutations (n = 26)	No Prior Response on Ofatumumab (n = 64)
Overall response rate, n (%)	69 (77)	20 (77)	47 (73)
95% CI[a]	67.9-85.4	60.7-93.1	62.6-84.3
Best overall response, n (%)			
CR	0	0	0
CRi[b]	4 (4)	3 (12)	1 (2)
PR	55 (61)	15 (58)	40 (63)
PRwL	10 (11)	2 (8)	6 (9)
Stable disease	13 (14)	4 (15)	11 (17)
PD	1 (1)	0	1 (2)
Other[c]	7 (8)	2 (8)	5 (8)
Median duration of response, months[d]	14.9	11.3	14.9
95% CI	9.0-18.6	5.1-21.2	7.3-18.6

Table 2. Response by investigator. [a] Binominal method. [b] Patients with CLL only. [c] Includes unknown responses due to missing, incomplete, or inadequate data; no evidence of disease if radiological and clinical data indicated no disease involvement; not evaluable if no target lesions were identified at baseline and the radiological and clinical data after baseline did not support the disease response of PD or unknown. [d] Patients with a response (all patients: n = 26 [before crossover], n = 69 [after crossover]; del(17p) and/or *TP53* mutations: n = 7 [before crossover], n = 20 [after crossover]).

	Duvelisib After Crossover (n = 90)	
	Any Grade	Grade ≥ 3
Any TEAE, n (%)	**90 (100)**	**80 (89)**
Hematologic TEAEs in > 5% of patients, n (%)		
Neutropenia	**23 (26)**	**21 (23)**
Thrombocytopenia	**9 (10)**	**5 (6)**
Anemia	**7 (8)**	**2 (2)**
Nonhematologic TEAEs in ≥ 10% of patients, n (%)		
Diarrhea	**42 (47)**	**21 (23)**
Pyrexia	**22 (24)**	**4 (4)**
Rash	**21 (23)**	**4 (4)**
Colitis	**12 (13)**	**10 (11)**
Pneumonia	**12 (13)**	**10 (11)**
Cough	**12(13)**	**0**
Asthenia	**11 (12)**	**0**
Abdominal pain	**10 (11)**	**1 (1)**
Vomiting	**10 (11)**	**0**
Decreased appetite	**9 (10)**	**0**
Nausea	**9 (10)**	**0**

Table 3. Treatment-emergent adverse events (hematologic in > 5% of patients; nonhematologic in ≥ 10% of patients)

Figure Legends

Figure 1. A, Median changes from baseline in ALC and the sum of products of diameters (SPD) of target nodal lesions over time (n = 78).

Figure 1. B, Best percent change in the SPD of nodal target lesions per investigator (n = 78). [a]Some patients had the cycle 4-day 1 assessment at approximately month 2. [b]The upper CI for ALC at 20 months exceeded 225% (443%).

Figure 2. Progression-free survival in the study population and subgroup of patients with del(17p) and/or *TP53* mutations.

Figure 3. Rates of grade ≥ 3 AESI and AESI leading to discontinuation in the study population.

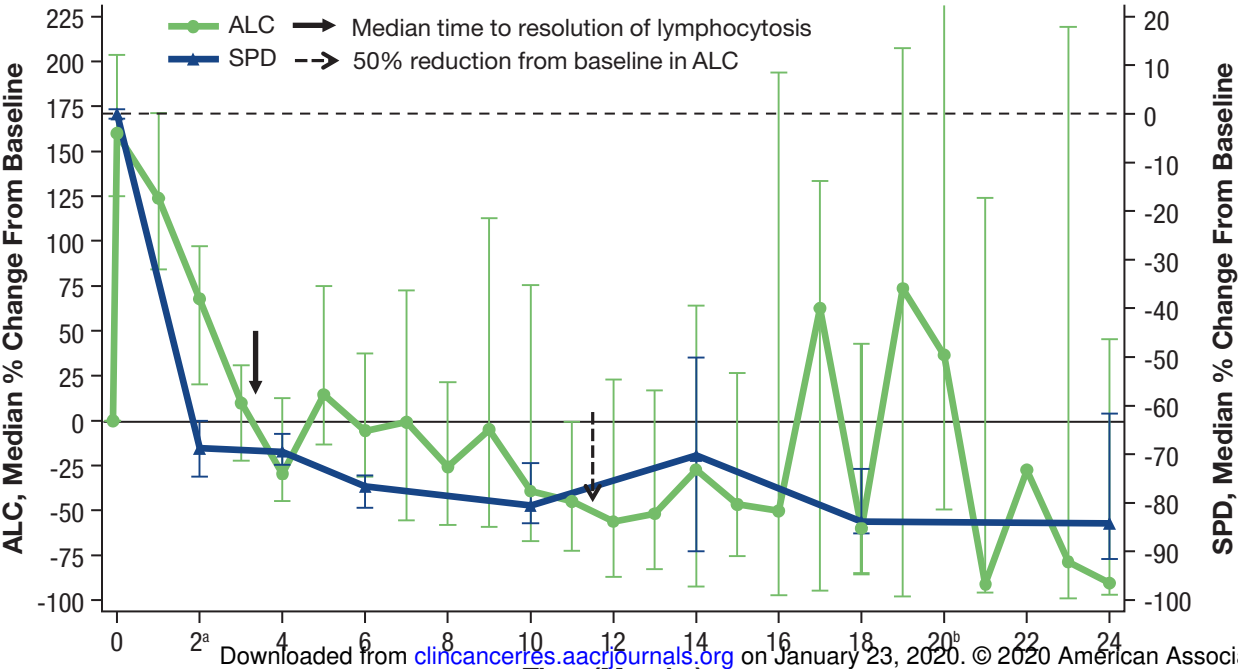
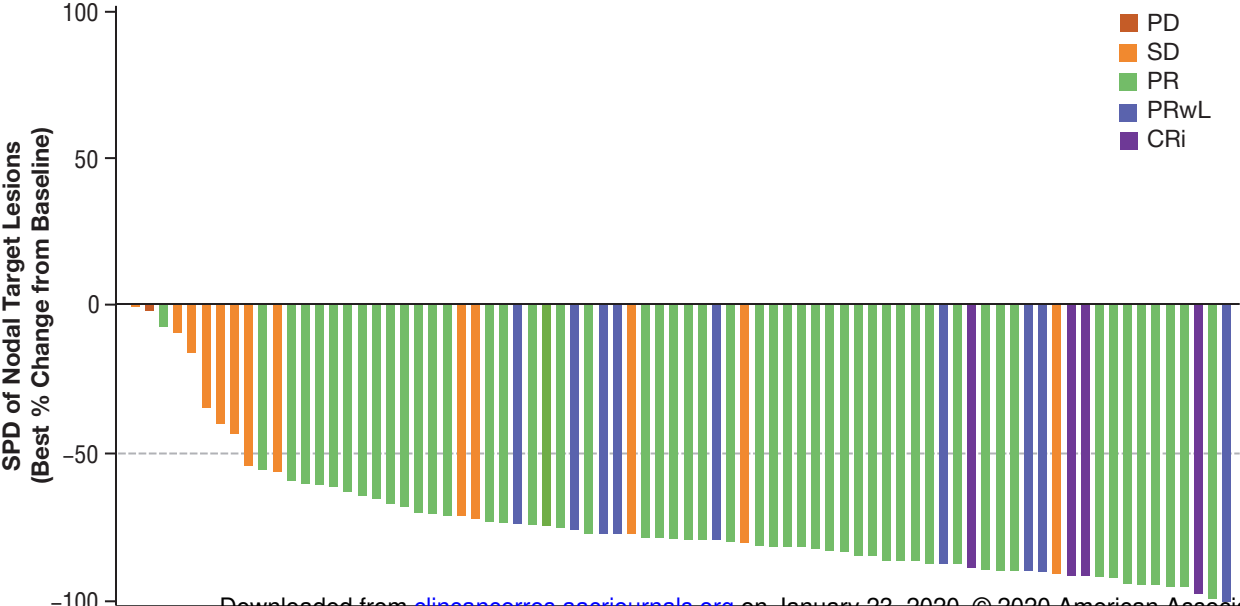


Figure 1B



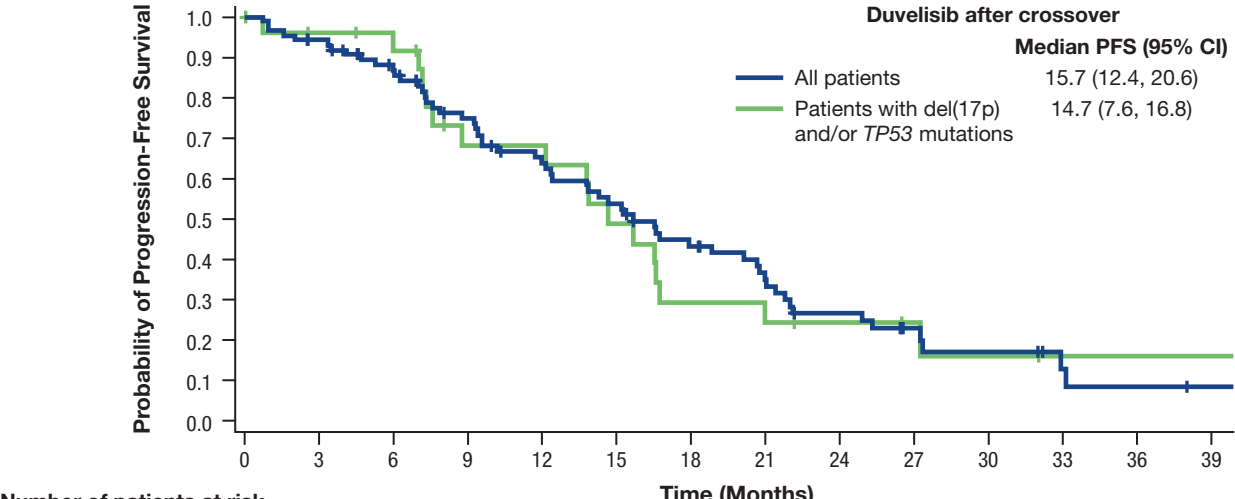
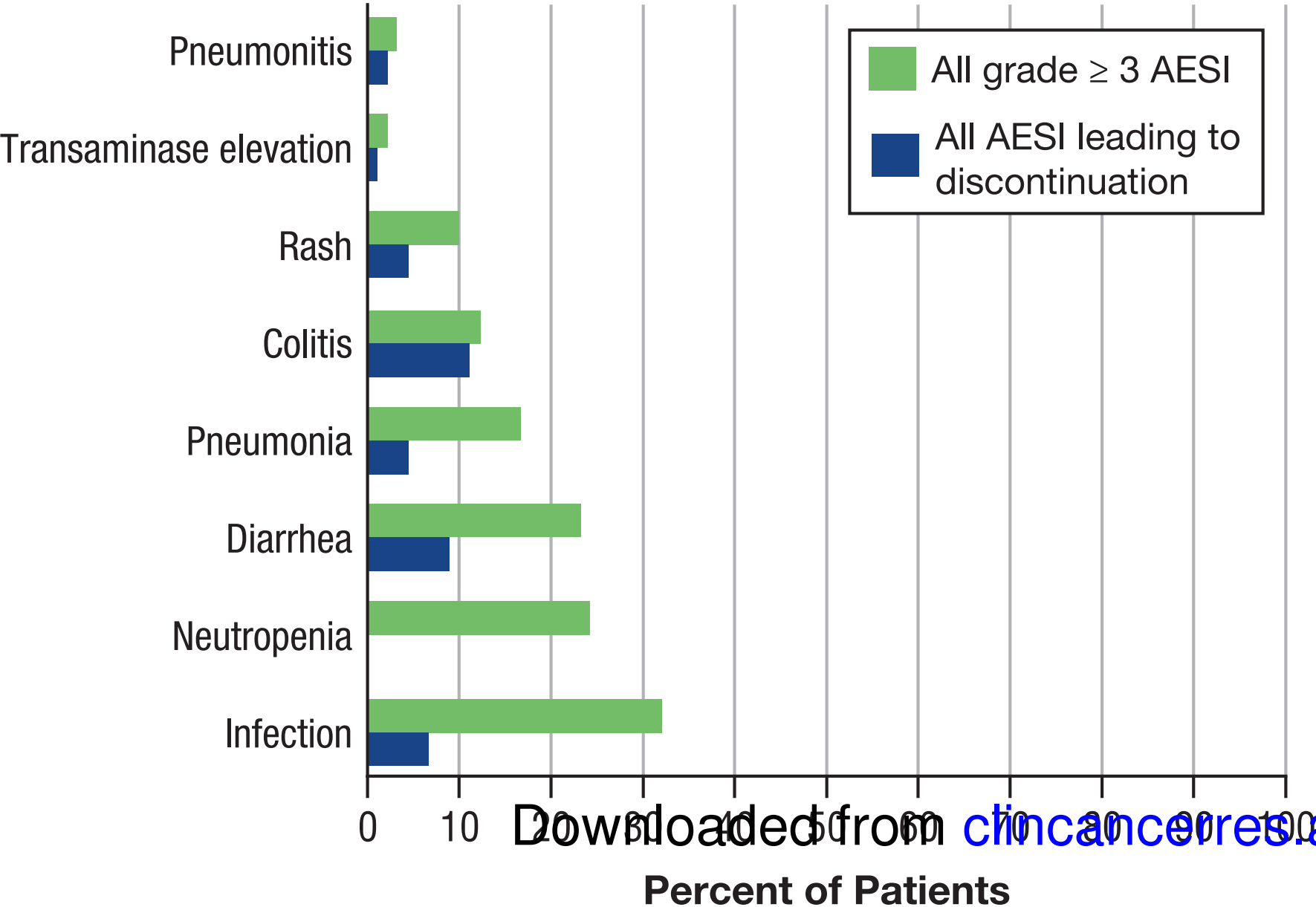


Figure 3



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