The phase III DUO trial of PI3K inhibitor duvelisib *versus* ofatumumab in relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma: final analysis including overall survival

The DUO trial was a global, multicenter, open-label, randomized phase III study (NCT02004522) designed to compare the efficacy and safety of the oral phosphoinositide 3-kinase-δ/γ (PI3K) inhibitor duvelisib to ofatumumab, an anti-CD20 antibody, in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) that progressed during or relapsed after one or more prior therapies. These patients had limited treatment options due to intolerance, co-morbidities, progression, or resistance to other therapies.[1] Results from DUO suggest that duvelisib monotherapy may offer an effective treatment for CLL/SLL patients in need of additional therapeutic options.

In the DUO trial, patients with active disease and no prior treatment with a Bruton tyrosine kinase (BTK) inhibitor or PI3K inhibitor were eligible. The patients' stratification at randomization included a pre-specified criterion of stratification by refractory/early relapse to purine analog-based therapy (defined as progression <12 months after fludarabine/pentostatin).[1]

At the initiation of the DUO trial in 2013, newer agents such as BTK inhibitors had not been integrated into the treatment landscape, and the standard of care for R/R CLL/SLL was chemoimmunotherapy.[2] Ofatumumab was chosen as a comparator because it was an approved active monotherapy and a standard of therapy at the time.[1]

The results from DUO led to the approval of duvelisib in 2018. This approval was based on a *post hoc* subgroup analysis of patients who had received two or more prior therapies (N=196), because the benefit-to-risk ratio appeared to be greater in this more heavily treated group.[3] Therefore, outcomes for this subgroup, representing the Food and Drug Administration (FDA)-labeled indication, are included here. Subsequently, ongoing discussion has focused on the benefit-to-risk profile of the class of PI3K inhibitors in hematologic malignancies, particularly in indolent non-Hodgkin lymphoma and CLL.[4] Relevant to this discussion, we now report the primary and final analyses from the DUO trial.

For the intent-to-treat population (ITT), 319 patients were randomized 1:1 to receive duvelisib 25 mg orally twice daily (N=160) or ofatumumab (N=159) intravenously (8 weekly infusions, then monthly for 4 months).[1,3] Patients were required to receive pneumocystis prophylaxis concomitant with study drug treatment. Prophylaxis against herpes viruses (herpes simplex, vesicular stomatitis) and cytomegalovirus was recommended. The median age of the ITT population was 69 years (range, 39-90), 61.4% had received two or more prior therapies, and 32% were high-risk with del(17p) and/or *TP53* mutations.[1,3]

In the primary analysis of the ITT population (N=319), duvelisib demonstrated significantly superior progression-free survival (PFS) per independent review committee *versus* ofatumumab with a median of 13.3 (95% confidence interval [95% CI]: 12.1-16.8) months *versus* 9.9 (95% CI: 9.2-11.3) months, respectively; hazard ratio (HR)=0.52; $P<0.0001$.[1] Duvelisib maintained a PFS advantage across all subgroups, including high-risk patients. The median OS was not reached on either treatment arm at the primary analysis, with a 12-month probability of survival of 86% for both treatments (HR=0.99; 95% CI: 0.65-1.50).[1]

In the primary exploration of the *post hoc* subgroup analysis of patients who had received two or more prior lines of therapy (95 duvelisib; 101 ofatumumab), the median PFS per independent review committee was 16.4 (duvelisib) *versus* 9.1 months (ofatumumab); HR=0.40.[3] With a median follow-up of 24 months, the median OS was not reached in either arm; the HR was 0.82 (95% CI: 0.49-1.37).[4]

Within 3 months of progressive disease after either treatment on the DUO trial, patients had the option to receive the other study treatment in an open-label phase III crossover extension study (NCT02049515).[5] A substantial amount of crossover occurred, with 90 patients (57%) crossing over from ofatumumab to duvelisib and nine patients (6%) crossing over from duvelisib to ofatumumab upon progression.[4] A response was seen in 77% (69/90) of the patients who switched from ofatumumab to duvelisib (median duration of response: 14.9 months; median PFS: 15.7 months; median OS: 43 months).[5]

The final OS analysis of the DUO trial occurred in 2021 at a median follow-up of 63 months, when all patients were off treatment. In the ITT population, the median OS was 52.3 (95% CI: 41.8-68.0) months (duvelisib) and 63.3 (95% CI: 41.2-not estimable) months (ofatumumab, including the 90/159 patients who crossed over to duvelisib). The HR was 1.09 (95% CI: 0.79-1.51).[4] In the subgroup population of patients who had received two or more prior therapies, the median OS was 43.9 (95% CI: 32.4-56.5) months (duvelisib)

and 46.8 (95% CI: 28.6-74.9) months (ofatumumab). The HR was 1.06 (95% CI: 0.71-1.58). In both patient populations, OS was not statistically significantly different between treatment arms (Figure 1).[4] In the prespecified refractory/early relapse subgroup of the ITT population (N=98), the HR was 0.77 (95% CI: 0.43-1.38).[4] Kaplan-Meier curves for PFS and OS of patients who had dose reductions or discontinued treatment because of adverse events are shown in *Online Supplementary Figure S1* (Data on file, Secura Bio).

The confidence intervals of the HR for the endpoint of OS (ITT population) are quite large, indicating that there is not enough information for the HR to assess group differences.[4] The 5-year restricted mean survival time (RMST) may be a better metric to quantify group differences because the event rate after 5 years was very low (4 deaths [duvelisib]; 3 deaths [ofatumumab]), and low event rate can affect the precision of the HR estimate.[6,7] To enhance interpretation and precision, we provide the 5-year RMST summary to assess treatment differences (Table 1)[8] (Data on file, Secura Bio).

The 5-year RMST difference was neutral (ITT population: 12 days fewer for duvelisib; population with ≥2 prior therapies: 27 days greater for duvelisib).[9] The protocol-specified refractory/early relapse status subgroup (N=98) demonstrated a difference of 6.2 months in favor of duvelisib.[8] While the analysis of the refractory/early relapse status subgroup is considered exploratory, results demonstrate a trend towards benefit in heavily pretreated or refractory patients treated with duvelisib *versus* ofatumumab.[4,8]

The large imbalance in patients crossing over from ofatumumab to duvelisib (N=90) due to progressive disease after a maximum fixed duration of only seven cycles of ofatumumab essentially meant that comparison of deaths as the study progressed was between patients who were receiving duvelisib on both arms. Data on subsequent therapies following discontinuation of study drug are not available for all patients. However, available data show that ≥20 additional different therapeutic agents were administered during the follow-up period (Data on file, Secura Bio). Unfortunately, further analysis of subsequent therapies is not possible due to incomplete patients' data.

When evaluating the safety profile of duvelisib and ofatumumab in the DUO trial ITT population, it is important to recognize that time on study drug was more than twice as long in the duvelisib arm than in the ofatumumab arm. Duvelisib was administered continuously until progressive disease or unacceptable toxicity, whereas ofatumumab was limited to 12 doses within a maximum of seven cycles, as per approved product label.[5] The median exposure was 12 (range, 0.2-72) months in the duvelisib arm and 5 (range,

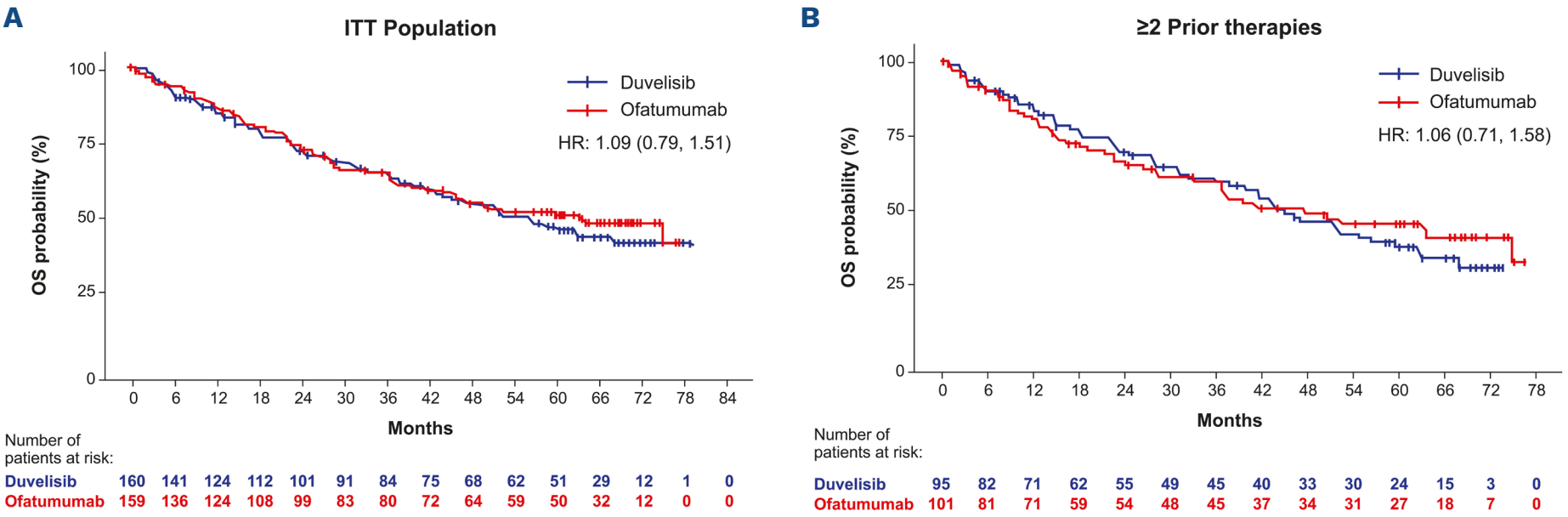

Figure 1. Final overall survival analysis of the DUO trial. (A) Overall survival results for the intent-to-treat population (N=319). (B) Overall survival results for patients who had received two or more prior therapies (N=196).[4] ITT: intent-to-treat; HR: hazard ratio; OS: overall survival.

Table 1. Five-year restricted mean survival time analysis (investigator-assessed).[8,Data on file]

	Duvelisib months	Ofatumumab months	Difference months (95% CI)
ITT population (N=319)	41.6	42.0	-0.4 (-5.3 to 4.5)
≥2 prior therapies (N=196)	39.5	38.6	0.9 (-5.7 to 7.3)
Refractory/early relapse subgroup (N=98)	42.6	36.4	6.2 (-3.0 to 15.5)

95% CI: 95% confidence interval; ITT: intent-to-treat. OS: overall survival.

0-6) months in the ofatumumab arm.[4]

The adverse event profile in patients treated with duvelisib is important when evaluating the benefit-to-risk ratio of the class of PI3K inhibitors in hematologic malignancies. An overall summary of treatment-emergent adverse events is shown in Table 2[4] (Data on file, Secura Bio). Seven categories of adverse events of special interest were prospectively defined for this analysis and incorporate FDA feedback based on the known safety profile and mechanism of action of duvelisib; these categories are detailed in *Online Supplementary Table S1* (Data on file, Secura Bio), along with serious adverse events in patients treated with duvelisib. Treatment-emergent adverse events resulting in death for patients treated with duvelisib are shown in *Online Supplementary Table S2* (Data on file, Secura Bio).

Despite approval of novel agents for CLL, the disease remains incurable for most patients. Agents targeting BTK and BCL-2 are efficacious for many patients with R/R CLL, yet many develop therapeutic resistance or intolerance.[10] CLL patients whose disease has progressed on BTK and BCL-2 inhibitors present a particular unmet need where prospective studies of PI3K inhibitors, including duvelisib, may be warranted. We believe there is an unmet need for therapies with non-overlapping mechanisms of action, proven cardiac and renal safety, well-characterized overall safety profiles, and the convenience of oral dosing in the third-line setting and beyond.

While PI3K inhibitors are active in R/R CLL,[1,11] clinical use has been challenging due to class effects such as immune-mediated and infectious toxicities.[3,11] Fatal and serious toxicities (infections, diarrhea or colitis, cutaneous reactions, pneumonitis) are included in labeled warnings.[3] Treatment recommendations include prophylaxis and monitoring for infections, including *Pneumocystis jirovecii* pneumonia, cytomegalovirus, and varicella zoster virus reactivation. Avoidance of neutropenia with the use of growth factors is also warranted. However, with close monitoring and management of PI3K inhibitor-associated adverse events, these agents continue to have a role in the treatment of R/R CLL.[12]

Duvelisib is an oral monotherapy treatment that provides clinical efficacy and manageable safety in patients with R/R CLL/SLL. Overall, the benefit-to-risk balance for duvelisib remains positive after the final analysis of the phase III DUO trial. Of note, two targeted agents used as monotherapy to treat R/R CLL within the same time frame as the DUO trial showed all-cause mortality of 12% (ibrutinib)[13] and 20% (idelalisib).[14] The treatment landscape has evolved since the initiation of the DUO trial, and patient populations (particularly in the United States) have also changed because prior therapies can now include BTK or BCL-2 inhibitors in countries where these treatments are available. In light of these changes, future studies to generate prospective data on the efficacy and safety of PI3K inhibitors in the post-BTK inhibitor setting, use of duvelisib in combination with other agents, and use of duvelisib as a bridge to other therapies would be informative for clinical practice.

Table 2. Summary of treatment-emergent adverse events for patients treated with duvelisib.[4,Data on file]

Category, N (%)	Duvelisib N=158
Patients with any TEAE	158 (100)
TEAE grade ≥3	144 (91.1)
Serious TEAE	124 (78.5)
TEAE leading to discontinuation	70 (44.3)
TEAE leading to dose reduction	48 (30.4)
TEAE with outcome of death	24 (15.2)

TEAE: treatment-emergent adverse event.

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Contributions

JRB, AVD, IWF, MSD, DS, BG, and OB were involved in conception of the publication, acquisition of data, manuscript review, and approval. AVD and IWF were involved in DUO trial research. JRB, AVD, IWF, MSD, DS, BG, and OB were involved in data analysis and interpretation.

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Data-sharing statement

Data from the DUO trial (NCT02004522) are available upon request; please contact Scientific Affairs at securabio@tmacmail.com.

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