An Improved Benefit-Risk Profile of Duvelisib in Patients With Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma Who Received ≥ 2 Prior Therapies

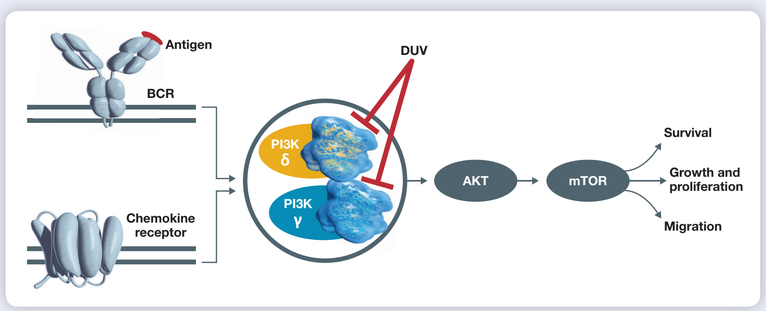
Ian W. Flinn,[1] Matthew S. Davids,[2] Peter Hillmen,[3] Marco Montillo,[4] Julio Delgado,[5] Bryone J. Kuss,[6] Constantine S. Tam,[7] Ulrich Jäger,[8] Paolo Ghia,[9] Stephan Stilgenbauer,[10] Stephanie Lustgarten,[11] David T. Weaver,[11] Hagop Youssoufian,[11] Florence Cymbalista[12]

[1]Lymphoma Research, Sarah Cannon Research Institute, Nashville, TN, USA; [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [3]Experimental Haematology, St James's University Hospital, Leeds, UK; [4]Department of Haematology and Oncology, Niguarda Cancer Center, Niguarda Hospital, Milan, Italy; [5]Department of Hematology, Hospital Clinic, Barcelona, Spain; [6]Molecular Medicine and Pathology, Flinders Medical Centre, Flinders University, Bedford Park, Australia; [7]St Vincent's Hospital and University of Melbourne, Peter MacCallum Cancer Centre, Melbourne, Australia; [8]Division of Hematology and Hemostaseology, Department of Medicine, Medical University of Vienna, Wien, Austria; [9]Università Vita-Salute San Raffaele, IRCCS Istituto Scientifico San Raffaele, Milano, Italy; [10]Department III of Internal Medicine, University Hospital Ulm, Ulm, Germany; [11]Medical Affairs, Verastem Oncology, Needham, MA, USA; [12]Laboratoire d'hématologie, Hôpital Avicenne, Paris, France

BACKGROUND

- Duvelisib (DUV) is a first-in-class, oral dual inhibitor of phosphoinositide 3-kinase δ,γ (PI3K-δ,γ)[1] approved by the US Food and Drug Administration for treatment of relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in patients who have received ≥ 2 prior therapies[2]
- DUV targets key signaling pathways that promote the growth and survival of hematologic malignancies[3-6] (**Figure 1**)
- The unique therapeutic potential of dual PI3K-δ/PI3K-γ inhibition offers a novel approach to treat patients with R/R CLL/SLL

Figure 1: Duvelisib Dual Inhibitor of PI3K-δ,γ Mechanism of Action



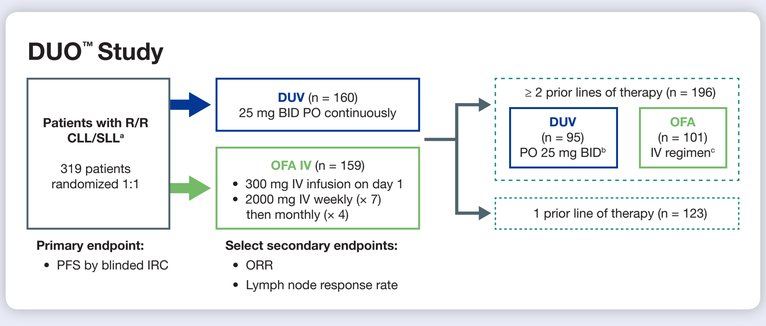
BCR, B-cell receptor; **mTOR**, mechanistic target of rapamycin.

- In the phase 3 DUO™ study, DUV monotherapy resulted in statistically significant improvement in progression-free survival (PFS) and overall response rate (ORR) compared with ofatumumab (OFA) in patients with R/R CLL/SLL, including those with del(17p)/*TP53* mutations[7]
- The adverse event (AE) profile with DUV monotherapy in patients with R/R CLL/SLL was consistent with previous reports and manageable with appropriate intervention via dose modifications, routine medical care, and prophylactic measures[8,9]
- We describe the safety and efficacy of DUV in the population of patients with R/R CLL or SLL who had received ≥ 2 prior lines of therapy in the DUO trial (**Figure 2**)

STUDY DESIGN

- DUO (IPI-145-07; NCT02004522) is an open-label, 2-arm, randomized, phase 3, superiority trial designed to evaluate the efficacy and safety of DUV compared with OFA administered to patients who had been diagnosed with R/R CLL/SLL
  - Radiologically measurable disease, defined as tumor mass measuring > 1.5 cm by computed tomography (CT) scan or ≥1 lymph node, was required
  - Pneumocystis prophylaxis was required for all patients

Figure 2. DUO Trial Design



IRC, independent review committee; **IV**, intravenous; **PO**, oral.

[a] A total of 312 patients had CLL; 7 patients had SLL (N = 319).[1] [b] DUV was administered at 25 mg BID in 28-day treatment cycles until progressive disease or unacceptable toxicity.[1] [c] OFA was administered at an initial dose of 300 mg IV on day 1, followed a week later by 7 weekly doses of 2000 mg IV, followed 4 weeks later by 2000 mg IV every 4 weeks for 4 doses. Patients received a total of 12 doses of OFA. The median duration of exposure to OFA was 5 months (range, < 0.1 to 6 months).[1]

RESULTS

- Baseline characteristics for those patients who had received ≥ 2 prior therapies (**Table 1**) were similar to those of the overall DUO population

Table 1: Baseline Characteristics and Prognostic Features

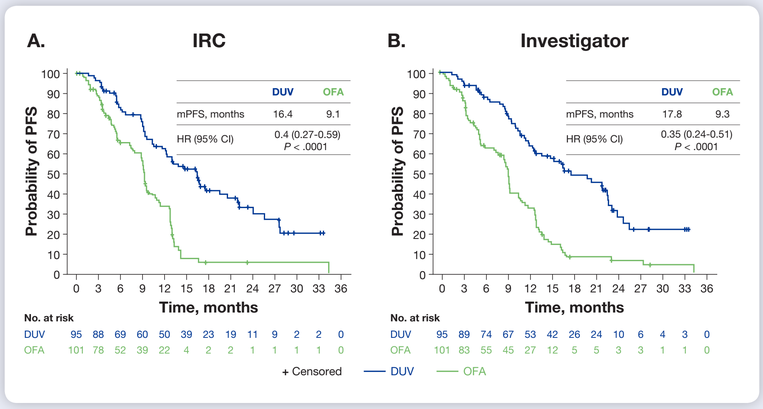
Characteristics	Duvelisib (n = 95)	Ofatumumab (n = 101)
Median age (range), years	70 (40-90)	68 (44-89)
Male, %	62	54
ECOG PS 2, %	8	11
CLL/SLL, %	97/3	98/2
Median time from initial diagnosis, years	9	7.7
Rai stage ≥ III/Binet Stage C, %	20/6	17/12
Bulky disease (≥ 5 cm target lesion), %	52	53
Abnormal liver, %	16	21
Abnormal spleen, %	37	33
Baseline lymphocytes, median, × 10^9/L	29	35
Grade 4 cytopenia, %[a]	6	7
Refractory/early relapse to purine therapy[b]	20	30
Prior therapy		
2 Prior therapies, %	47	46
≥ 3 Prior therapies, %	53	54
Prior number of therapies, range	2-10	2-8
Molecular features (per central laboratory), %		
17p deletion	19	25
TP53 mutation	19	16
17p deletion and/or *TP53* mutation	32	30
Unmutated *IGHV*	68	69
CD38 positive	45	42

ECOG PS, Eastern Cooperative Oncology Group performance status; **IGHV**, immunoglobulin heavy chain variable region.

[a] Thrombocytopenia and/or neutropenia. [b] Progression < 12 months after fludarabine/pentostatin.

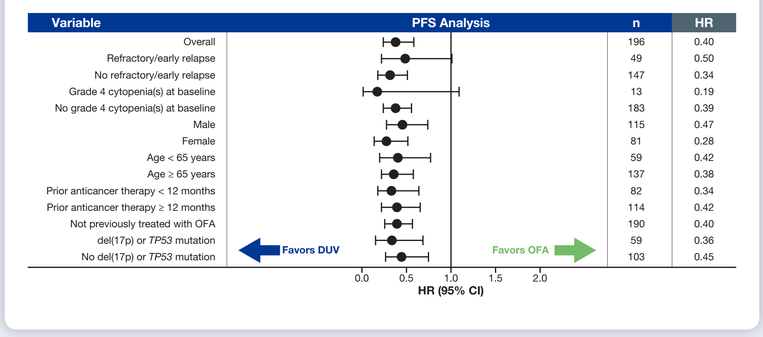
- With a median overall follow-up of 22.4 months, median PFS (mPFS) by blinded IRC review was significantly longer in the DUV arm compared with the OFA arm in patients who had received ≥ 2 prior therapies (16.4 vs 9.1 months; hazard ratio [HR], 0.4 [95% CI, 0.27-0.59]; *P* < .0001) (**Figure 3A**)
- In this same patient population, improvement in PFS with DUV compared with OFA was also observed per investigator assessment (17.8 vs 9.3 months; HR, 0.35 [95% CI, 0.24-0.51]; *P* < .0001) (**Figure 3B**)

Figure 3: Duvelisib Improves PFS (Kaplan-Meier estimates) in Patients Who Had Received ≥ 2 Prior Therapies



- Among patients who had received ≥ 2 prior therapies, an improvement in PFS was observed across multiple predefined CLL/SLL subgroups with DUV, including patients with high-risk cytogenetics (**Figure 4**)

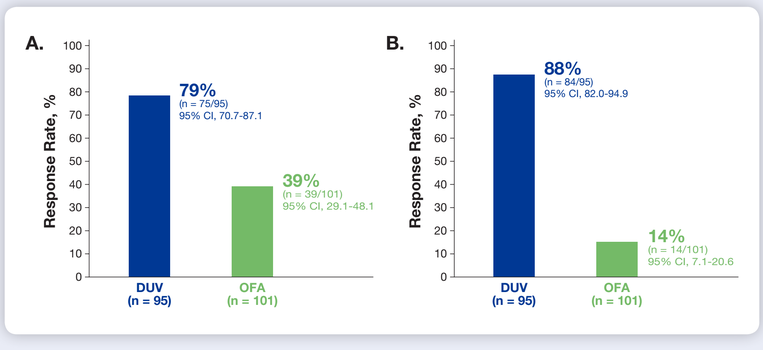
Figure 4: Duvelisib Improved mPFS in High-Risk Patients[a]



[a] This analysis was not powered to show statistical significance in PFS across these prespecified subgroups.

- The ORR per IRC response assessment for duvelisib was also significantly higher compared with ofatumumab (79% vs 39%; *P* < .0001) in patients who had received ≥ 2 prior therapies (**Figure 5A**)
- Among patients who had received ≥ 2 prior therapies, DUV resulted in a lymph node response by IRC assessment of 88% compared with 14% in the OFA arm (*P* < .0001; **Figure 5B**)

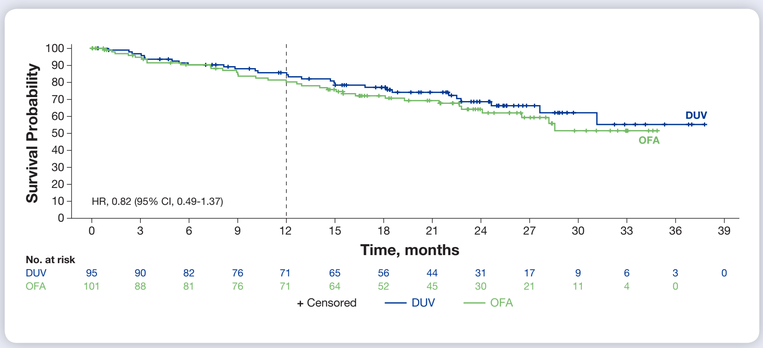
Figure 5: ORR[a] and Lymph Node Response Rate[b] in Patients Who Had Received ≥ 2 Prior Therapies



[a] Includes complete response, complete response with incomplete count recovery, partial response, and partial response except for lymphocytosis per International Workshop on Chronic Lymphocytic Leukaemia criteria. [b] Lymph node response was defined as ≥ 50% reduction in target lesion size, as determined by the IRC.

- Among patients who had received ≥ 2 prior therapies, overall survival at 12 months was 75% with DUV compared with 70% with OFA (**Figure 6**)

Figure 6: Overall Survival (Kaplan-Meier estimates) in Patients Who Had Received ≥ 2 Prior Therapies



- Median duration of treatment of DUV was 13 months, with 80% of patients receiving ≥ 6 months and 52% receiving ≥ 12 months[1]
- The median duration of exposure to OFA was 5 months[1]
- The safety profile in this heavily treated population was consistent with that previously reported for DUV in CLL/SLL (**Table 2**); no new safety signals were reported
- Many AEs were successfully managed through dose modifications, with dose reductions occurring in 28% of patients and dose interruptions in 74% of patients who had received ≥ 2 prior therapies who received DUV
  - Diarrhea/colitis (26%) and neutropenia (14%) were the most common treatment-emergent AEs (TEAEs) leading to dose interruptions with DUV
    - This includes TEAEs leading to dose reductions, the most common of which were diarrhea/colitis (10% of patients who had received ≥ 2 prior therapies who received DUV) and neutropenia (5%)
  - Diarrhea/colitis (n = 8), pneumonia (n = 3), and pneumonitis (n = 2) were the only treatment-related (as assessed by investigator) events leading to discontinuation in > 1 patient
  - 11 patients (12%) treated with DUV experienced a fatal AE
    - The only fatal events to occur in > 1 patient were hemorrhagic stroke (n = 2) and pneumonia (n = 3)
    - Other causes included sepsis, septic shock, enterococcal sepsis, and bronchopulmonary aspergillosis

Table 2. TEAEs

AE Category, n (%)	All Grades		Grade ≥ 3	
	DUV 25 mg BID (n = 93)	OFA (n = 98)	DUV 25 mg BID (n = 93)	OFA (n = 98)
Any AEs	92 (99)	92 (94)	82 (88)	55 (56)
Hematologic AEs				
Neutropenia	37 (40)	27 (28)	35 (38)	23 (23)
Anemia	20 (22)	10 (10)	9 (10)	4 (4)
Thrombocytopenia	13 (14)	7 (7)	8 (9)	3 (3)
Nonhematologic AEs				
Diarrhea/colitis	54 (58)	13 (13)	22 (24)	2 (2)
Pyrexia	31 (33)	13 (13)	2 (2)	1 (1)
Upper respiratory tract infection	28 (30)	13 (13)	0	0
Pneumonia	27 (29)	9 (9)	20 (22)	5 (5)
Fatigue	24 (26)	21 (21)	3 (3)	6 (6)
Cough	21 (23)	13 (13)	1 (1)	0
Lower respiratory tract infection	19 (20)	9 (9)	4 (4)	2 (2)
Nausea	18 (19)	7 (7)	0	0
Musculoskeletal pain	18 (19)	12 (12)	1 (1)	1 (1)
Abdominal pain	17 (18)	5 (5)	4 (4)	0
Rash	17 (18)	10 (10)	5 (5)	0
Vomiting	15 (16)	7 (7)	0	0
Dyspnea	14 (15)	6 (6)	3 (3)	0
Constipation	14 (15)	7 (7)	1 (1)	0
Respiratory tract infection	10 (11)	2 (2)	0	0
Hypokalemia	10 (11)	4 (4)	4 (4)	0
Transaminase elevation	11 (12)	2 (2)	5 (5)	1 (1)

CONCLUSIONS

- DUV, a first-in-class oral dual PI3K-δ,γ inhibitor, demonstrated clinical activity with a manageable safety profile in patients with R/R CLL or SLL after ≥ 2 prior therapies
- Patients who were treated with DUV had > 7-month mPFS advantage vs patients treated with OFA after ≥ 2 prior therapies
- DUV decreased the risk of progression in nearly all prespecified high-risk patient subgroups
- The majority of heavily pretreated patients responded to DUV (ORR, 79% vs 39%; *P* < .0001), with more DUV-treated patients achieving ≥ 50% reduction in target lymph nodes compared with OFA-treated patients (88% vs 14%; *P* < .0001)
- DUV monotherapy represents a new, effective treatment option for heavily pretreated patients with R/R CLL or SLL for whom limited treatment options exist

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