Patterns of Duvelisib-Induced Lymphocytosis in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Including Those With High-Risk Factors Treated in the DUO Trial

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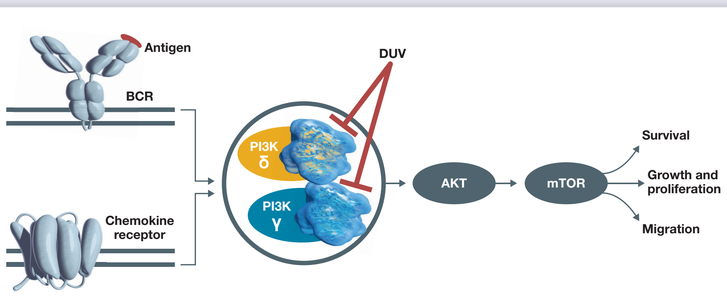
BACKGROUND

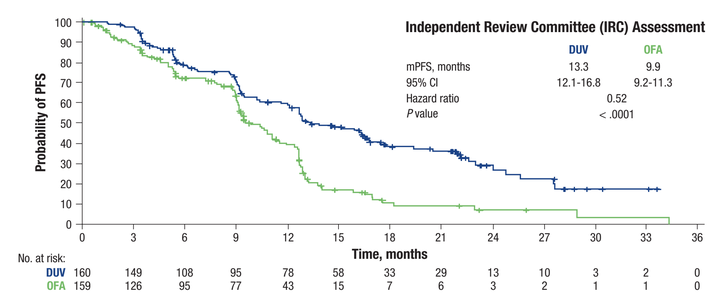
- Lymphocytosis is a defining feature of chronic lymphocytic leukemia (CLL) and a recognized class effect of treatment with B-cell receptor pathway inhibitors, including phosphoinositide 3-kinase (PI3K) and Bruton tyrosine kinase inhibitors[1-5]
- Duvelisib (DUV) is a first-in-class oral dual PI3K-δ,γ inhibitor approved by the US Food and Drug Administration for the treatment of patients with relapsed/refractory (R/R) CLL or small lymphocytic lymphoma (SLL) after ≥ 2 prior therapies or R/R follicular lymphoma after ≥ 2 prior systemic therapies[6]
- DUV targets key signaling pathways involved in the growth and survival of malignant B cells and the supportive tumor microenvironment (**Figure 1**).[6-10] In preclinical studies, dual inhibition of PI3K-δ and PI3K-γ with DUV was more effective at inhibiting CLL B cells and reducing the number of CLL-supporting cells in vivo than PI3K-δ inhibition alone[7,8]
- In the phase 3 DUO trial, DUV monotherapy 25 mg twice daily (BID) demonstrated a manageable safety profile and significantly improved efficacy vs ofatumumab (OFA) in patients with R/R CLL/SLL (**Figure 2**)[11]
  - Median progression-free survival [mPFS]: 13.3 vs 9.9 months (hazard ratio, 0.52 [$P < .0001$])
  - Overall response rate (ORR): 74% vs 45% ($P < .0001$)
- Herein, we aimed to characterize the clinical profile and kinetics associated with DUV-related lymphocytosis in patients with R/R SLL or CLL, including the subgroup of patients with poor prognostic indicators who received DUV 25 mg BID in the DUO trial

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



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

Figure 2. Duvelisib Significantly Improved PFS vs OFA in Patients With R/R CLL/SLL[11]



METHODS

Study Design: DUO Trial

- 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 when administered to patients diagnosed with R/R CLL/SLL (**Figure 3**)[11]

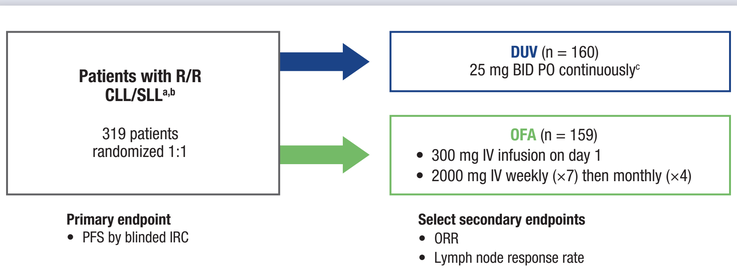
Assessment of Lymphocytosis

- Absolute lymphocyte count (ALC) was measured by local laboratories to determine peak ALC, median time to 50% reduction from baseline (BL) ALC, and median time to onset and resolution of lymphocytosis
  - Lymphocytosis was defined as an ALC of ≥ 5 × 10^9/L and a ≥ 50% increase of ALC from BL
  - Median time to resolution was defined as ALC ≤ BL value or ALC of < 5 × 10^9/L, whichever occurred first
  - Duration of first lymphocytosis was defined as the time to onset of first lymphocytosis until resolution of lymphocytosis or last ALC value, whichever occurred first
  - Prolonged lymphocytosis was defined as ALC ≥ 5 × 10^9/L for > 12 months

Assessment of Response

- Response (ORR; per IRC determination) was defined as the best response of complete response/remission (CR), CR with incomplete marrow recovery (CRi), partial response (PR), or PR with lymphocytosis (PRwL), according to the International Workshop on CLL25[1,12] or Revised International Working Group response criteria,[13] with modification for treatment-related lymphocytosis
- Data were summarized using descriptive statistics, including medians for continuous variables and proportions for discrete variables

Figure 3. DUO Trial Design



IV, intravenous; **PO**, oral.
[a] A total of 312 patients had CLL; 7 patients had SLL (N = 319). [b] Patients received ≥ 1 prior therapy. [c] DUV was administered at 25 mg BID in 28-day treatment cycles until progressive disease or unacceptable toxicity.[6]

In Vivo Assessment of PI3K-δ or PI3K-γ Inhibition of CLL in a Patient-Derived Xenograft (PDX) Murine Model

- As previously described,[8] a PDX murine model of CLL was used to assess the impact of PI3K-δ– or PI3K-γ–selective inhibition on the numbers of patient-derived CLL cells
  - $CD3^+$ T cells were isolated from peripheral blood mononuclear cells (PBMCs) derived from patients with CLL using RosetteSep (STEMCELL Technologies Inc) and preactivated with CD3/CD28-coated Dynabeads (ThermoFisher Scientific) and interleukin (IL)-2 1000 U/mL for 7 to 10 days
  - Alymphoid NOD-scid IL-$2R\gamma^{null}$ mice were injected retro-orbitally (RO) with 0.5 × 10^6 or 2 × 10^6 activated T cells and 20 × 10^6 CLL PBMCs, which were allowed to engraft for 2 weeks
  - After 2 weeks, the mice were treated with a PI3K-δ–specific inhibitor (PI3K-δi; IPI-3063) and/or a PI3K-γ–specific inhibitor (PI3K-γi; IPI-5243) at indicated concentrations for 3 weeks
  - After 3 weeks of treatment, the mice spleens were assessed by flow cytometry for patient-derived CLL B cells (gated on $hCD45^+CD19^+CD5^+$cells) and proliferating CLL B cells ($hCD45^+CD19^+Ki\text{-}67^+$cells)

RESULTS

Baseline Characteristics

- The baseline characteristics and stratification of study patients were well balanced between the 2 treatment arms (**Table 1**)
  - Patients were predominantly male (60%) with a median age of 69 years and a median of 2 prior therapies in both arms
  - Nearly half of DUV- and OFA-treated patients had bulky disease (46% and 45%, respectively)
  - Approximately one-third of patients (DUV, 31%; OFA, 33%) had del(17p) and/or *TP53* mutation
  - Unmutated immunoglobulin heavy chain (*IGHV*) status occurred in 69% and 73% of DUV and OFA patients, respectively

Table 1. DUO Baseline Characteristics

Characteristic	DUV (n = 160)	OFA (n = 159)
CLL/SLL, %	97/5	99/2
Median age (range), years	69 (39-90)	69 (39-89)
Male, %	60	60
ECOG PS 2, %	7	10
Rai stage ≥ 3/Binet stage C, %	56/41	56/34
Bulky disease (≥ 5-cm target lesion), %	46	45
Grade 4 cytopenia(s), %	11	11
Molecular features (per central laboratory), %		
17p deletion	21	28
TP53 mutation	20	18
17p deletion and/or *TP53* mutation	31	33
Unmutated *IGHV*	69	73
ZAP70 positive (≥ 20%)	54	52
Prior therapy		
Refractory/early relapse to purine therapy, %[a]	31	30
Median number of prior anticancer regimens (range)	2 (1-10)	2 (1-8)
Median time since completion of last therapy (range), months	22 (1-149)	18 (1-106)

ECOG PS, Eastern Cooperative Oncology Group performance status.
[a] Progression 12 months after fludarabine or pentostatin.

Lymphocytosis and Nodal Response

- In the DUO trial, 78% of patients receiving DUV experienced lymphocytosis; 16% of patients receiving OFA experienced lymphocytosis (**Table 2**)
- DUV-related lymphocytosis occurred rapidly, with a median time to onset of 1 week; the first assessment for local hematology was completed at cycle 1 day 8 (≈ 1 week receiving DUV treatment)
- The median duration of DUV-related lymphocytosis was 14.3 weeks
- The incidence of prolonged lymphocytosis and hyperleukocytosis[3] was low among patients receiving DUV (**Table 2**)

Table 2. Summary of Lymphocytosis in Patients With R/R CLL/SLL Receiving Duvelisib

	DUV (n = 160)
Patients with lymphocytosis, n (%)	124 (78)
Median time to onset of lymphocytosis (range), weeks	1.1 (0.4-69.3)
Median duration of lymphocytosis (range), weeks	14.3 (1.1-153.0)
Median time to resolution of lymphocytosis (range), weeks	14.1 (1.1-63.0)
Patients with prolonged lymphocytosis, n (%)[a]	12 (8)
Patients with hyperleukocytosis, n (%)[b]	9 (6)
Median baseline ALC × 10^9/L (range)	41.0 (0.2-381.7)
Median peak ALC × 10^9/L (range)	109.9 (0.5-709.1)

[a] Prolonged lymphocytosis was defined as ALC ≥ 5 × 10^9/L for > 12 months. [b] Hyperleukocytosis was defined as ALC ≥ 400 × 10^9/L.[3]

Lymphocytosis and Nodal Response

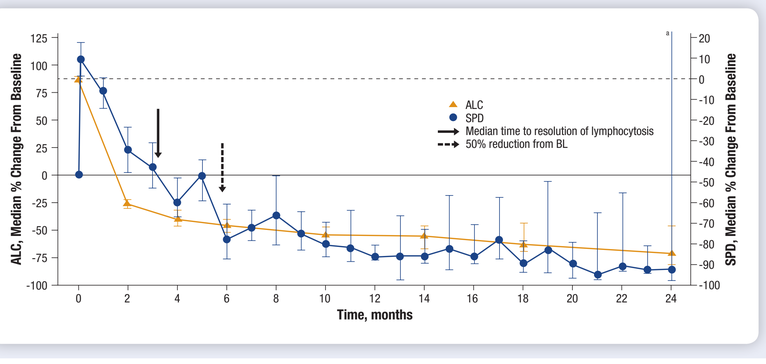
- Rapid shrinkage of lymph nodes was noted with DUV, with 86% of patients achieving lymph node response (**Table 3**; **Figure 4**)
- Resolution of lymphocytosis occurred between cycles 3 and 4 at a median of 14 weeks (**Figure 4**; solid arrow), with a 50% reduction from BL ALC at 21 weeks (**Figure 4**; dashed arrow)
- At the time of assessment of nodal response at cycle 3, day 1, the median change from BL in sum of the product diameters (SPD) and ALC with DUV was –60% and 72% (52 × 10^9/L), respectively (**Table 3**)
- Continued reduction in lymphadenopathy was noted at the start of cycle 5 with DUV; the median change from baseline in SPD was –68% (**Table 3**; **Figure 4**)
  - The median change from baseline in ALC was 16% (31 × 10^9/L)

Table 3. Median Change From Baseline ALC and LNRR

	DUV (n = 160)
LNRR, n (%) [95% CI]	136 (86) [80-91]
Median change from BL ALC, %	
Cycle 1, day 8	121
Cycle 3, day 1	72
Cycle 5, day 1	16
Median change from BL SPD, %	
Cycle 3, day 1 (first nodal assessment)	–60
Cycle 5, day 1	–68
Nadir ALC, n (%)	
≥ BL	18 (11)
< 25% reduction from BL	11 (7)
25%-50% reduction from BL	9 (6)
> 50% reduction from BL	84 (53)

LNRR, lymph node response rate.

Figure 4. Median Changes From BL in ALC and Lymph Node SPD Over Time With Duvelisib



[a] The upper CI for ALC at 24 months exceeds 125%.

Lymphocytosis and Response

- Most patients who had a response to DUV at first or second assessment experienced lymphocytosis (78% and 86%, respectively)
- The median time to onset of lymphocytosis was the same regardless of response at first or second assessment (1.1 weeks [range, 0.7-63.0] and 1.1 weeks [range, 1.1-1.3], respectively)
- Among patients with a response, small differences were observed for time to resolution at first or second assessment, with a longer median time to resolution observed for patients getting a PR at second assessment (11.6 weeks [range, 1.1-62.3] and 18.1 weeks [range, 2.1-63.0], respectively)

Lymphocytosis in High-Risk Patients

- The pattern of lymphocytosis with DUV was similar among patients with R/R CLL/SLL who had high-risk factors and the overall patient population (**Table 4**)
- Of note, the BL ALC was lower in patients with bulky disease and del(11q) compared with those without bulky disease and del(11q), which may account for the lower time to PR in these patients

Table 4. Lymphocytosis in High-Risk Patients With R/R CLL/SLL Receiving Duvelisib

	IGHV Unmutated (n = 110)	*IGHV* Mutated (n = 29)	del(17p) and/or *TP53* Mutation (n = 48)	No del(17p) /*TP53* Mutation (n = 83)	del(11q) (n = 38)	No del(11q) (n = 106)	Bulky Disease (n = 74)	No Bulky Disease (n = 85)
Patients with lymphocytosis, n (%)	84 (76)	21 (72)	35 (73)	63 (76)	31 (82)	78 (74)	60 (81)	63 (74)
Median time to onset of lymphocytosis (range), weeks	1.1 (0.4-69.3)	1.1 (1.0-3.1)	1.1 (0.4-5.1)	1.1 (0.6-63.0)	1.1 (0.9-7.1)	1.1 (0.4-69.3)	1.1 (0.9-63.0)	1.1 (0.4-69.3)
Median duration of lymphocytosis (range), weeks	14.1 (2.1-153.0)	14.3 (1.1-79.6)	14.1 (2.1-96.0)	17.0 (1.1-79.6)	18.3 (2.1-79.6)	14.2 (1.1-153.0)	12.7 (2.1-79.6)	18.1 (1.1-153.0)
Median time to resolution of lymphocytosis (range), weeks	13.4 (2.1-62.3)	13.1 (1.1-46.6)	14.1 (2.1-38.1)	16.8 (1.1-63.0)	18.3 (2.1-63.0)	12.6 (1.1-62.3)	10.9 (2.1-54.4)	17 (1.1-63.0)
Time to first PR, PRwL, CR, or CRi per IRC, days	58 (42.0-500.0)	55 (49.0-409.0)	54 (49.0-279.0)	57 (50.0-500)	67 (48.0-500)	56 (42.0-409)	70.5 (42.0-281)	56 (49.0-500)
Baseline ALC × 10^9/L (range)	32.6 (0.2-381.7)	81.5 (0.7-264.0)	61.6 (0.5-381.7)	35.9 (0.2-351.9)	25.1 (1.8-351.9)	43.6 (0.2-381.7)	20.3 (0.4-381.7)	60.6 (0.2-264.0)
Peak ALC × 10^9/L (range)	101.0 (0.5-554.8)	174.4 (2.4-709.1)	137.4 (2.9-709.1)	109.9 (0.5-554.8)	91.8 (2.7-554.8)	116.0 (0.5-709.1)	80.5 (0.8-709.1)	126.4 (0.5-489.5)

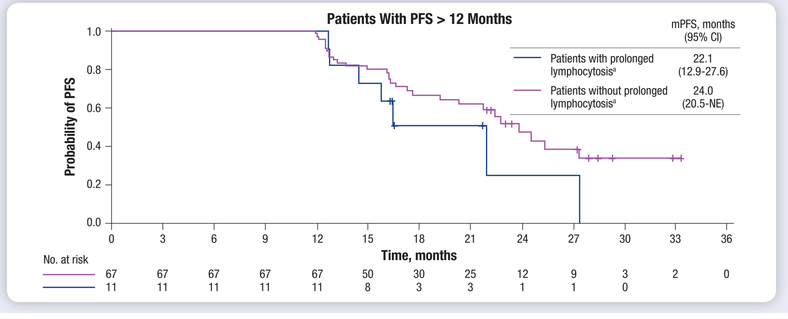
Lymphocytosis by Prior Therapy

- The time to onset of lymphocytosis was similar among all patients with R/R CLL/SLL receiving DUV regardless of the time since prior chemotherapy or number of prior therapies
  - Median time to onset of 1.1 weeks (range, 0.6-69.3 weeks) and 1.1 weeks (range, 0.4-63.0 weeks) in patients who had received 1 prior therapy or those who received ≥ 2 prior therapies, respectively
  - Median time to onset of 1.1 weeks (range, 0.9-69.3 weeks) and 1.1 weeks (range, 0.4-63.0 weeks) in patients who were ≤ 6 and > 6 months since prior chemotherapy, respectively
- The time to resolution and duration were also similar in all patients with R/R CLL/CLL, regardless of the time since prior chemotherapy or number of prior therapies
  - Median time to resolution of 12.6 weeks (range, 1.1-63.0 weeks) and 18.1 weeks (range, 2.1-62.3 weeks) in patients who had received 1 prior therapy or those who received ≥ 2 prior therapies, respectively
  - Median time to resolution of 9.0 weeks (range, 2.1-60.0 weeks) and 14.1 weeks (range, 1.1-63.0 weeks) in patients who were ≤ 6 and > 6 months since prior chemotherapy, respectively
  - Median duration of 13.1 weeks (range, 1.1-69.3 weeks) and 18.1 weeks (range, 2.1-153.0 weeks) in patients who had received 1 prior therapy or those who received ≥ 2 prior therapies, respectively
  - Median duration of 16.8 weeks (range, 2.1-153.0 weeks) and 14.3 weeks (range, 1.1-96.0 weeks) in patients who were ≤ 6 and > 6 months since prior chemotherapy, respectively

Prolonged Lymphocytosis With Duvelisib

- Patients were evaluated for the influence of prolonged lymphocytosis on PFS by comparing DUV–treated patients with or without lymphocytosis who had > 12 months of PFS. Among these patients, PFS was similar for those with and without prolonged lymphocytosis (**Figure 5**)

Figure 5. Patients With Prolonged Lymphocytosis Have a Similar PFS to Duvelisib-Treated Patients Without Prolonged Lymphocytosis

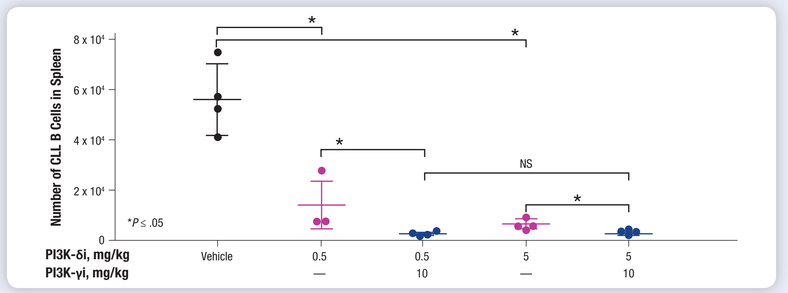


NE, not estimable
[a] Prolonged lymphocytosis is defined as ALC ≥ 5 × 10^9/L for > 12 months.

Dual Inhibition of PI3K-δ and PI3K-γ Impaired Patient-Derived CLL B Cells In Vivo

- A CLL PDX model was used to assess the relative contributions of inhibiting PI3K-δ and PI3K-γ toward reducing the numbers of CLL B cells in vivo[8]
- The combination of PI3K-δi and PI3K-γi significantly reduced the number of CLL B cells in the spleen vs treatment with PI3K-δi alone (**Figure 6**)
- The reduction in CLL B cells by PI3K-δi was dose dependent, but the maximum reduction in CLL B cells was observed in combination with PI3K-γi regardless of PI3K-δi dose

Figure 6. Inhibition of PI3K-δ and PI3K-γ Significantly Reduces the Number of CLL B Cells in the Spleen of a CLL PDX Model[8]



NS, not significant.

CONCLUSIONS

- DUV monotherapy induced rapid lymphocytosis that occurred within 1 week of treatment in patients with R/R CLL/SLL
- Lymphocytosis was transient and resolved after approximately 14 weeks
- DUV-related lymphocytosis was concurrent with an accompanying reduction in lymphadenopathy
- DUV, a dual PI3K-δ,γ inhibitor, resulted in a 50% reduction from BL ALC. In preclinical studies, dual PI3K-δ,γ inhibition was more effective than PI3K-δ inhibition in reducing CLL B cells
- Similar patterns of lymphocytosis were observed in patients regardless of poor prognostic indicators and were not correlated with worse outcomes

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