Effect of Dose Modifications on Response to Duvelisib in Patients With Relapsed/Refractory CLL/SLL in the DUO Trial

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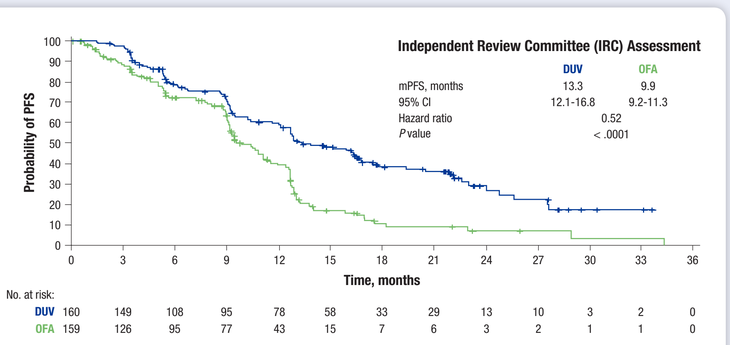
BACKGROUND

- Duvelisib (DUV) is a first-in-class oral dual phosphoinositide 3-kinase (PI3K)-δ,γ inhibitor approved by the US Food and Drug Administration for the treatment of patients with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) after ≥ 2 prior therapies or R/R follicular lymphoma after ≥ 2 prior systemic therapies[1]
- DUV targets key signaling pathways involved in the growth and survival of malignant B cells and the supportive tumor microenvironment[2-5]
- In the phase 3 DUO trial, DUV monotherapy 25 mg twice daily (BID) significantly improved efficacy vs ofatumumab (OFA) in patients with R/R CLL/SLL[6]
  - Median progression-free survival (mPFS): 13.3 vs 9.9 months (HR, 0.52; $P < .0001$) (**Figure 1**)
  - Overall response rate (ORR): 74% vs 45% ($P < .0001$)
- 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[7,8]
- Here, we report results from retrospective analyses conducted to examine dose-modification patterns and their impact on response to DUV in the DUO trial

Figure 1. Duvelisib Significantly Improved PFS vs OFA in Patients With R/R CLL/SLL[6]

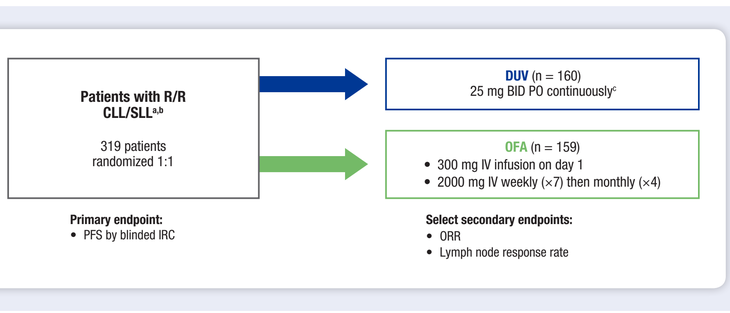


METHODS

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 in patients who were diagnosed with R/R CLL/SLL (**Figure 2**)[6]
- Dose interruption (DI) or reduction (DR) to 15, 10, or 5 mg BID was permitted per study protocol to manage treatment-emergent adverse events (TEAEs)[6]

Figure 2. DUO Trial Design



IV, intravenous; **PO**, orally.
[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]

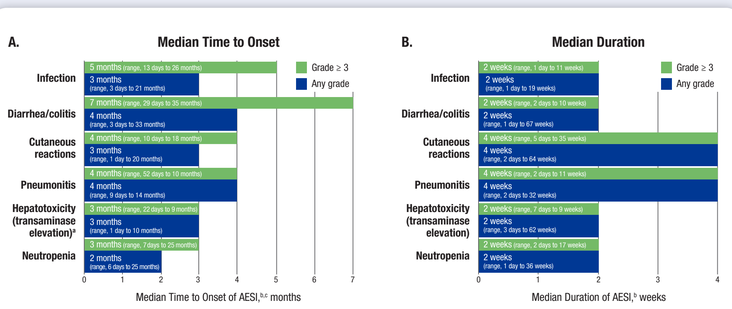
- TEAEs were defined as AEs that occurred from when the first dose of DUV was administered to 30 days after the last dose[1]
- TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1[6]
- TEAE severity was assessed by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03[6]
- TEAEs of special interest (AESI) related to duvelisib were defined as groupings of infections, diarrhea, colitis, neutropenia, cutaneous reactions, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) elevation, and pneumonitis[6]
- Response was assessed before and after dose modifications, and PFS was assessed in patients with and without dose modifications; response was analyzed using descriptive statistics, and PFS was estimated using Kaplan-Meier methods[6]
  - Response was assessed per IRC according to International Workshop on CLL (iwCLL)[9,10] or International Working Group (IWG) Response Criteria,[11] with modification for treatment-related lymphocytosis
  - PFS was defined as time from randomization to first documentation of progressive disease (PD) as determined by an IRC or death due to any cause

RESULTS

Exposure and AESI

- Among 158 DUV-treated patients, the median duration of DUV exposure was 11.6 months (range, 0.2 to 36.8 months)
- The median overall DUV dose intensity (total dose taken/total expected dose [25 mg BID]) was 97.7 (range, 34.7 to 100)
  - Median dose intensity was highest during the first 3 months, then decreased slightly during months 3 to 6 (first 3 months, 100 [range, 6.6 to 100]; first 6 months, 93.3 [range, 3.3 to 100])
- Median time to onset across AESI after starting DUV ranged from 2.2 to 4.3 months (**Figure 3A**); median duration across AESI was up to 4 weeks (**Figure 3B**)
- Proportions of patients experiencing AESI were stable or decreased over time after 3 to 6 months (**Table 1**)

Figure 3. Onset and Duration of AESI



[a]The onset of hepatotoxicity is calculated using adverse event reported terms of hepatoxicity. [b]Grouped term for reactions with multiple preferred terms. [c]For patients with multiple events within an AESI category, time to onset is calculated for the first event in the category.

Table 1. Rates of AESI Over Time

AESI, n (%)[a,b]	0-3 Months n = 158	> 3-6 Months n = 137	> 6-9 Months n = 114	> 9-12 Months n = 100
Any-grade AESI	**101 (64)**	**86 (63)**	**54 (47)**	**52 (52)**
Infection	57 (36)	43 (31)	29 (25)	30 (30)
Neutropenia	33 (21)	21 (15)	13 (11)	11 (11)
Diarrhea/colitis	31 (20)	28 (20)	22 (19)	21 (21)
Cutaneous reactions	22 (14)	17 (12)	7 (6)	6 (6)
Hepatotoxicity (transaminase elevation)	8 (5)	9 (7)	4 (4)	3 (3)
Pneumonitis	4 (3)	6 (4)	0	2 (2)

[a]Grouped term for reactions with multiple preferred terms. [b]Within each time period, patients were counted once for the first occurrence of an AESI grouping within the period; a patient may be counted multiple times for multiple time periods.

Dose Modification

- Baseline characteristics of patients with DI or DR are described in **Table 2**
- Among DUV-treated patients, DI occurred more frequently than DR (80% vs 27%)
  - In patients with DI, some had multiple DI (1 DI, 34%; 2 DI, 20%; ≥ 3 DI, 26%)
  - All patients with DR had only 1 DR; re-escalation to 25 mg BID occurred in 2 patients
- The median time to first DI and DR occurred within the first 6 months of DUV treatment (DI, 4 months [range, 0.1 to 25 months]; DR, 5 months [range, 1 to 23 months])
  - DI typically coincided with time to onset of AESI
  - The median durations of DI and DR were 2 weeks (range, 1 day to 19 weeks) and 17 weeks (range, 2 days to 98 weeks), respectively
- The most common AESI leading to DI or DR were diarrhea/colitis, infections, neutropenia, and cutaneous reactions (**Table 3**)
- Rates of AESI that occurred after DR are depicted in **Figure 4**
- Steroid treatment was required for management of AESI (diarrhea, n = 15; cutaneous reactions, n = 10; pneumonitis, n = 5)
- Individual AESI seldom led to discontinuation (≤ 10% of all DUV-treated patients [n = 158]): diarrhea/colitis, 10%; infection, 7%; cutaneous reactions, 4%; pneumonitis, 3%; neutropenia, 1%; transaminase elevation, 1%

Table 2. Baseline Characteristics for Patients With DI or DR

Characteristic	DUV DI n = 126[a]	DUV DR n = 47[a]
Median age (range), years	69 (40-86)	69 (40-86)
Median time since completion of most recent therapy (range), months	23 (0.8-149)	23 (1.2-149)
Bulky Disease (≥ 5 cm target lesion), n (%)	54 (43)	21 (45)
Molecular features (per central laboratory), n (%)		
17p deletion	26 (21)	6 (13)
TP53 mutation	23 (18)	7 (15)
17p deletion and/or *TP53* mutation	36 (29)	10 (21)
Unmutated *IGHV*	88 (70)	30 (64)
Median prior systemic therapies (range)	2 (1-10)	2 (1-7)
≥ 3 prior lines of therapy, n (%)	38 (31)	11 (23)

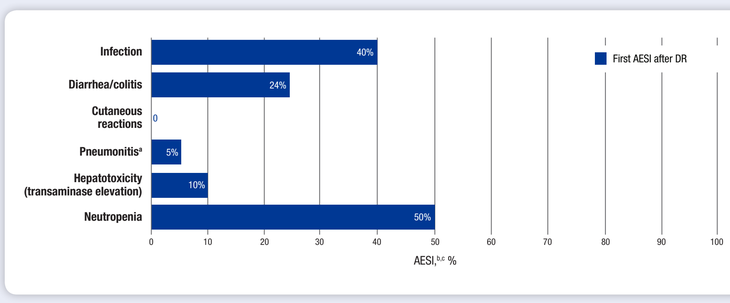
IGHV, immunoglobulin heavy variable.
[a]Intent-to-treat population.

Table 3. AESI Resulting in DI or DR

AESI, n (%)[a]	DUV n = 158 DI	DUV n = 158 DR
Diarrhea/colitis	45 (28)	13 (8)
Infection	43 (27)	4 (3)
Cutaneous reactions	20 (13)	7 (4)
Neutropenia	19 (12)	6 (4)
Hepatotoxicity (transaminase elevation)	9 (6)	5 (3)
Pneumonitis	7 (4)	2 (1)

[a]Grouped term for reactions with multiple preferred terms.

Figure 4. Rates of First AESI After DR



[a]Pneumonitis after DR, regardless of prior events. [b]Grouped term for reactions with multiple preferred terms. [c]Percentage for first AESI after DR is based on the total number of patients who never had an AESI before their first DR.

Efficacy and Dose Modification

- Among responders (n = 118), median time to first response on DUV was 1.9 months, and estimated median duration of response was 11.1 months
- Response to DUV was improved or maintained in most patients evaluated for response who had ≥ 1 DI for > 1 week (84%) or > 2 weeks (82%) followed by ≥ 3 weeks on DUV (**Table 4**)
- Response to DUV was maintained in patients after a DR (≥ 30 days, 53%; ≥ 90 days, 45%; ≥ 120 days, 44%)
  - Among 25 patients who had a DR after a complete response (CR) or partial response (PR), the median time to DR was 5.6 months (range, 1 to 21.3 months), and the median duration at a reduced dose was 3.4 months

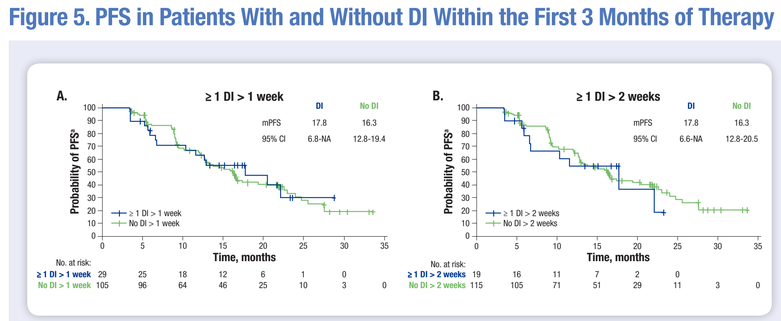
Table 4. Response in Patients With DI

Patients, n (%)	DUV ≥ 1 DI for > 1 Week Followed by ≥ 3 Weeks on DUV n = 50[a]	DUV ≥ 1 DI for > 2 Weeks Followed by ≥ 3 Weeks on DUV n = 38[a]
Response unchanged or improved after DI	**42 (84)**	**31 (82)**
PR to CR	0	0
SD to PR	5 (10)	2 (5)
CR to CR	0	0
PR to PR	26 (52)	19 (50)
SD to SD	6 (12)	6 (16)
Other[b]	5 (10)	4 (11)
Progressed after DI	**8 (16)**	**7 (18)**
CR to PD	0	0
PR to PD	7 (14)	7 (18)
SD to PD	1 (2)	0

SD, stable disease.
[a]Response evaluable. [b]Patients with documented evidence prior to DI with continued assessments of PD.

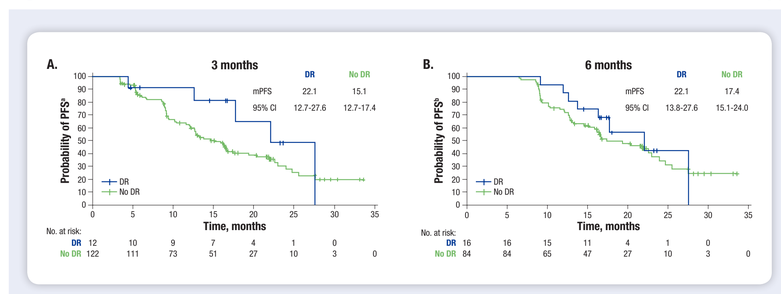
- PFS was similar between patients with ≥ 1 DI and those without DI for > 1 week or > 2 weeks within the first 3 months of therapy (mPFS: > 1 week, 17.8 vs 16.3 months; > 2 weeks, 17.8 vs 16.3 months) (**Figure 5**)
- PFS did not appear shorter in patients with DR vs those without DR within the first 3 and 6 months of therapy (**Figure 6**)

Figure 5. PFS in Patients With and Without DI Within the First 3 Months of Therapy



[a]Patients with PFS ≥ 3 months.

Figure 6. PFS in Patients With and Without DR Within the First 3 and 6 Months of Therapy



[a]Patients with PFS ≥ 3 months. [b]Patients with PFS ≥ 6 months.

CONCLUSIONS

- DUV is a new, oral treatment option for patients with R/R CLL/SLL that has the potential for durable responses and good tolerability over time
- Response to DUV was rapid, occurring prior to first DI or DR in most patients
  - AESI coincided with median onset of DI and DR and in most cases did not lead to treatment discontinuation
- DI of > 1 week or DR did not negatively impact efficacy outcomes with DUV
- Taken together, these data suggest that DI/DR can contribute to the effective management of TEAEs with DUV in patients with R/R CLL/SLL

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