# Safety Profile and Management of Adverse Events Associated With Duvelisib in Patients With Advanced Hematologic Malignancies

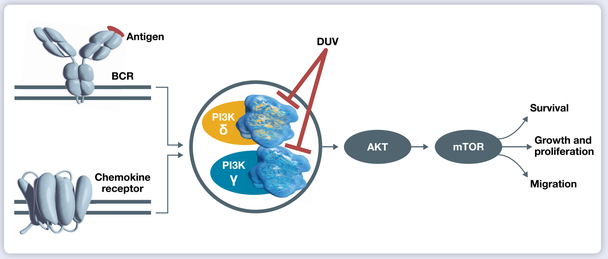
Karen Francoeur, BSN, RN,[1] Jeff Haney, MA,[2] Michael Baglio, PharmD,[2] Dan Powers, DO,[2] Josie Bazemore, NP[1]

[1]Dana-Farber Cancer Institute, Boston, MA; [2]Verastem Oncology, Needham, MA

## INTRODUCTION

- Duvelisib (DUV), a first-in-class, oral, dual inhibitor of PI3K-δ,γ, targets key signaling pathways in malignant B cells and the tumor microenvironment that promote the growth and survival of hematologic malignancies (**Figure 1**)[1-5]

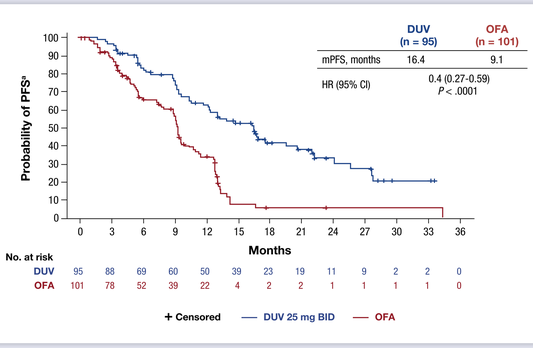
### Figure 1. Mechanism of Action of DUV, a Dual Inhibitor of PI3K-δ,γ




mTOR, mechanistic target of rapamycin; PI3K, phosphatidylinositol-3 kinase.

- DUV was 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) who have received ≥ 2 prior therapies and patients with R/R follicular lymphoma (FL) who have received ≥ 2 prior systemic therapies[6]
  - In the randomized phase 3 DUO trial,[7] DUV 25 mg twice daily (BID) showed a significant improvement in efficacy vs ofatumumab (OFA) (mPFS, 16.4 vs 9.1 mo; HR, 0.4 [*P*<.0001]; ORR, 79% vs 39% [*P*<.0001]) in patients with R/R CLL or SLL who had received ≥ 2 prior therapies (**Figure 2**)[6,8]
  - In the phase 2 DYNAMO trial,[9] the overall response rate was 42.2% with DUV 25 mg BID in 83 patients with R/R FL who had received ≥ 2 prior systemic therapies[6,9]

### Figure 2. DUV Improves PFS (Kaplan-Meier estimates) in Patients With R/R CLL or SLL Who Had Received ≥ 2 Prior Therapies in the DUO Trial[6,8]




HR, hazard ratio.
[a] PFS per independent review committee assessment.

## OBJECTIVE

- To present an overview of the safety profile of DUV 25 mg BID in patients primarily with R/R CLL, SLL, or FL from a pooled analysis of 4 clinical trials,[7,9-11] highlighting adverse events of special interest (AESI) and key aspects of AESI management relevant to oncology nurses

## METHODS

- Safety data from 442 patients primarily with R/R CLL, SLL, or FL treated with DUV 25 mg BID monotherapy across 4 studies were evaluated in a pooled analysis (**Figure 3**)
- Treatment-emergent AEs were defined as AEs that occurred from the time that the first DUV dose was administered to 30 days after the last dose
- AEs and laboratory values were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1
- AE severity was assessed by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03

### Figure 3. Overview of Patients Included in the Pooled Safety Analysis

Patients (N = 442) with previously treated B-cell malignancies received DUV 25 mg orally BID in 1 of 4 clinical trials: 2 single-arm, open-label trials (DYNAMO, phase 1 dose escalation),[9,10] 1 open-label–extension clinical trial (DUO crossover),[11] and 1 randomized, open-label, phase 3 actively controlled clinical trial (DUO)[7]

- Median duration of treatment, 9 months (range: 0.1 to 53 months)
- 36% of patients were exposed to DUV for ≥ 1 year

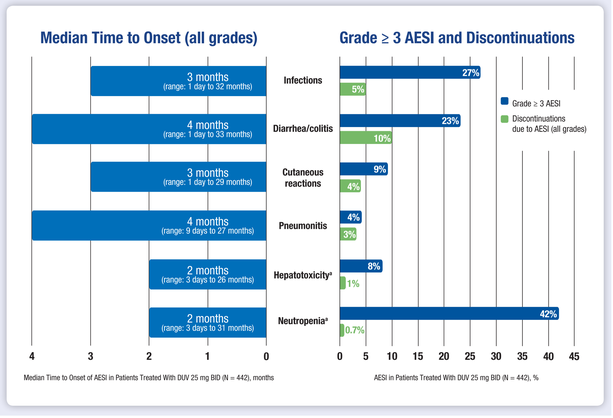
## RESULTS

- Summary of AESI associated with DUV is presented in **Table 1**
  - The most frequent SAEs ranged from 0.7 to 18%, except infection, which occurred in 31% of patients
  - The AESI of diarrhea or colitis resulted in discontinuations in 10% of patients. No other AESI resulted in rates of discontinuations of > 5%
  - Diarrhea/colitis was the AESI that most commonly caused a dose reduction in 6% of patients (**Table 1**; **Figure 4**)
- Median time to onset of AESI ranged from 2 to 4 months (**Figure 4**)
- Median time to first dose modification or discontinuation due to an AESI was 4 months; most occurred within 7 months[6]

### Table 1. Safety With DUV 25 mg BID in Patients With R/R CLL, SLL, or FL[6]

| Patients With a Treatment-Emergent AE, % | Any-Grade AESI | Grade ≥ 3 AESI | Serious AESI | Death Due to AESI | Dose Reduction Due to AESI | Discontinuation Due to AESI |
|---|---|---|---|---|---|---|
| **Infection** | 63 | 27 | 31 | 4 | 2 | 5 |
| Upper respiratory infection | 21 | 0.5 | 2 | 0 | 0.2 | 0.2 |
| Pneumonia | 21 | 15 | 17 | 2 | 0.5 | 3 |
| Lower respiratory infection | 10 | 3 | 3 | 0.2 | 0 | 0.2 |
| **Diarrhea/colitis** | 50 | 23 | 18 | 0.2 | 6 | 10 |
| **Cutaneous reactions** | 31 | 9 | 5 | 0.4 | 2 | 4 |
| **Pneumonitis** | 7 | 4 | 5 | 0.2 | 0.7 | 3 |
| **Hepatotoxicity (transaminase elevation)** | 15 | 8 | 0.9 | 0 | 4 | 1 |
| **Neutropenia** | 34 | 30 | 0.7 | 0 | 3 | 0.7 |

### Figure 4. Median Time to Onset of and Discontinuations Due to AESI With DUV 25 mg BID[6]




[a] Median time to onset and incidence of grade ≥ 3 AESI for hepatotoxicity and neutropenia are derived from laboratory assessments.

- **Tables 2 and 3** provide guidelines regarding monitoring, treatment and DUV dose administration for these AEs based on grade, toxicity, and symptomatology
- To mitigate infection risks, prophylactic with antivirals is recommended for cytomegalovirus (CMV) infection and reactivation and antibiotics prophylaxis for *Pneumocystus jiroveci* (PJP)
  - Following completion of DUV treatment, continue PJP prophylaxis until absolute CD4+ T-cell count is > 200 cells/μL

### Table 2. Recommended Management of AESI[6]

| AESI | Definition/Grade | Investigator-Recommended Management |
|---|---|---|
| **Infection** | Grade ≥ 3 infection | – **Withhold** DUV until resolved<br>– **Resume** at the same or a reduced dose (see **Table 3**) |
| | Clinical CMV infection or viremia (positive PCR or antigen test) | – **Withhold** DUV until resolved<br>– **Resume** at the same or a reduced dose (see **Table 3**)<br>– If DUV is resumed, monitor patients for CMV reactivation (by PCR or antigen test) at least monthly |
| | PJP | – For suspected PJP, **withhold** DUV until evaluated<br>– For confirmed PJP, **discontinue** DUV |
| **Noninfectious diarrhea or colitis** | Mild/moderate diarrhea (grade 1/2; up to 6 stools per day over baseline) and responsive to antidiarrheal agents<br>***or***<br>Asymptomatic (grade 1) colitis | – No change in dose<br>– **Initiate** supportive therapy with antidiarrheal agents as appropriate<br>– **Monitor** at least weekly until resolved |
| | Mild/moderate diarrhea (grade 1/2; up to 6 stools per day over baseline) and unresponsive to antidiarrheal agents | – **Withhold** DUV until resolved<br>– **Initiate** supportive therapy with enteric acting steroids (eg, budesonide)<br>– **Monitor** at least weekly until resolved<br>– **Resume** at a reduced dose (see **Table 3**) |
| | Abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs<br>***or***<br>Severe diarrhea (grade 3; > 6 stools per day over baseline) | – **Withhold** DUV until resolved<br>– **Initiate** supportive therapy with enteric acting steroids (eg, budesonide) or systemic steroids<br>– **Monitor** at least weekly until resolved<br>– **Resume** at a reduced dose (see **Table 3**)<br>– For recurrent grade 3 diarrhea or recurrent colitis of any grade, **discontinue** DUV |
| | Life-threatening | – **Discontinue** DUV |
| **Cutaneous reaction** | Grade 1/2 | – No change in dose<br>– **Initiate** supportive therapy with emollients, antihistamines (for pruritus), or topical steroids<br>– **Monitor** closely |
| | Grade 3 | – **Withhold** DUV until resolved<br>– **Initiate** supportive therapy with emollients, antihistamines (for pruritus), or topical steroids<br>– **Monitor** at least weekly until resolved<br>– **Resume** at a reduced dose (see **Table 3**)<br>– If severe cutaneous reaction does not improve, worsens, or recurs, **discontinue** DUV |
| | Life-threatening | – **Discontinue** DUV |
| | SJS, TEN, DRESS (any grade) | – **Discontinue** DUV |
| **Pneumonitis without suspected infectious cause** | Moderate symptomatic pneumonitis (grade 2) | – **Withhold** DUV<br>– **Treat** with systemic steroid therapy<br>– If pneumonitis recovers to grade 0 or 1, DUV may be **resumed** at a reduced dose (see **Table 3**)<br>– If noninfectious pneumonitis recurs or patient does not respond to steroid therapy, **discontinue** DUV |
| | Severe (grade ≥ 3) or life-threatening pneumonitis | – **Discontinue** DUV<br>– **Treat** with systemic steroid therapy |
| **Transaminase elevation** | 3 to 5 × ULN (grade 2) | – **Maintain** DUV dose<br>– **Monitor** at least weekly until return to < 3 × ULN |
| | > 5 to 20 × ULN (grade 3) | – **Withhold** DUV and **monitor** at least weekly until return to < 3 × ULN<br>– **Resume** DUV at the same dose (for first occurrence) or at a reduced dose for subsequent occurrences (see **Table 3**) |
| | > 20 × ULN (grade 4) | – **Discontinue** DUV |
| **Neutropenia** | ANC 0.5 to 1.0 Gi/L[a] | – **Maintain** DUV dose<br>– **Monitor** ANC at least weekly |
| | ANC < 0.5 Gi/L[a] | – **Withhold** DUV<br>– **Monitor** ANC until > 0.5 Gi/L[a]<br>– **Resume** DUV at the same dose (for first occurrence) or at a reduced dose for subsequent occurrences (see **Table 3**) |

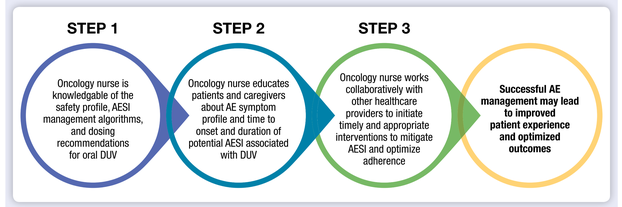
ANC, absolute neutrophil count; DRESS, drug reaction with eosinophilia and systemic symptoms; Gi/L, giga/liter; PCR, polymerase chain reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; ULN, upper limit of normal.
[a] Gi/L = $10^3$/mm$^3$ or $10^3$/μL.

### Table 3. Dose Modification Levels[6]

| Dose Level | Dose |
|---|---|
| **Initial dose** | 25 mg BID |
| **Dose reduction** | 15 mg BID |
| **Subsequent dose modification** | **Discontinue** if patient is unable to tolerate 15 mg BID |

- Oncology nurses are the cornerstone of patient care and play a pivotal role in optimizing patient outcomes through patient education, AE monitoring, and early intervention from the time of diagnosis and throughout care of patients who are receiving DUV (**Figure 5**)

### Figure 5. Nursing Considerations for Patient Education and Monitoring AESI in Patients Receiving DUV




- Oncology nurses should educate the patient and caregiver on the safety profile of DUV to increase patient awareness and set expectations regarding potential AEs
- For example, with diarrhea, early identification and intervention are critical for effective management and resolution of most AESI to allow patients to remain on DUV (**Figure 6**)

### Figure 6. Role of Nurses in Management of the AESI Noninfectious Diarrhea or Colitis

| | |
|---|---|
| **Nurse educates patient on DUV safety profile** | • Nurse educates the patient and caregiver on the AE profile and gastrointestinal issues (eg, diarrhea is a common symptom associated with DUV treatment) |
| **Patient/caregiver reports symptom** | • Patient receiving DUV 25 mg BID has mild/moderate diarrhea (grade 1/2; up to 6 stools per day over baseline) that is unresponsive to antidiarrheal agents |
| **Nurse initiates early intervention** | • Nurse has patient come into the office for stool workup<br>• **Patient initiates** supportive therapy with enteric acting steroids (eg, budesonide) |
| **Nurse uses AE management algorithm** | • **Withhold DUV** until diarrhea has resolved<br>• **Nurse monitors patient** progress **at least weekly** until diarrhea has resolved |
| **Follow-up and resolution of symptoms** | • Nurse confirms **diarrhea has resolved after 1-2 weeks** |
| **Follow-up and outcome** | • **Patient resumes** DUV treatment **at a reduced dose (15 mg BID)**<br>• **Nurse monitors patient** weekly for 3-4 weeks after resuming DUV to ensure that patient is **tolerating treatment**<br>• For **recurrent grade 3 diarrhea** or **recurrent colitis** of any grade, **discontinue DUV** |

## CONCLUSIONS

- DUV is a new oral treatment option for patients with R/R CLL, SLL, or FL, with the potential for durable responses and good tolerability over time
- In this heavily pretreated population of patients with advanced hematologic malignancies, DUV demonstrated a manageable safety profile
  - AESI were generally reversible, often managed through dose modifications, and, in most cases, did not lead to treatment discontinuation
- Nurses play a pivotal role in patient education, AE monitoring, early intervention, and use of algorithms for AESI management
- Early identification and intervention are critical for effective management and resolution of most AESI, which may result in low rates of discontinuation, improved patient quality of care, and enhanced adherence to therapy

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