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Characterization of Duvelisib in Patients With Refractory Marginal Zone Lymphoma: Data From the Phase 2 DYNAMO Trial

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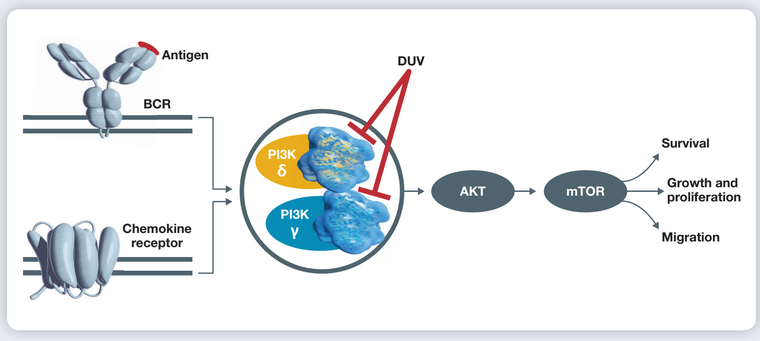
BACKGROUND

- Duvelisib (DUV) is a first-in-class, oral dual inhibitor of phosphoinositide 3-kinase δ,γ (PI3K-δ,γ)[1] approved in the United States for the treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma after ≥ 2 prior therapies and for follicular lymphoma after ≥ 2 prior systemic therapies[2]
- DUV targets key signaling pathways that promote the growth and survival of hematologic malignancies[3-6] (**Figure 1**)
  - In preclinical studies, dual PI3K-δ,γ inhibition with duvelisib was more effective at inhibiting B cells and modifying cells in the tumor microenvironment in vivo than PI3K-δ inhibition alone[3,4]
- DUV offers a novel therapeutic approach for patients with marginal zone lymphoma (MZL), for which few effective treatment options exist[7]
  - MZL is a subtype of non-Hodgkin's lymphoma (NHL), and MZL cases make up 8% of all NHL cases diagnosed[8,9,a]
  - MZLs originate in lymphoid follicle marginal zones in mucosa-associated lymphoid tissues, spleen, and lymph nodes[8]
  - Although response rates are high with frontline anti-CD20–based regimens, relapses are common

[a] In the United States between 1998 and 2011.

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

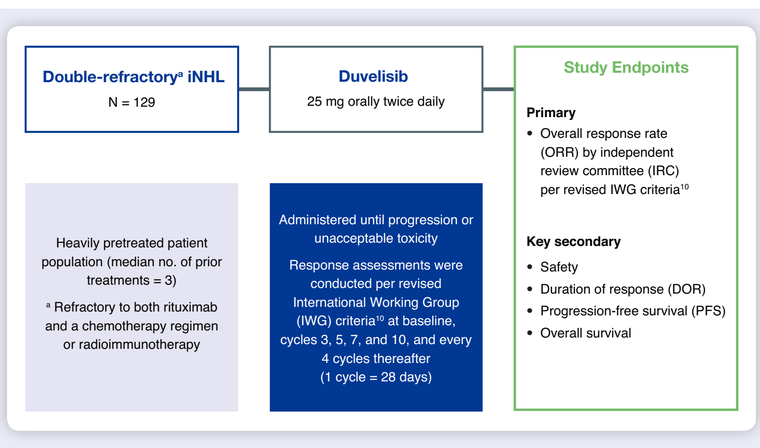


BCR, B-cell receptor; **DUV,** duvelisib; **mTOR,** mechanistic target of rapamycin.

STUDY DESIGN

- DYNAMO (IPI-145-06; NCT01882803) was an open-label, single-arm, phase 2 trial that evaluated the safety and efficacy of DUV monotherapy in indolent NHL (iNHL), including in patients with MZL[6] (**Figure 2**)

Figure 2. DYNAMO Trial Design



RESULTS

- Of 129 patients enrolled in the DYNAMO trial, 18 demonstrated MZL histology[6]
  - Extranodal (50%) was the most common MZL subtype, followed by splenic (28%) and nodal (22%) (**Table 1**)
- Most patients were heavily pretreated, having received a median number of 2 prior regimens (range, 1-8) (**Table 2**)
  - All patients were previously treated with rituximab[a] and alkylating agents,[a] and 94% were refractory to these agents
  - The majority of patients (67% [n = 12]) were refractory to ≥ 2 prior regimens

[a] As a single agent or in combination.

Table 1. Background Characteristics of Patients

	N = 18
Age, years	
Median	67
Min-max	61-77
Sex, n (%)	
Male	13 (72)
Female	5 (28)
Time from initial diagnosis to first dose, months	
Median	29
Min-max	10-117
Time since completion of last therapy, months	
Median	6.5
Min-max	1-58
Type of MZL, n (%)	
Extranodal	9 (50)
Nodal	4 (22)
Splenic	5 (28)

Max, maximum; **min,** minimum.

Table 2. Prior Regimens and Degree of Refractory Disease

	N = 18
No. of prior regimens	
Median	2
Min-max	1-8
Disease refractory to most recent regimen, n (%)	18 (100)
Disease refractory to ≥ 2 regimens, n (%)	12 (67)
Exposure to selected anticancer therapies (occurring in > 25%), n (%)[a]	
Rituximab[b]	18 (100)
Alkylating agent/purine analogue[b]	18 (100)
Alkylating agent[b]	18 (100)
Combination of rituximab and alkylating agent	16 (89)
Bendamustine[b,c]	11 (61)
Anthracycline[b]	11 (61)
Bendamustine-rituximab	8 (44)
R-CHOP	5 (28)
R-CVP	5 (28)
Refractory to selected anticancer therapies (occurring in > 25%), n (%)	
Rituximab[b]	17 (94)
Alkylating agent/purine analogue	17 (94)
Alkylating agent	17 (94)
Combination of rituximab and alkylating agent	16 (89)
Bendamustine[c]	10 (56)
Bendamustine-rituximab[b,c]	7 (39)
Anthracycline	9 (50)
R-CHOP	5 (28)
R-CVP	5 (28)

R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; **R-CVP,** rituximab, cyclophosphamide, vincristine, and prednisone.
[a] One patient received a stem cell transplant (deviation from protocol). [b] As a single agent or in combination.
[c] Includes bendamustine and bendamustine hydrochloride.

- The median duration of DUV exposure was 8.4 months (range, 0.9-31.3 months) (**Table 3**)
- Most patients experienced dose modifications, including dose interruptions (89%) and dose reductions (17%), similar to the overall population[9]

Table 3. Exposure to Duvelisib

	N = 18
Duration, months	
Median	8.4
Min-max	0.9-31.3
Q1-Q3	3.7-17.5

- The ORR with DUV per IRC response assessment was 39% (95% CI, 17.3%-64.3%), including 1 complete response (CR) and 6 partial responses (PRs) (**Table 4**)
  - The ORR was 75% for nodal subtype, 80% for splenic subtype
    - No patients with extranodal subtype achieved a response
- The median time to response with DUV was 3.7 months (range, 1.8-8.4 months)

Table 4. Overall Response Rate[a]

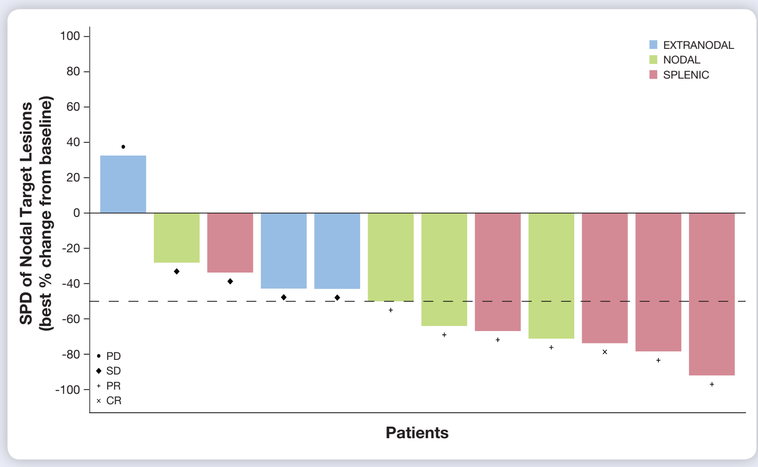
	N = 18
ORR per IRC, n (%)	
ORR	7 (39)
95% CI	17.3-64.3
CR	1 (6)
PR	6 (33)
DCR	16 (89)
SD	9 (50)
PD	1 (6)
Unkown	1 (6)
Time to response per IRC, months	
Median (min-max)	3.7 (1.8-8.4)
Duration of response IRC (95% CI), months	
Median (50th percentile)	NE[b] (1.3-NE)

[b]Estimated median DOR > 13 months (to be confirmed by IRC)

DCR, disease control rate; **NE,** not estimable; **PD,** progressive disease; **SD,** stable disease.
[a] May 18, 2018 data cutoff. The median length of follow-up was 31.2 months.

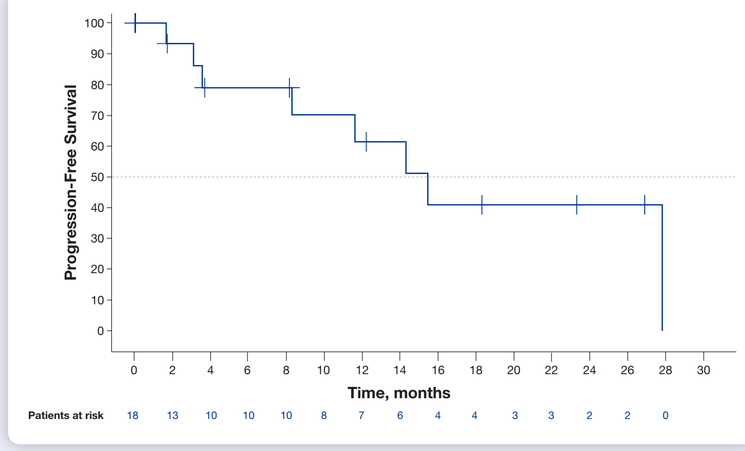
- 12 of 18 patients were evaluable for the change in the sum of the products of diameters (SPD) of nodal target lesions (**Figure 3**)
  - 11 of 12 patients showed some level of shrinkage

Figure 3. Best Percent Change in SPD of Nodal Target Lesions per IRC



- The median PFS per IRC assessment was 15.5 months (95% CI, 3.6-27.8 months) (**Figure 4**)

Figure 4. Progression-Free Survival in Patients With MZL



- All patients experienced ≥ 1 adverse event (AE)
- Most AEs were mild to moderate in nature (grade ≤ 2)
  - Neutropenia and diarrhea were among the most common grade ≥ 3 AEs, occurring in 28% and 17% of patients, respectively
- Treatment-emergent AEs (**Table 5**) resulted in 33% of treatment discontinuations
  - Causes of discontinuation: diarrhea (grade 2), pneumonitis (grade 2), pneumonia cytomegaloviral (grade 2), eczema (grade 3), pneumonia/respiratory failure (grade 4)
  - One death (due to pancolitis) occurred and was classified as potentially related to DUV treatment
  - Of the 3 in PR at discontinuation, follow-up imaging was not available for 1 patient, but the other 2 had sustained responses of > 1 year as of the most recent imaging after treatment discontinuation

Table 5. Treatment-Emergent Adverse Events in ≥ 20% of Patients

Preferred Term	All Grades N = 18	Grade ≥ 3[a] N = 18	All Grades Leading to Discontinuation N = 18
Patients with any event, n (%)	18 (100)	17 (94)	6 (33)
Diarrhea/colitis[b]	9 (50)	3 (17)	1 (6)
Cough	6 (33)	–	–
Neutropenia	6 (33)	5 (28)	–
Pyrexia	6 (33)	–	–
Arthralgia	5 (28)	–	–
Decreased appetite	5 (28)	1 (6)	–
Fatigue	5 (28)	–	–
Nausea	5 (28)	–	–
Anemia	4 (22)	–	–
Abdominal pain	4 (22)	–	–
Oedema peripheral	4 (22)	1 (6)	–
Vomiting	4 (22)	–	–

[a] Additional grade ≥ 3 treatment-emergent adverse events in ≥ 1 patient were alanine aminotransferase increased in 2 patients (11%), colitis in 2 patients (11%), and hypokalemia in 1 patient (6%). [b] Of patients with diarrhea, 3 (17%) had colitis and 1 (6%) had enterocolitis.

CONCLUSIONS

- DUV demonstrated clinically meaningful antitumor activity in patients with high-risk MZL double refractory to previous anticancer therapy
  - 67% of patients were refractory to ≥ 2 prior regimens
- The ORR with DUV was 39% (95% CI, 17.3%-64.3%), with durable responses observed (median not yet reached)
  - The DCR (CR + PR + SD) was 89%
- The median PFS with DUV was 15.5 months (95% CI, 3.6-27.8 months)
- Based on the types of AEs observed in the study and this high-risk patient population, DUV had a manageable safety profile, consistent with previous reports in other advanced hematologic malignancies[7,11]
- These preliminary findings suggest that DUV may be a promising oral treatment for patients with double-refractory MZL for whom there are limited treatment options

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