

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

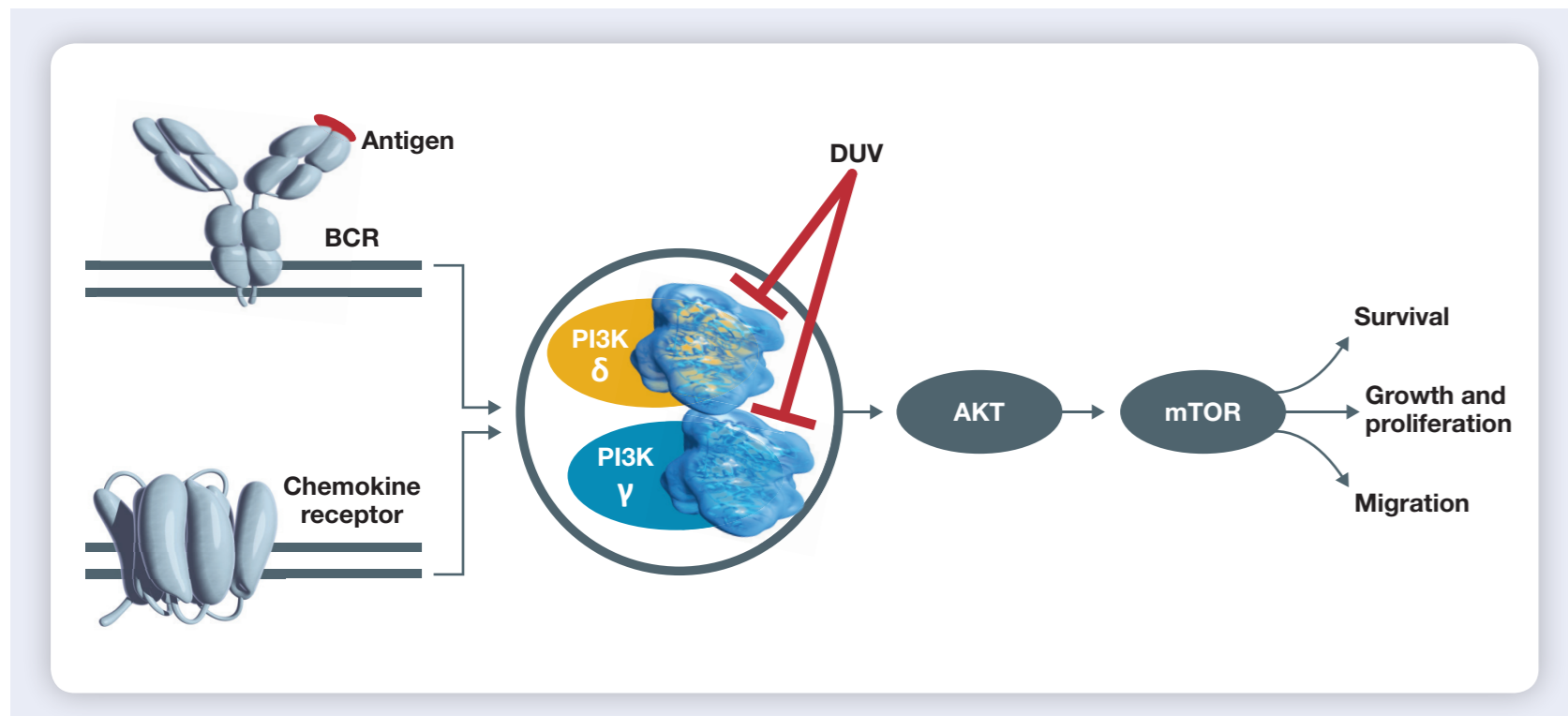
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BACKGROUND

- Duvelisib (DUV) is a first-in-class, oral dual inhibitor of phosphoinositide 3-kinase δ, γ (PI3K- δ, γ)¹ approved 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 therapies²
- DUV targets key signaling pathways that promote the growth and survival of hematologic malignancies³⁻⁶ (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



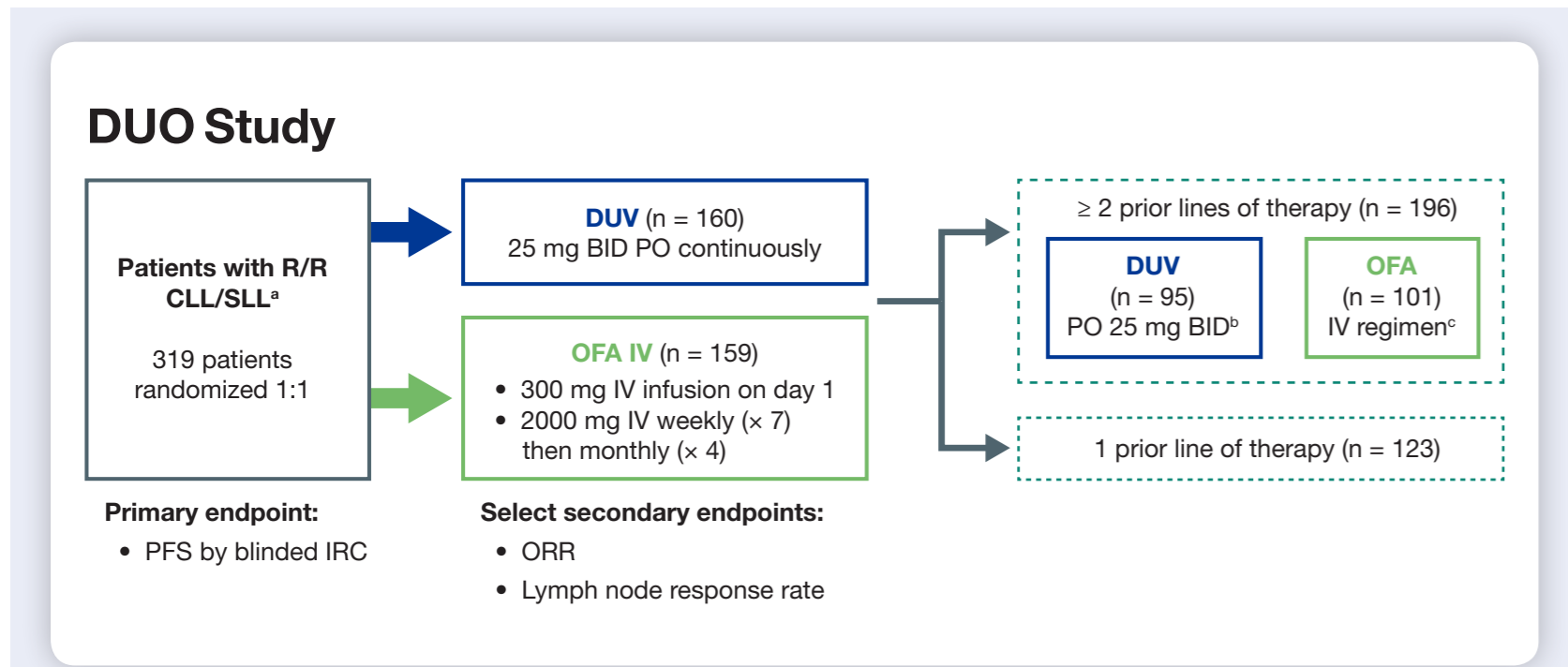
BCR, B-cell receptor; mTOR, mechanistic target of rapamycin.

- 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 mutations⁷
- 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 in patients 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.

^aA total of 312 patients had CLL; 7 patients had SLL (N = 319).¹ DUV was administered at 25 mg BID in 28-day treatment cycles until progressive disease or unacceptable toxicity.¹ 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

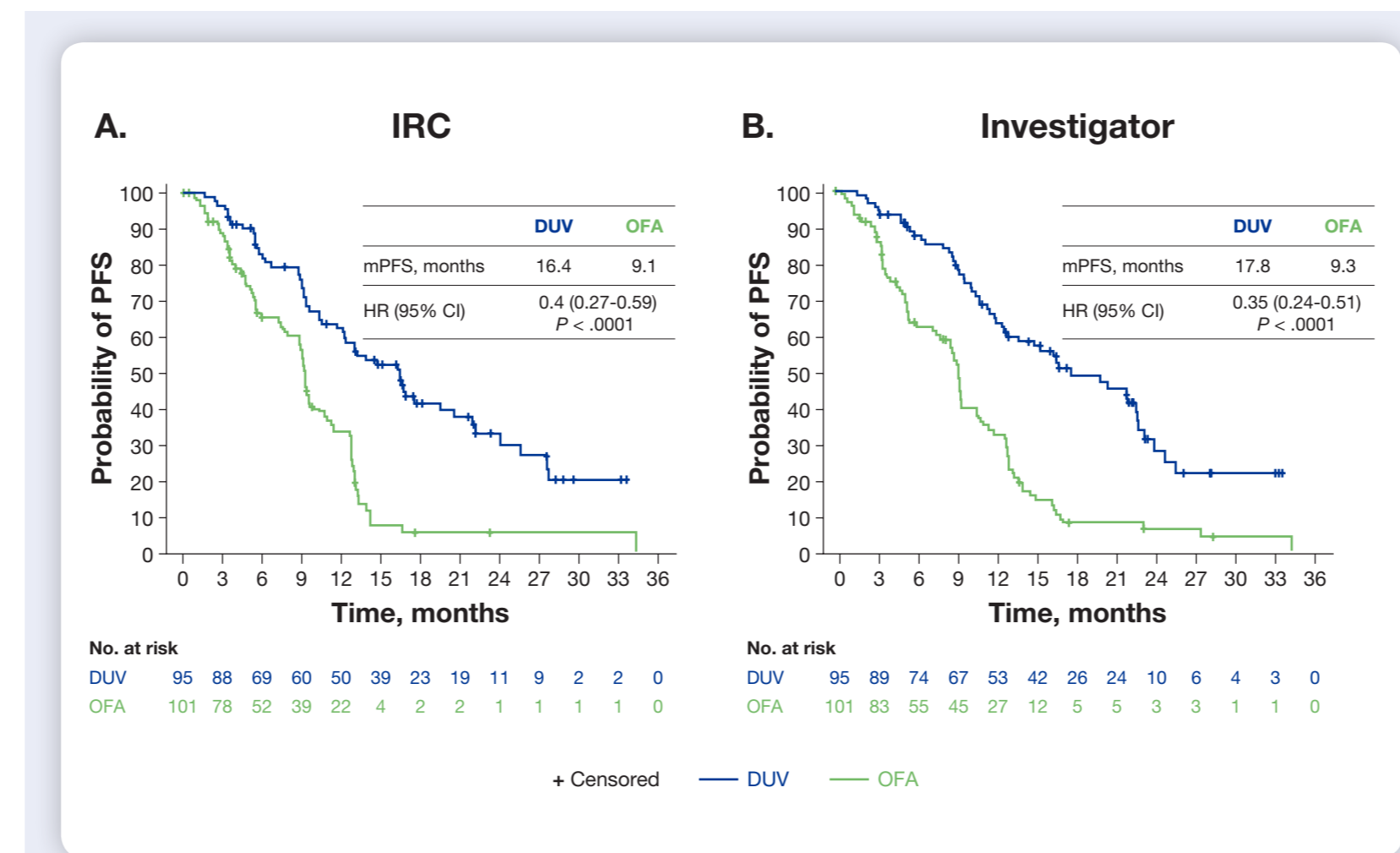
Table 1. Baseline Characteristics and Prognostic Features

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 \geq 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, $\times 10^9/L$	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. ^aThrombocytopenia and/or neutropenia. ^bProgression < 12 months after fludarabine/pentostatin.

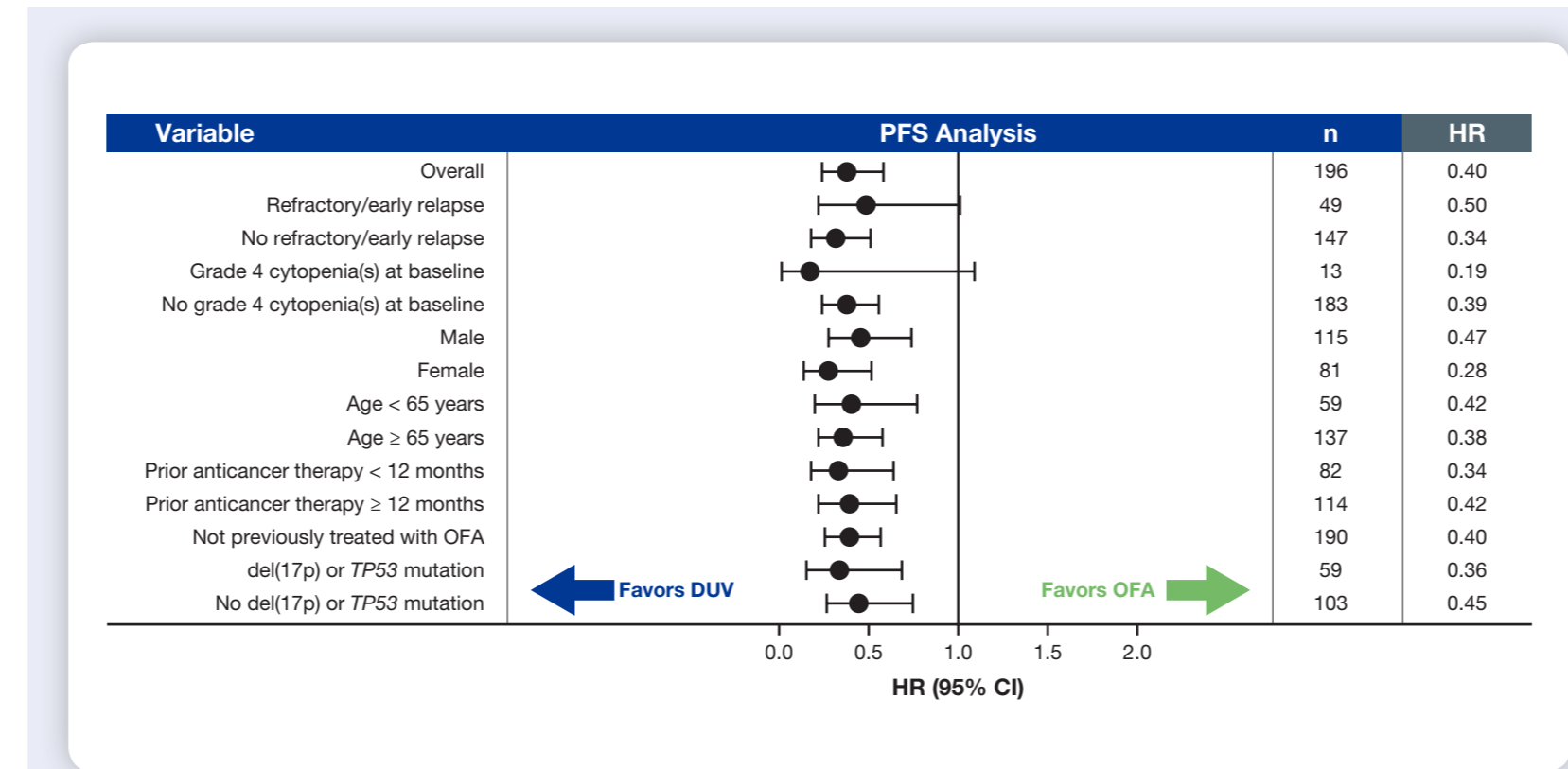
- With a median overall follow-up of 22.4 months, median PFS (mPFS) by blinded IRC review was significantly longer in the DUV arm compared with the OFA arm in patients who had received ≥ 2 prior therapies (16.4 vs 9.1 months; hazard ratio [HR], 0.4 [95% CI, 0.27-0.59]; $P < .0001$) (Figure 3A)
- In this 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)

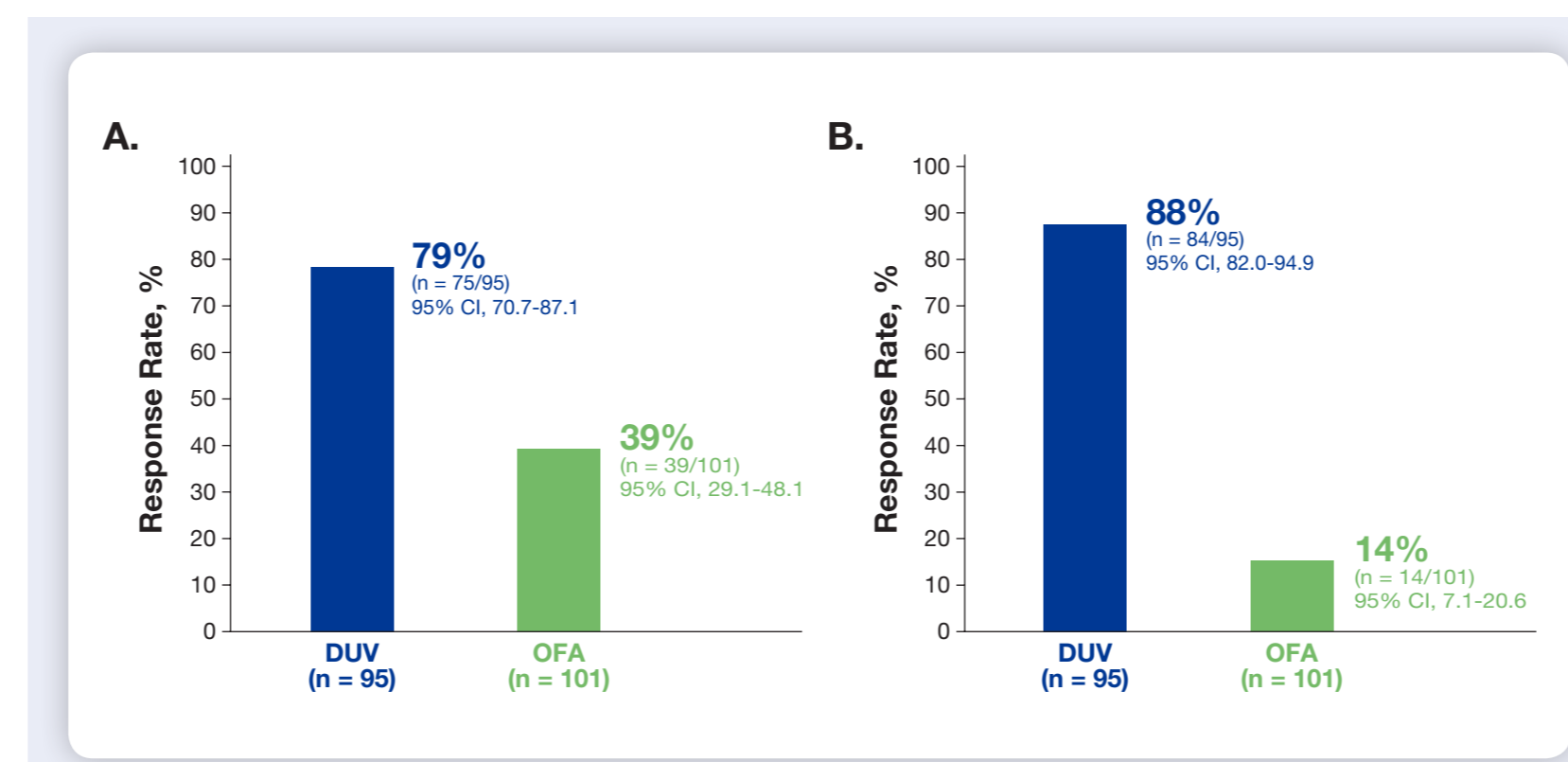
Figure 4. Duvelisib Improved mPFS in High-Risk Patients^a



^aThis analysis was not powered to show statistical significance in PFS across these prespecified subgroups.

- The ORR per IRC response assessment for DUV was also significantly higher compared with OFA (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)

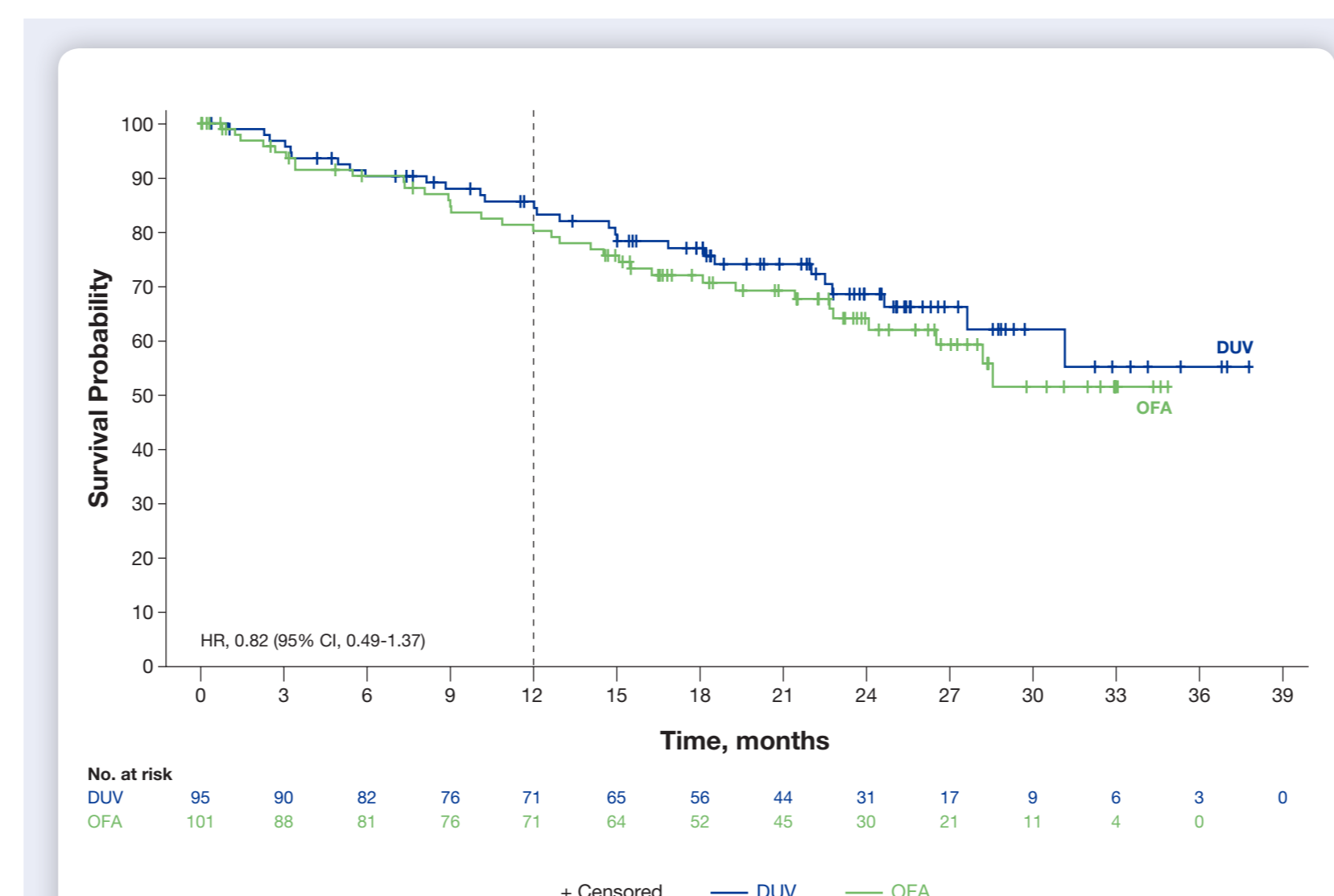
Figure 5. ORR^a and Lymph Node Response Rate^b in Patients Who Had Received ≥ 2 Prior Therapies



^aIncludes complete response, complete response with incomplete count recovery, partial response, and partial response except for lymphocytosis per International Workshop on Chronic Lymphocytic Leukemia criteria. ^bLymph node response was defined as $\geq 50\%$ 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 months¹
- The median duration of exposure to OFA was 5 months¹
- 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	
	Duvelisib 25 mg BID (n = 93)	Ofatumumab (n = 98)	Duvelisib 25 mg BID (n = 93)	Ofatumumab (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 $\geq 50\%$ 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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