original report abstract

DYNAMO: A Phase II Study of Duvelisib (IPI-145) in Patients With Refractory Indolent Non-Hodgkin Lymphoma

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PURPOSE Indolent non-Hodgkin lymphoma (iNHL) remains largely incurable and often requires multiple lines of treatment after becoming refractory to standard therapies. Duvelisib was approved by the Food and Drug Administration for relapsed or refractory (RR) chronic lymphocytic leukemia or small lymphocytic lymphoma (SLL) and RR follicular lymphoma (FL) after two or more prior systemic therapies. On the basis of the activity of duvelisib, a first-in-class oral dual inhibitor of phosphoinositide 3-kinase-δ,-γ, in RR iNHL in a phase I study, the safety and efficacy of duvelisib monotherapy was evaluated in iNHL refractory to rituximab and either chemotherapy or radioimmunotherapy.

PATIENTS AND METHODS Eligible patients had measurable iNHL (FL, SLL, or marginal zone B-cell lymphoma) double refractory to rituximab (monotherapy or in combination) and to either chemotherapy or radioimmunotherapy. All were treated with duvelisib 25 mg orally twice daily in 28-day cycles until progression, unacceptable toxicity, or death. The primary end point was overall response rate (ORR) using the revised International Working Group criteria for malignant lymphoma.

RESULTS This open-label, global phase II trial enrolled 129 patients (median age, 65 years; median of three prior lines of therapy) with an ORR of 47.3% (SLL, 67.9%; FL, 42.2%; MZL, 38.9%). The estimated median duration of response was 10 months, and the estimated median progression-free survival was 9.5 months. The most frequent any-grade treatment-emergent adverse events (TEAEs) were diarrhea (48.8%), nausea (29.5%), neutropenia (28.7%), fatigue (27.9%), and cough (27.1%). Among the 88.4% of patients with at least one grade 3 or greater TEAE, the most common TEAEs were neutropenia (24.8%), diarrhea (14.7%), anemia (14.7%), and thrombocytopenia (11.6%).

CONCLUSION In the DYNAMO study, oral duvelisib monotherapy demonstrated clinically meaningful activity and a manageable safety profile in heavily pretreated, double-refractory iNHL, consistent with previous observations. Duvelisib may provide a new oral treatment option for this patient population of which many are elderly and in need of additional therapies.

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ASSOCIATED CONTENT

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Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the fifth most frequent malignancy in Western countries, with an expected 74,680 patients being diagnosed in the United States in 2018.[1] Indolent NHL (iNHL) constitutes approximately one third of NHLs, with follicular lymphoma (FL), the most common type, accounting for 20% to 30%.[2] Other indolent subtypes include small lymphocytic lymphoma (SLL) and marginal zone B-cell lymphoma (MZL, which includes nodal and splenic marginal zone), which account for approximately 7% and 4% of all NHLs, respectively.[3] The disease course for iNHL is variable, with some patients remaining asymptomatic for extended periods and others requiring immediate intervention.

For more than a decade, combinations of the anti-CD20 monoclonal antibody rituximab with alkylator or purine analog-based chemotherapy regimens (ie, chemoimmunotherapy) have been the cornerstone of frontline and relapsed iNHL therapy.[4-8] With such treatment, median progression-free survival (PFS) and overall survival (OS) for FL are 6 to 8 and 12 to 15 years, respectively. However, the approximately 20% of patients with FL treated with frontline rituximab plus cyclophosphamide, doxorubicin, and prednisone (R-CHOP) who progress within 2 years of initial diagnosis also have a lower 5-year OS rate (50%) than patients without early progression (90%).[9]

Although outcomes are favorable for most patients, the relapsing nature of indolent lymphomas necessitates

serial retreatment, and advanced-stage disease remains incurable, whichnecessitates lifelong management.[10] Despite recent drug approvals, alternative targeted therapies remain the focus of clinical trials that address disease resistance, which reduces options for patients with multiple treatment failures.[11]

Phosphoinositide 3-kinase (PI3K) is a lipid kinase whose catalytic subunit has four isoforms: α, β, γ, and δ. The α- and β-isoforms are widely expressed in many tissues; PI3K-γ and PI3K-δ are preferentially expressed in hematopoietic cells[12,13] and play predominantly nonoverlapping roles in (MZL, which includes nodal and splenic), B-cell survival. Pathways mediated by PI3K-δ and PI3K-γ are involved in cell growth, migration, differentiation, and metabolism, all critical to the pathogenesis and progression of B-cell malignancies.[14,15] PI3K-δ inhibition targets malignant B-cell proliferation and survival through blockade of tumor cell autonomous and tumor microenvironment (TME)–mediated cytokine receptor signaling, whereas PI3K-γ inhibition disrupts the formation of the TME by inhibiting T-cell and macrophage migration and macrophage polarization to a tumor-supporting M2 phenotype.[16-20] The TME is also important in the development and maintenance of hematologic malignancies, including iNHL.[21] Thus, the cooperation of PI3K-γ and PI3K-δ in the interplay between tumor cells and the TME, and in the establishment/maintenance of the TME, makes dual inhibition an attractive therapeutic target.

Duvelisib, an oral dual inhibitor of PI3K-δ and -γ, was approved by the US Food and Drug Administration (FDA) in September 2018 for treatment of relapsed or refractory (RR) chronic lymphocytic leukemia (CLL) or SLL after two or more prior therapies and for RR FL after two or more prior systemic therapies.[22] Approval of 25 mg twice daily was supported by phase I findings that plasma exposure at higher doses did not further increase either response rates or markers of PI3K-δ inhibition; 25 mg twice daily demonstrated clinical activity and an acceptable safety profile in advanced hematologic malignancies in IPI-145-02 (ClinicalTrials.gov identifier: NCT01476657).[23] In that study, the overall response rate (ORR) among 31 patients with RR iNHL treated with duvelisib monotherapy was 58.1%, including six (19.4%) complete responses (CRs).[23,24]

Duvelisib's dual mechanism of PI3K-δ,-γ inhibition may represent both a therapeutic advantage over selective PI3K-δ inhibitors and a new alternative for treating B-cell malignancies. With consideration of the need for effective new therapies for chemoimmunotherapy-refractory iNHL, the therapeutic value of duvelisib monotherapy in this high-risk population became the focus of the Duvelisib in Subjects With Refractory Indolent Non-Hodgkin Lymphoma (DYNAMO) study and duvelisib's FDA approval.

PATIENTS AND METHODS

Study Design and Treatment

DYNAMO was a single-arm, phase II, open-label study of the antitumor activity and safety of oral duvelisib monotherapy in patients with relapsed iNHL refractory to rituximab (ie, no response or disease progression [PD] within 6 months after completion of therapy) and to either chemotherapy or radioimmunotherapy (RIT). The study was conducted at 56 sites across 12 countries in Europe, Canada, and the United States. Institutional review boards and/or ethics committees approved protocols at all sites. Study conduct followed International Conference on Harmonisation Guidelines for Good Clinical Practice, including written informed consent from all patients and rigorous data monitoring.

Oral duvelisib 25 mg twice daily was self-administered continuously in 28-day cycles until PD, unacceptable toxicity, or death. Up to two dose reductions for the same treatment-emergent adverse event (TEAE) were permitted. Prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP), herpes simplex virus (HSV), and herpes zoster virus (HZV) was required.

The primary end point was ORR assessed by an independent review committee (IRC) and defined as a CR or partial response (PR) per revised International Working Group (IWG) criteria.[25] Secondary efficacy end points included duration of response (DOR), PFS, OS, and time to response (TTR).

Patient Eligibility

Patients were 18 years of age or older with histologically confirmed FL, SLL, or MZL (splenic, nodal, and extranodal) and radiologically measurable disease with a lymph node or tumor mass greater than or equal to 1.5 cm in at least one dimension. Patients with grade 3B FL or clinical evidence of transformation to an aggressive lymphoma subtype were excluded. Eligible patients had disease refractory (defined under Study Design and Treatment) to both rituximab (monotherapy or in combination) and either chemotherapy or RIT. At least one prior chemotherapy regimen (with or without rituximab) must have contained an alkylating agent or a purine analog. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 to 2 and adequate renal (serum creatinine less than or equal to two times the upper limit of normal [ULN]) and hepatic function (total bilirubin less than or equal to one and a half times ULN and aminotransferases less than or equal to three times ULN). Key exclusion criteria were prior PI3K or Bruton's tyrosine kinase inhibitor therapy; prior, current, or chronic viral infections (HIV, hepatitis B virus, or hepatitis C virus); ongoing treatment with long-term immunosuppressants; and inability to receive PJP, HSV, or HZV prophylaxis. There were no restrictions with regard to cytopenias.

Study Assessments

Response was assessed at cycles 3, 5, 7, and 10 and every four cycles thereafter until 2 years from the start of study treatment. Response was based on revised IWG response criteria for NHL using consistent imaging: computed tomography, positron emission tomography/computed tomography, or magnetic resonance imaging.[25]

Safety assessments included physical examinations, electrocardiograms, and adverse event (AE) and clinical laboratory monitoring. Severity of TEAEs and laboratory abnormalities was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).[26] An independent data monitoring committee reviewed all safety information. After treatment discontinuation, survival data were collected every 6 months for up to 3 years from treatment initiation.

Statistical Methods

Using a group sequential design with one interim analysis, 120 patients provided more than 90% power to test the hypothesis of an ORR greater than or equal to 45% against the null hypothesis of an ORR less than or equal to 30% at a one-sided overall significance level of .025. A *P* value and a two-sided 95% exact CI for ORR were calculated using the binomial distribution.

Best tumor response (CR, PR, stable disease, or PD) was assessed for each patient. PFS was the time from first duvelisib dose to first documentation of PD or any-cause death. DOR was the time from first documentation of best response (CR or PR) to first documentation of PD or any-cause death. OS was the time from first dose to date of death, and TTR was the time from first dose to first documentation of response. The lymph node response rate (greater than or equal to 50% reduction in the sum of the product of the longest perpendicular dimensions of the target lesion) also was calculated, and time-to-event end points were calculated using the Kaplan-Meier method.

A formal futility interim analysis was conducted approximately 4 months after 30 patients initiated treatment, and the independent data monitoring committee recommended study continuation. The final analysis was performed after the last enrolled patient completed 6 months of therapy or experienced PD; these data, with 2 additional years of follow-up, are presented here, with an analysis cutoff date of May 2018.

RESULTS

Patient Characteristics

From June 2013 to October 2015, 129 patients were enrolled and received at least one dose of duvelisib. Histologic subtypes included FL (83 patients), SLL (28 patients), and MZL (18 patients). Patient characteristics are listed in Table 1.

Most patients (68.2%) were male, 89.9% were white, and the median age was 65 years (range, 30 to 90 years). Most patients (85%) had advanced-stage (III or IV) iNHL, and 67% had elevated lactate dehydrogenase. Patients had an Eastern Cooperative Oncology Group performance status of 1 (94.6%) or 2 (5.4%) at enrollment. Among patients with FL, 87% were intermediate or high risk per the Follicular Lymphoma International Prognostic Index.

Patients had received a median of three (range, one to 18) prior systemic anticancer regimens, and 52 patients (40%) received four or more prior regimens. Nearly two thirds of patients had prior bendamustine (82 patients [64%]). Common prior regimens were rituximab plus bendamustine (64 patients [50%]), R-CHOP (48 patients [37%]), and rituximab plus cyclophosphamide and prednisone (38 patients [30%]). Six patients (5%) had prior autologous stem-cell transplantation.

Nearly all patients had disease refractory to rituximab either alone or in combination (127 patients [98%]), 119 patients (92%) had disease refractory to an alkylating agent or purine analog, and 117 patients (91%) had disease refractory to combination therapy with rituximab and an alkylating agent. Nearly all patients had disease refractory to the most recent regimen (124 patients [96%]), and 95 patients (77%) had disease refractory to two or more regimens. Among the 39 patients with FL who received an R-CHOP (or equivalent) chemoimmunotherapy regimen as first therapy, 30 (77%) experienced early relapse (no response during treatment or PD or time to next treatment less than 2 years). No notable differences in demographics were observed across lymphoma subtypes.

Disposition

Of 171 screened patients, 42 were excluded as a result of screen failures, yielding 129 in the full analysis set. As of the May 2018 data cutoff, five patients were still on treatment. Of the 124 who discontinued treatment, approximately one half (66 patients [51.2%]) did so because of PD; one fourth (31 patients [24%]) because of AEs; and the remaining one fourth because of investigator decision, death, patient withdrawal, or noncompliance. As of May 2018, 33 patients (25.6%) remained in the survival follow-up (Appendix Fig A1, online only).

Efficacy

Median follow-up time (from first dose until last contact date or death) was 32.1 months. Table 2 lists the primary and secondary efficacy end points on the basis of IRC and investigator response assessment by disease subtype.

The ORR per IRC-assessed response was 47% (95% CI, 38% to 56%), which included almost exclusively PRs (59 *v* two CRs). The study met the primary end point ($P < .001$ against the null hypothesis that ORR was less than or equal to 30% per IRC). ORR per investigator response assessment was 60% (Table 2), with differences per IRC between

TABLE 1. Patient Demographics and Disease Characteristics

Characteristic	No. (%)
No. of patients	129
Age, years	
Median	65.0
Range	30-90
Race	
White	116 (89.9)
Black	6 (4.7)
Asian	1 (0.8)
American Indian or Alaskan Native	1 (0.8)
Other	1 (0.8)
Unknown/Missing	4 (3.1)
Sex	
Male	88 (68.2)
Female	41 (31.8)
Time since NHL diagnosis, months	
Median	54.15
Range	3.9-324.0
Stage at entry	
I-II	19 (14.7)
III-IV	109 (84.5)
Missing	1 (0.8)
ECOG performance status	
0-1	122 (94.6)
2	7 (5.4)
Histologic subtype	
Small lymphocytic	28 (21.7)
Marginal zone	18 (14.0)
Extranodal	9 (6.9)
Splenic	5 (3.8)
Nodal	4 (3.1)
Follicular	83 (64.3)
FLIPI risk category (score)	
Low (0-1)	11 (13.3)
Intermediate (2)	17 (20.5)
High (> 2)	54 (65.1)
Missing	1 (1.2)
Elevated LDH at baseline	
Yes	86 (66.7)
No	42 (32.6)
Missing	1 (0.8)
No. of prior anticancer regimens	
Median	3.0
Range	1-18
Time since completion of last therapy, months	
Median	3.5
Range	0-121
Prior therapy	
Rituximab	129 (100)
Alkylating agent/purine analog	129 (100)
Alkylating agent	127 (98.4)
Combination of rituximab and alkylating agent	122 (94.6)
Bendamustine	82 (63.6)
Anthracycline	78 (60.5)
Rituximab + bendamustine	64 (49.6)
R-CHOP	48 (37.2)
Time since completion of last rituximab-containing therapy, months	
Median	5.9
Range	1-121
Time since completion of last alkylating agent/purine analog therapy, months	
Median	7.7
Range	1-141
Prior therapy to which the disease was refractory	
Rituximab	127 (98.4)
Alkylating agent/purine analog	119 (92.2)
Alkylating agent	117 (90.7)
Bendamustine	66 (51.2)
Anthracycline	51 (39.5)
Combination of rituximab and alkylating agent	117 (90.7)
Rituximab + bendamustine	55 (42.6)
R-CHOP	36 (27.9)
R-CVP	34 (26.4)
Disease refractory to most recent regimen	124 (96.1)
Disease refractory to two or more regimens	99 (76.7)
Bulky disease* at baseline	51 (39.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; NHL, non-Hodgkin's lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone.

*Bulky disease is the longest diameter of nodal target lesion greater than or equal to 5 cm.

some subgroups (Fig 1). For example, ORR was numerically higher in US patients (46 patients; ORR, 59%) than in non-US patients (83 patients; ORR, 41%). ORR was lower in patients with prior bendamustine therapy (82 patients; ORR, 39%) than in those without prior bendamustine therapy (47 patients; ORR, 62%).

TABLE 2. Summary of Efficacy in Full Analysis Set

Efficacy	Response by IRC, No. (%)	Response by Investigator, No. (%)
All patients (N = 129)		
ORR (CR + PR)	61 (47.3)	77 (59.7)
95% Exact binomial CI	38.4 to 56.3	50.7 to 68.2
Best response		
CR	2 (1.6)	4 (3.1)
PR	59 (45.7)	73 (56.6)
SD	42 (32.6)	38 (29.5)
PD	18 (14.0)	8 (6.2)
Unknown	7 (5.4)	6 (4.7)
No evidence of disease*	1 (0.8)	0
Median DOR by IWG, months	10.0	10.0
95% CI	6.3 to 10.5	6.5 to 12.5
Median PFS, months	9.5	10.0
95% CI	8.1 to 11.8	8.3 to 11.7
Median OS, months	28.9	—
95% CI	21.4 to NE	—
Median TTR, months	1.87	1.87
Range	1.4-11.7	1.0-12.3
Follicular lymphoma (n = 83)		
ORR (CR + PR)	35 (42.2)	44 (53.0)
95% Exact binomial CI	31.4 to 53.5	41.7 to 64.1
Best response		
CR	1 (1.2)	2 (2.4)
PR	34 (41.0)	42 (50.6)
SD	29 (34.9)	28 (33.7)
PD	14 (16.9)	7 (8.4)
Unknown	5 (6.0)	4 (4.8)
Small lymphocytic lymphoma (n = 28)		
ORR (CR + PR)	19 (67.9)	24 (85.7)
95% Exact binomial CI	47.6 to 84.1	67.3 to 96.0
Best response		
CR	0	1 (3.6)
PR	19 (67.9)	23 (82.1)
SD	4 (14.3)	3 (10.7)
PD	3 (10.7)	0
Unknown	1 (3.6)	1 (3.6)
No evidence of disease*	1 (3.6)	0
Marginal zone B-cell lymphoma (n = 18)		
ORR (CR + PR)	7 (38.9)	9 (50.0)
95% Exact binomial CI	17.3 to 64.3	26.0 to 74.0
Best response		
CR	1 (5.6)	1 (5.6)
PR	6 (33.3)	8 (44.4)
SD	9 (50.0)	7 (38.9)
PD	1 (5.6)	1 (5.6)
Unknown	1 (5.6)	1 (5.6)

Abbreviations: CR, complete response; DOR, duration of response; IRC, independent review committee; IWG, International Working Group; NE, not estimable; ORR, overall response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response.

*No evidence of disease at baseline and no postbaseline assessment of PD in one patient with a single extranodal target lesion (nasopharynx) evaluated as CR by the investigator.

ORR per IRC was 42%, 68%, and 39% in FL, SLL, and MZL subtypes, respectively (Table 2). Overall, 99 (83%) of 119 patients experienced reductions in lymph node tumor burden (Fig 2).

Responses were rapid and durable. Median TTR was 1.87 months (range, 1.4 to 11.7 months), with 59% and 84% of patients responding by 2 and 4 months, respectively. Median DOR was 10 months (95% CI, 6.5 to 10.5 months; Fig 3A), with estimated probabilities of remaining in response at 6 and 12 months of 69% and 35%. Median PFS was 9.5 months (95% CI, 8.1 to 11.8 months; Fig 3B), with the probability of surviving and being progression free at 6 months estimated at 62%. Median OS was 28.9 months (95% CI, 21.4 months to not estimable; Fig 3C), and OS at 1 year was estimated at 77% (Table 2).

Safety

Median duration of treatment exposure was 6.7 months (range, 0.4 to 45.5 months). Most patients started six or more cycles of duvelisib (77 patients [59.7%]), and 42 patients (32.6%) started 12 or more cycles. TEAEs reported in more than 10% of patients are listed in Table 3. The most frequent any-grade AEs were diarrhea (48.8%), nausea (29.5%), neutropenia (28.7%), fatigue (27.9%), and cough (27.1%). The most frequent grade 3 or greater AEs were neutropenia (24.8%), diarrhea (14.7%), anemia (14.7%), and thrombocytopenia (11.6%). Colitis and pneumonitis were reported in 10 patients (7.8%) and six patients (4.7%), respectively. Three patients experienced the following serious opportunistic infections and recovered: bronchopulmonary aspergillosis, cytomegaloviral pneumonia, and PJP in a patient prescribed sulfamethoxazole and trimethoprim prophylaxis on day 1. The most frequent grade 3 or greater nonhematologic laboratory TEAEs were elevated levels of serum lipase (7%), ALT (5.4%), and AST (3.1%).

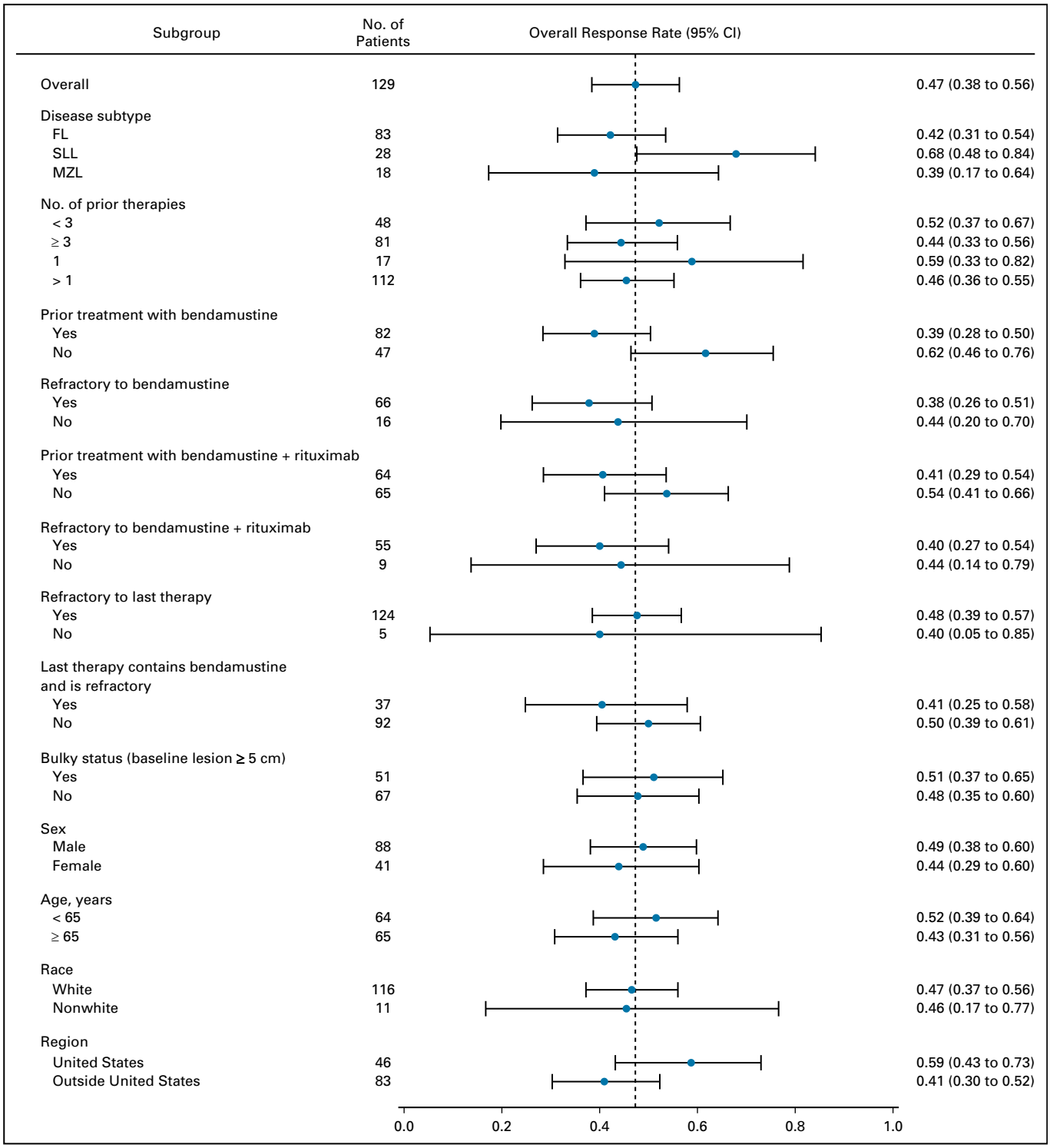

FIG 1. Subgroup analysis of overall response rate (ORR) per independent review committee (full analysis set). FL, follicular lymphoma; MZL, marginal zone B-cell lymphoma; SLL, small lymphocytic lymphoma.

Forty patients (31%) discontinued duvelisib as a result of a TEAE. The only TEAEs that led to discontinuation in more than one patient were pneumonitis (four patients [3.1%]); pneumonia, colitis, and diarrhea (three patients [2.3%] each); and generalized rash (two patients [1.6%]). TEAEs were managed with dose interruption or reduction in 85 patients (66%). Doses were reduced in 25 patients (19.4%), four (3.1%) of whom subsequently increased their dose as allowed per protocol. Dose reductions occurred most commonly with diarrhea (nine

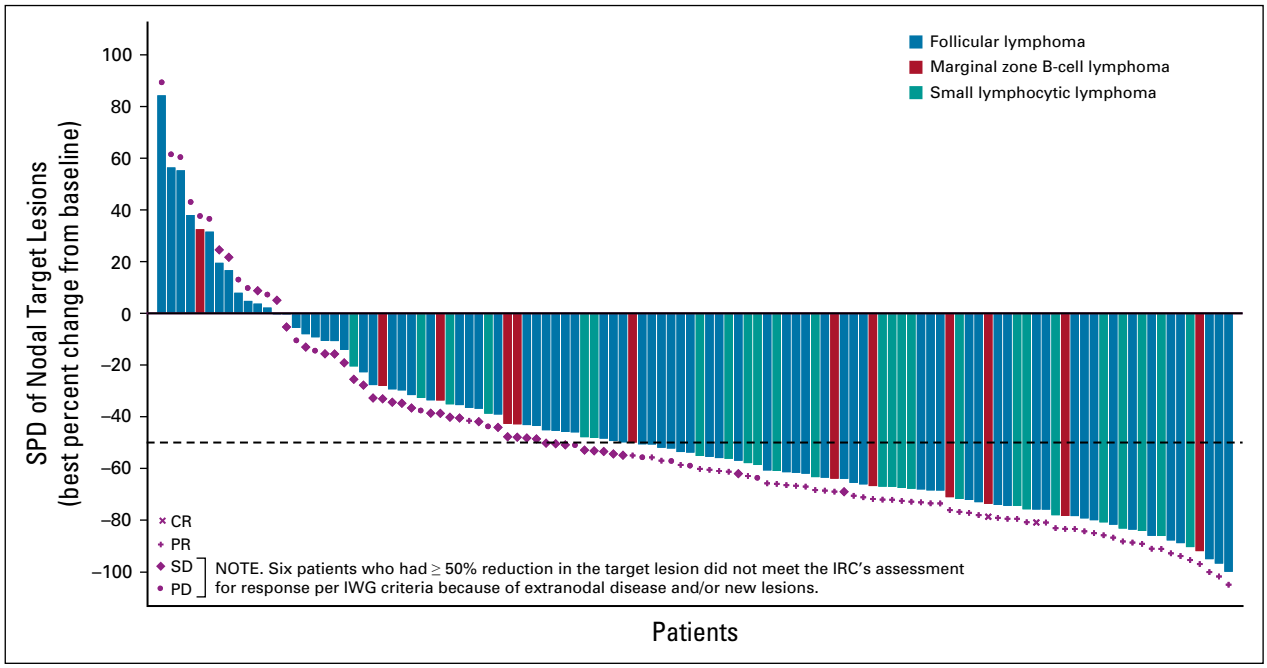

FIG 2. Best percent change in the sum of the product of the longest perpendicular dimensions (SPD) of nodal target lesions per independent review committee (IRC; full analysis set). CR, complete response; IWG, International Working Group; PD, disease progression; PR, partial response; SD, stable disease.

patients [7.0%]) followed by febrile neutropenia and lipase increases (three patients [2.3%] each). No clinically meaningful safety differences were observed among lymphoma subtypes (FL, SLL, and MZL).

Seventeen deaths (13.2%) occurred on treatment (within 30 days of the last dose of duvelisib). Nine (7%) were attributed to PD. Of the remaining eight, three (2.3%) were deemed unrelated to treatment: a 61-year-old female with cardiac and respiratory, thoracic, and mediastinal disorders died as a result of cardiopulmonary arrest and respiratory failure; a 79-year-old patient with ongoing cardiopulmonary disease died as a result of cardiac failure; and a 62-year-old patient with diabetes and cardiopulmonary and thrombotic disease died as a result of a scrotal phlegmon. Five deaths (3.9%) were considered treatment related: a 90-year-old man developed fatal pancolitis, an 82-year-old man experienced a fatal suspected viral infection after approximately 8 months of treatment, and an 83-year-old man with baseline grade 4 neutropenia and thrombocytopenia experienced fatal septic shock after only 21 days of treatment. The remaining two deaths were from severe skin toxicity as a result of drug reaction with eosinophilia and systemic symptoms syndrome and toxic epidermal necrolysis. However, both events were confounded by concomitant administration of medications associated with severe and fatal drug reaction with eosinophilia and systemic symptoms syndrome and toxic epidermal necrolysis. One additional treatment-related death as a result of pneumonia occurred approximately 36 days after the last dose of duvelisib.

DISCUSSION

Although most patients with iNHL initially respond to chemoimmunotherapy and experience long periods of remission, virtually all will eventually progress or develop recurrent disease.[27,28] Despite several approved options for relapsed iNHL, cumulative toxicities from multiple therapies and resistance or transformation to high-grade or aggressive lymphomas remain major challenges.[29,30] With few patients eligible for potentially curative allogeneic stem-cell transplantation, new therapies are needed.

The DYNAMO study evaluated the safety and efficacy of oral duvelisib monotherapy in patients whose disease had become refractory to standard therapies and, therefore, represent the greatest unmet need. Among a heavily pretreated and high-risk iNHL study population, the ORR was 47% (two CRs, 59 PRs), and lymph node disease was reduced in 83% of patients. Responses generally occurred within the first 2 months of therapy and were durable (median DOR, 10 months).

The safety profile was similar across lymphoma subtypes and consistent with that observed in the phase I IPI-145-02 study.[23,24] AEs were generally low grade and manageable with protocol-specified risk mitigation measures, including dose reductions/interruptions (70% of patients). Similar to observations with other PI3K inhibitor and immuno-oncology therapies,[30,31] immune-related toxicities,

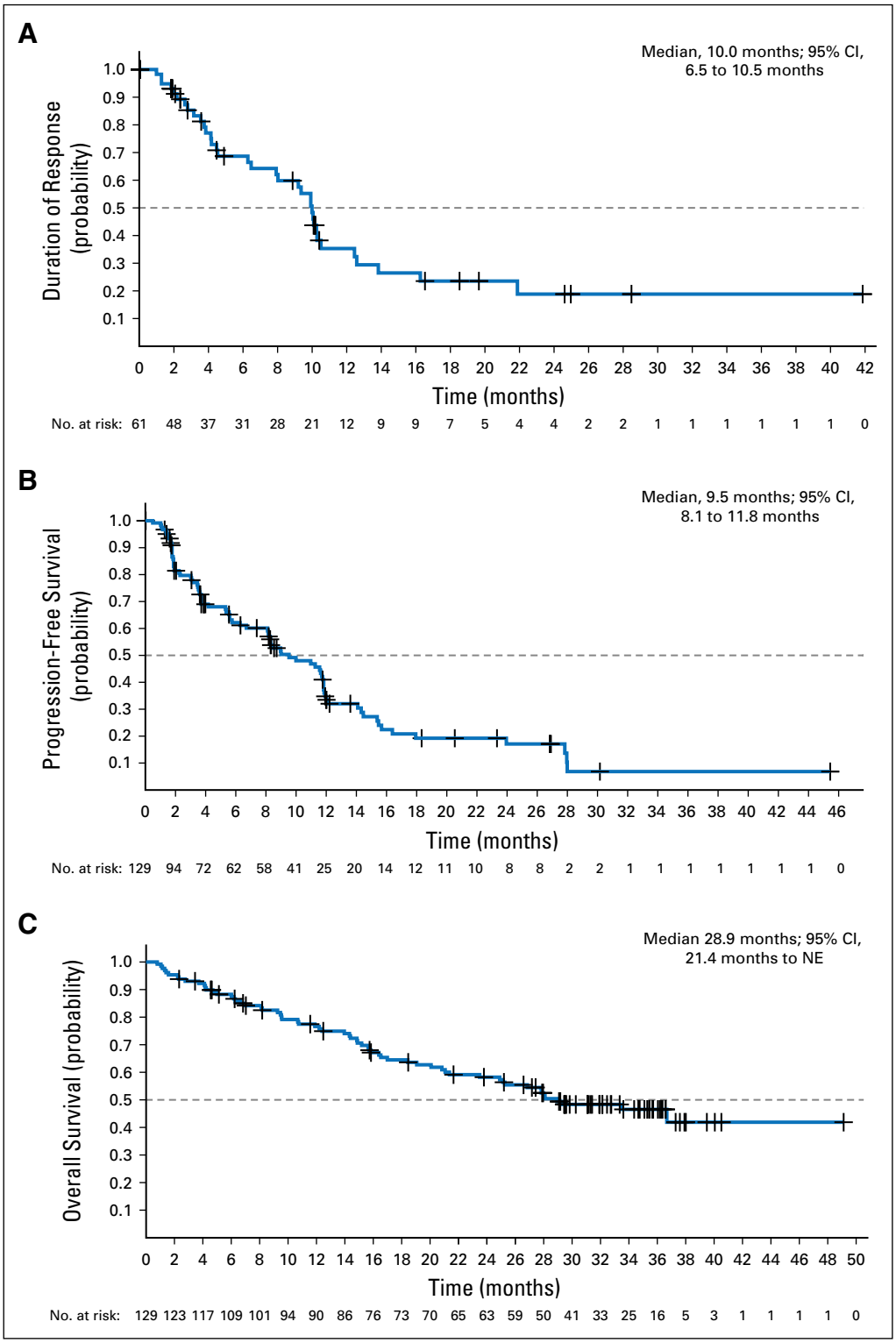

FIG 3. (A) Duration of response per independent review committee (IRC) assessment (full analysis set). (B) Progression-free survival per IRC assessment (full analysis set). (C) Overall survival (full analysis set). NE, not estimable.

including pneumonitis, transaminase elevations, colitis, and rash, were observed, requiring treatment discontinuation in 31% of patients. Prophylaxis for PJP, HSV, and HZV infections was required per protocol. Serious opportunistic infections occurred in less than 5% of patients and were not associated with fatal outcomes.

The efficacy demonstrated by duvelisib monotherapy is clinically meaningful, considering that nearly all patients had disease refractory to prior rituximab and chemotherapy, including the most recent prior therapy. Most patients (approximately 75%) experienced early relapse (no response on treatment or PD or time to next treatment less

TABLE 3. All-Grade TEAEs (> 10%) or Grade 3 or Greater TEAEs (> 5%) in the Full Analysis Set

TEAE	All Grades, No. (%)	Grade ≥ 3, No. (%)
No. of patients	129	129
Patients with at least one TEAE	128 (99.2)	114 (88.4)
Diarrhea	63 (48.8)	19 (14.7)
Nausea	38 (29.5)	2 (1.6)
Neutropenia	37 (28.7)	32 (24.8)
Fatigue	36 (27.9)	6 (4.7)
Cough	35 (27.1)	0
Anemia	34 (26.4)	19 (14.7)
Pyrexia	32 (24.8)	0
Rash	24 (18.6)	6 (4.7)
Thrombocytopenia	24 (18.6)	15 (11.6)
Vomiting	24 (18.6)	5 (3.9)
Decreased appetite	19 (14.7)	1 (0.8)
Headache	20 (15.5)	0
Edema peripheral	22 (17.1)	3 (2.3)
ALT increased	18 (14.0)	7 (5.4)
Back pain	17 (13.2)	1 (0.8)
Arthralgia	19 (14.7)	0
Abdominal pain	19 (14.7)	2 (1.6)
Hypokalemia	17 (13.2)	4 (3.1)
Constipation	15 (11.6)	0
Asthenia	15 (11.6)	3 (2.3)
AST increased	13 (10.1)	4 (3.1)
Night sweats	13 (10.1)	0
Febrile neutropenia	12 (9.3)	12 (9.3)
Lipase increased	12 (9.3)	9 (7.0)
Pneumonia	10 (7.8)	7 (5.4)
Colitis	10 (7.8)	7 (5.4)

Abbreviation: TEAE, treatment-emergent adverse event.

than 2 years) after their first treatment regimen. Among patients with FL, 27 (33%) experienced early progression (less than 2 years after initial diagnosis) after frontline R-CHOP (or equivalent) therapy and represent a population with substantially poorer OS.[9] This extent of treatment refractoriness and the prevalence of other high-risk clinical features (eg, high Follicular Lymphoma International Prognostic Index risk and elevated lactate dehydrogenase) distinguish a more difficult-to-treat study population. An examination of efficacy in the subgroup of patients with FL who received R-CHOP (or the equivalent) as their first therapy and experienced early relapse (as defined in Discussion) showed an ORR of 33%, median DOR of 12.6 months, and median PFS of 8.2 months.

With the recent FDA approval of duvelisib, there are now several different treatment options for patients who have received two or more prior therapies: in addition to duvelisib, the PI3K inhibitors copanlisib (intravenous inhibitor of PI3K-α,-δ) and idelalisib (oral inhibitor of PI3K-δ). Although these three new treatment options are important for both physicians and patients, evaluating them side by side for the treatment of FL is challenging because cross-trial comparisons are undermined by variability in patient selection and treatments. For instance, in the phase II CHRONOS-1 study, copanlisib demonstrated an ORR of 59%. Although prior rituximab and alkylator therapy was required, only 56% and 42% of patients had disease that was refractory to rituximab and an alkylating agent, respectively.[32] In addition, the AE profile of copanlisib, specifically including hyperglycemic effects mediated through PI3K-α isoform inhibition[33,34] and hypertension, merits consideration before use in an elderly patient population with a high prevalence of these comorbidities. In a phase II trial in patients with disease refractory to both rituximab and chemotherapy, idelalisib demonstrated an ORR of 57%.[35] The AE profile was similar to duvelisib, except for a higher incidence of grade 3 or higher aminotransferase increase with idelalisib (13% *v* 5.4%). Although many new therapies are being investigated for patients with RR indolent lymphoma (lenalidomide and rituximab, cellular therapies, bispecific antibodies, and other small molecules), treatment options beyond the PI3K inhibitors are still limited. RIT rarely is used, and one of the two FDA-approved therapies was withdrawn from the market for lack of use. The cumulative toxicities and decreasing efficacy of repeating cytotoxic chemotherapy, even combined with a different CD20 antibody like obinutuzumab, does not make this an attractive choice either.

The combination of obinutuzumab and bendamustine was recently approved for patients with FL who relapsed after or whose disease proved refractory to a rituximab-containing regimen on the basis of the results of the GADOLIN (Efficacy and Safety of Bendamustine Compared With Bendamustine + Obinutuzumab [GA101] in Rituximab-Refractory, Indolent Non-Hodgkin Lymphoma) study.[36] Given that the bendamustine and rituximab regimen is increasingly used as first-line treatment of FL in the United States, duvelisib monotherapy may offer an alternative for the considerable number of patients whose disease is refractory to bendamustine or who are unable to tolerate bendamustine. Patients previously treated with bendamustine had an ORR of 39% per IRC. Although this was nominally lower than what was seen in patients not previously exposed to bendamustine, it nevertheless suggests that duvelisib has clinical activity for a population not appropriate for treatment with bendamustine therapy.

Despite recent therapeutic advances, iNHL remains largely incurable, with treatment resistance and cumulative toxicity limiting options for many patients. Older patients, whose comorbidities may preclude aggressive

treatment and for whom dependence on hospitals and clinic visits for infusional therapies represents a significant challenge, are likely to benefit greatly from oral monotherapy. The efficacy and consistent, manageable safety profile of duvelisib demonstrated in the DYNAMO study support its potential as a novel therapy for patients with refractory iNHL who currently lack sufficient treatment options.

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REFERENCES

1. National Cancer Institute SEER Program: Cancer Stat Facts: Non-Hodgkin Lymphoma. https://seer.cancer.gov/statfacts/html/nhl.html
2. Bello C, Zhang L, Naghashpour M: Follicular lymphoma: Current management and future directions. Cancer Contr 19:187-195, 2012
3. Swerdlow SH, Campo E, Harris NL, et al: WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. International Agency for Research on Cancer, Sep 18, 2017. pp. 216,223,263
4. Schulz H, Bohlius JF, Trelle S, et al: Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: A systematic review and meta-analysis. J Natl Cancer Inst 99:706-714, 2007
5. Hiddemann W, Kneba M, Dreyling M, et al: Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 106:3725-3732, 2005
6. Marcus R, Imrie K, Solal-Celigny P, et al: Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol 26:4579-4586, 2008
7. Forstpointner R, Dreyling M, Repp R, et al: The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 104:3064-3071, 2004
8. Herold M, Haas A, Srock S, et al: Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: An East German Study Group Hematology and Oncology Study. J Clin Oncol 25:1986-1992, 2007
9. Casulo C, Byrtek M, Dawson KL, et al: Early relapse of follicular lymphoma after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone defines patients at high risk for death: An analysis from the National LymphoCare Study. J Clin Oncol 33:2516-2522, 2015

10. Sehn LH: Introduction to a review series: The paradox of indolent B-cell lymphoma. Blood 127:2045-2046, 2016
11. MacDonald D, Prica A, Assouline S, et al: Emerging therapies for the treatment of relapsed or refractory follicular lymphoma. Curr Oncol 23:407-417, 2016
12. Vanhaesebroeck B, Guillermet-Guibert J, Graupera M, et al: The emerging mechanisms of isoform-specific PI3K signalling. Nat Rev Mol Cell Biol 11:329-341, 2010
13. Okkenhaug K, Vanhaesebroeck B: PI3K in lymphocyte development, differentiation and activation. Nat Rev Immunol 3:317-330, 2003
14. Fruman DA, Rommel C: PI3Kδ inhibitors in cancer: Rationale and serendipity merge in the clinic. Cancer Discov 1:562-572, 2011
15. Courtney KD, Corcoran RB, Engelman JA: The PI3K pathway as drug target in human cancer. J Clin Oncol 28:1075-1083, 2010
16. Peluso M, Faia K, Winkler D, et al: Duvelisib (IPI-145) inhibits malignant B-cell proliferation and disrupts signaling from the tumor microenvironment through mechanisms that are dependent on PI3K-δ and PI3K-γ. Blood 124:328, 2014
17. Gyori D, Chessa T, Hawkins PT, et al: Class (I) phosphoinositide 3-kinases in the tumor microenvironment. Cancers (Basel) 9:24, 2017
18. Horwitz SM, Koch R, Porcu R, et al: Activity of the PI3K-δ,γ inhibitor duvelisib in a phase 1 trial and preclinical models of T-cell lymphoma. Blood 131:888-898, 2018
19. Burger JA, Gribben JG: The microenvironment in chronic lymphocytic leukemia (CLL) and other B cell malignancies: Insight into disease biology and new targeted therapies. Semin Cancer Biol 24:71-81, 2014
20. Chiu H, Mallya S, Nguyen P, et al: The selective phosphoinoside-3-kinase p110δ inhibitor IPI-3063 potently suppresses B cell survival, proliferation, and differentiation. Front Immunol 8:747, 2017
21. Burger JA, Gribben JG: The microenvironment in chronic lymphocytic leukemia (CLL) and other B cell malignancies: Insight into disease biology and new targeted therapies. Semin Cancer Biol 24:71-81, 2014
22. Food and Drug Administration: COPIKTRA prescribing information, 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211155s000lbl.pdf
23. Flinn IW, O'Brien S, Kahl B, et al: Duvelisib, a novel oral dual inhibitor of PI3K-δ,γ, is clinically active in advanced hematologic malignancies. Blood 131: 877-887, 2018
24. Flinn IW, Patel M, Oki Y, et al: Duvelisib, an oral dual PI3K-δ, γ inhibitor, shows clinical activity in indolent non-Hodgkin lymphoma in a phase 1 study. Am J Hematol 93:1311-1317, 2018
25. Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. J Clin Oncol 25:579-586, 2007
26. National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, 2009. https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
27. Hitz F, Ketterer N, Lohri A, et al: Diagnosis and treatment of follicular lymphoma. Swiss Med Wkly 141:w13247, 2011
28. Cheson BD: Current approaches to therapy for indolent non-Hodgkin's lymphomas. Oncology (Williston Park) 12:25-34, 1998 (suppl 8)
29. Federico M, Vitolo U, Zinzani PL, et al: Prognosis of follicular lymphoma: A predictive model based on a retrospective analysis of 987 cases. Intergruppo Italiano Linfomi. Blood 95:783-789, 2000
30. Coutré SE, Barrientos JC, Brown JR, et al: Management of adverse events associated with idelalisib treatment: Expert panel opinion. Leuk Lymphoma 56: 2779-2786, 2015
31. Naidoo J, Page DB, Li BT, et al: Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 26:2375-2391, 2015
32. Dreyling M, Santoro A, Mollica L, et al: Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. J Clin Oncol 35: 3898-3905, 2017
33. Greenwell IB, Ip A, Cohen JB: PI3K inhibitors: Understanding toxicity mechanisms and management. Oncology (Williston Park) 31:821-828, 2017
34. Patnaik A, Appleman LJ, Tolcher AW, et al: First-in-human phase I study of copanlisib (BAY 80-6946), an intravenous pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-Hodgkin's lymphomas. Ann Oncol 27:1928-1940, 2016
35. Gopal AK, Kahl BS, de Vos S, et al: PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med 370:1008-1018, 2014
36. Sehn LH, Chua N, Mayer J, et al: Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): A randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol 17:1081-1093, 2016

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DYNAMO: A Phase II Study of Duvelisib (IPI-145) in Patients With Refractory Indolent Non-Hodgkin Lymphoma

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APPENDIX

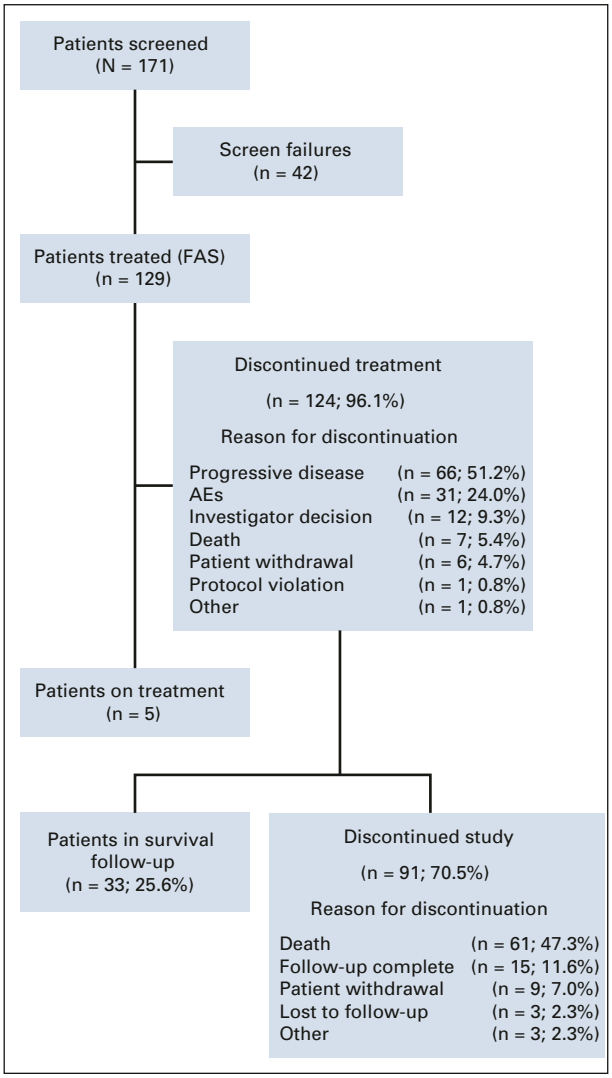

FIG A1. Overall patient distribution. Number of screen failures was derived from interactive voice response system. AE, adverse event; FAS, full analysis set.