**DYNAMO: A Phase 2 Study of Duvelisib (IPI-145) in Patients with Refractory Indolent Non-Hodgkin Lymphoma**

Ian W Flinn,1,2 CB Miller,3 KM Ardeshna,4 S Tetreault,5 SE Assouline,6 J Mayer,7 M Merli,8 SD Lunin,5 AR Pettitt,9 Z Nagy,10 O Tournilhac,11 KE Abou-Nassar,12 M Crump,13 ED Jacobsen,14 S de Vos,15 VM Kelly,16 W Shi,16 L Steelman,16 N Le,17 ND Wagner-Johnston,18 PL Zinzani,19

1 Sarah Cannon Research Institute, Nashville, TN, USA

2 Tennessee Oncology, Nashville, TN, USA

3 Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, The Johns Hopkins Medical Institutions, Baltimore, MD, USA

4 Lymphoma Service, Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK

5 Florida Cancer Specialists, Tallahassee, Florida, USA

6 Segal Cancer Center, Lady Davis Institute, Jewish General Hospital, McGill University, Montreal, QC, Canada

7 Interni hematologicka a onkologicka klinika-FN Brno, Czech Republic

8 Ospedale Di Circolo e Fondazione Macchi U.O. Ematologia, Varese, Italy

9 University of Liverpool, UK

10  Semmelweis Egyetem, I. sz. Belgyogyaszati Klinika, Budapest, Hungary

11 CHU Estaing - Service d'hématologie, Clermont-Ferrand, France

12 Centre intégré de santé et de services sociaux de l'Outaouais, Canada

13 Princess Margaret Cancer Center, Toronto, Canada

14 Dana-Farber Cancer Institute, Boston, Massachusetts, USA

15 Ronald Reagan UCLA Medical Center, Los Angeles, USA

16 Infinity Pharmaceuticals, Inc., Cambridge, MA, USA

17 Verastem Oncology, Inc., Needham, MA, USA

18 Siteman Cancer Center, Washington University, St Louis, USA

19 Institute of Hematology Serágnoli, University of Bologna, Bologna, Italy

Infinity Pharmaceuticals and Verastem Oncology provided financial support.

Corresponding author: Ian Flinn, Sarah Cannon Research Institute, 250 25th Ave North, Nashville, TN 37203; Phone: +1-615-329-7274; Fax: +1-615-986-0029; e-mail: [iflinn@tnonc.com](mailto:iflinn@tnonc.com)

**Running head**: Phase 2 study of oral duvelisib in refractory iNHL

* Notes: NCT01882803 (<https://clinicaltrials.gov/show/NCT01882803)>.
* The data upon which this study is based was presented at the 2016 meeting of the American Society of Hematology meeting in San Diego, CA, USA.
* Dr. Flinn has received funding/grant support from Acerta Pharma, Agios Pharmaceuticals, BeiGene, Celgene, Constellation Pharmaceuticals, Curis Inc, Forma Therapeutics, Forty Seven Inc., Genentech, Gilead Sciences, Incyte Corporation, Infinity Pharmaceuticals, Janssen Pharmaceutical, Kite Pharma, Merck, Pharmacyclics, Portola Pharmaceuticals, Seattle Genetics, Takeda Pharmaceuticals, TG Therapeutics, Inc., Trillium Therapeutics, Inc., and Verastem Oncology, Inc. Dr. V.M. Kelly is a former employee of Infinity Pharmaceuticals, Inc. and currently a consultant for Verastem Oncology, Inc.

**ABSTRACT**

**PURPOSE:**

Indolent NHL (iNHL) remains largely incurable, often requiring multiple lines of treatment after becoming refractory to standard therapies. Duvelisib was FDA approved for relapsed or refractory (RR) CLL or SLL and RR FL after ≥2 prior systemic therapies. Based on the activity of duvelisib, a first-in-class oral dual inhibitor of PI3K-,-, in RR iNHL in a Phase 1 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 MZL) 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 endpoint was ORR using the revised IWG criteria for malignant lymphoma.

**RESULTS:**

This open-label, global Phase 2 trial enrolled 129 patients (median age 65; median 3 prior lines of therapy), with overall observed ORR of 47.3% (SLL: 67.9%; FL: 42.2%; MZL: 38.9%). The estimated median DOR was 10 months, and estimated median PFS 9.5 months. The most frequent any-grade 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 TEAE, the most common 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, many of whom are elderly and in need of additional therapies.

# 

# INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the fifth most frequent malignancy in Western countries, with 74,680 new cases expected in the US in 2018.1 Indolent NHL constitutes approximately one-third of NHL cases, with follicular lymphoma (FL), the most common type, accounting for 20-30%.2 Other indolent subtypes include small lymphocytic lymphoma (SLL) and marginal zone B-cell lymphoma (MZL), accounting for approximately 5% and 4% of all NHL, respectively.3 The disease course for iNHL is variable, with some patients remaining asymptomatic for extended periods and others requiring immediate intervention.

For over a decade, combinations of the anti-CD20 monoclonal antibody rituximab with alkylator or purine analogue-based chemotherapy regimens (i.e., 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 6-8 and 12-15 years, respectively. However, the approximately 20% of patients with FL treated with frontline rituximab–cyclophosphamide–doxorubicin–prednisone (R-CHOP) who progress within two years of initial diagnosis also have lower 5-year overall survival (50%) compared to patients without early progression (90%).9

While outcomes are favorable for most patients, the relapsing nature of indolent lymphomas necessitates serial re-treatment, and advanced-stage disease remains incurable, necessitating lifetime management.10 Despite recent drug approvals, alternative targeted therapies remain the focus of clinical trials addressing disease resistance, which reduces options for patients with multiple treatment failures.11

Phosphatidylinositol 3-kinase (PI3K) is a lipid kinase whose catalytic subunit has four isoforms: α, β, γ, and δ. α and β isoforms are widely expressed in many tissues; PI3K-γ and PI3K-δ are preferentially expressed in hematopoietic cells12,13 and have predominantly non-overlapping roles in malignant 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, while 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.16-19 The TME is also important in the development and maintenance of hematologic malignancies including iNHL.20 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 ≥2 prior therapies, and for RR FL after ≥2 prior systemic therapies.21 Approval of 25 mg BID was supported by Phase 1 findings that plasma exposure at higher doses did not further increase either response rates or markers of PI3K-δ inhibition; 25 mg BID demonstrated clinical activity and an acceptable safety profile in advanced hematologic malignancies (IPI-145-02, NCT01476657).22 In that study, the ORR among 31 patients with RR iNHL treated with duvelisib monotherapy was 58.1%, including 6 (19.4%) CRs.22,23

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. Considering 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 DYNAMO study and duvelisib’s FDA approval.

# PATIENTS AND METHODS

**Study Design and Treatment**

DYNAMO was a single-arm, Phase 2, open-label study of the anti-tumor activity and safety of oral duvelisib monotherapy in patients with relapsed iNHL refractory to rituximab (i.e., no response or development of 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 US. 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 for all patients and rigorous data monitoring.

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

The primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC), defined as a CR or partial response (PR) per revised International Working Group criteria.24  Secondary efficacy endpoints included duration of response (DOR), PFS, OS, and time to response (TTR).

**Patient Eligibility**

Patients were ≥ 18 years old with histologically confirmed FL, SLL, or MZL (splenic, nodal, and extranodal) and radiologically measurable disease with a lymph node or tumor mass ≥ 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 above) to both rituximab (monotherapy or in combination) and to either chemotherapy or RIT. At least one prior chemotherapy regimen (with or without rituximab) must have contained an alkylating agent or a purine analogue. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and adequate renal (serum creatinine ≤ 2 × upper limit of normal [ULN]) and hepatic function (total bilirubin ≤ 1.5 × ULN and aminotransferases ≤ 3 × ULN). Key exclusion criteria included prior PI3K or BTK inhibitor therapy; prior, current, or chronic viral infections (human immunodeficiency virus, hepatitis B virus, or hepatitis C virus); ongoing treatment with chronic immunosuppressants, and inability to receive *Pneumocystis*, HSV, or HZV prophylaxis. There were no restrictions regarding cytopenias.

**Study Assessments**

Response was assessed at Cycles 3, 5, 7, 10, and every 4 cycles thereafter until 2 years from start of study treatment. Response was based on revised IWG response criteria for NHL, using consistent imaging: computed tomography (CT), positron emission tomography/CT, or magnetic resonance imaging.24

Safety assessments included physical examinations, electrocardiograms (ECGs), and 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).25  An independent data-monitoring committee (IDMC) reviewed all safety information.

Following treatment discontinuation, survival data were collected every 6 months 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 ≥45% against the null hypothesis of an ORR ≤30%, at a one-sided overall significance level of 0.025. A p-value and a two-sided 95% exact confidence interval (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 (≥ 50% reduction in the sum of the product of the longest perpendicular dimensions of the target lesion) rate was also calculated, and time-to-event endpoints were calculated using the Kaplan-Meier method.

A formal futility interim analysis was conducted approximately 4 months after 30 patients initiated treatment, and the IDMC recommended study continuation. The final analysis was performed after the last enrolled patient completed 6 months of therapy or experienced PD; these data, with two additional years of follow-up, are presented herein 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 (68.2%) patients were male, 89.9% were white, and median age was 65 years (range, 30-90). Most (85%) had advanced-stage (III or IV) iNHL, and 67% had elevated lactate dehydrogenase (LDH). Patients had an ECOG performance status of 1 (94.6%) or 2 (5.4%) at enrollment. Among FL patients, 87% were intermediate or high risk per the Follicular Lymphoma International Prognostic Index (FLIPI).

Patients had received a median of three prior systemic anticancer regimens (range, 1-18) and 52 patients (40%) received ≥4 prior regimens. Nearly two-thirds of patients (82; 64%) had prior bendamustine. Common prior regimens included rituximab-bendamustine (64 patients [50%]), R-CHOP (48 patients [37%]), and rituximab–cyclophosphamide–prednisone (R-CVP) (38 patients [30%]). Six patients (5%) had prior autologous stem-cell transplantation.

Nearly all patients had disease refractory (defined above) to rituximab either alone or in combination (127 patients, 98%), and 119 patients (92%) had disease refractory to an alkylating agent or purine analogue; 117 patients (91%) had disease refractory to combination therapy with rituximab and an alkylating agent. Nearly all (124, 96%) patients had disease refractory to the most recent regimen, and 95 (77%) patients had disease refractory to ≥ 2 regimens. Among the 39 FL patients who received a 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 < 2 years).

No notable differences in demographics were observed across lymphoma subtypes.

**Disposition**

Of 171 screened patients, 42 were excluded for screen failures, yielding 129 in the full analysis set (FAS). As of the May 2018 data cutoff, 5 subjects were still on treatment. Of the 124 who discontinued treatment, approximately half (66; 51.2%) did so because of PD, one-fourth (31; 24%) because of AEs, and the remaining fourth because of investigator decision, death, subject withdrawal, or noncompliance. As of May 2018, 33 patients (25.6%) remained in survival follow-up. Supplementary Figure 1 is a CONSORT diagram of patient disposition.

**Efficacy**

Median follow-up time (from first dose until last contact date or death) was 32.1 months. Table 2 shows primary and secondary efficacy endpoints based upon IRC and investigator response assessment by disease subtype.

The ORR per IRC–assessed response was 47% (95% CI, 38% to 56%), almost exclusively PRs (59 PRs, 2 CRs). The study met the primary endpoint (p<0.0001 against the null hypothesis that ORR was ≤30% per IRC). ORR per investigator–assessed response was 60% (Table 2), with differences per IRC between some subgroups (Figure 1). For example, ORR was numerically higher in US patients (n=46; ORR, 59%) than non-US patients (n=83; ORR, 41%). ORR was lower in patients with prior bendamustine (n=82; ORR, 39%) than patients without prior bendamustine (n=47; ORR, 62%).

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

Responses were rapid and durable. Median TTR was 1.87 months (range, 1.4-11.7 months) with 59% and 84% of responders responding by 2 and 4 months, respectively. Median DOR was 10 months (95% CI, 6.5 to 10.5) (Figure 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; Figure 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 to not estimable; Figure 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 (n=77; 59.7%) started ≥ 6 cycles of duvelisib, and 42 patients (32.6%) started ≥ 12 cycles.

TEAEs reported in >10% of patients are shown 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 AEs were neutropenia (24.8%), diarrhea (14.7%), anemia (14.7%), and thrombocytopenia (11.6%). Colitis and pneumonitis were reported in 10 (7.8%) and 6 (4.7%) patients, respectively. Three patients experienced serious opportunistic infections and recovered: bronchopulmonary aspergillosis, cytomegaloviral pneumonia, and *Pneumocystis jirovecii* pneumonia (PJP) in a patient prescribed Bactrim prophylaxis on Day 1.

The most frequent Grade ≥3 non-hematological laboratory elevation TEAEs were serum lipase (7%), alanine aminotransferase (5.4%), or aspartate aminotransferase (3.1%).

Forty patients (31%) discontinued duvelisib due to a TEAE. The only TEAEs that led to discontinuation in more than one patient were pneumonitis (4 patients; 3.1%), pneumonia, colitis, and diarrhea (3 patients; 2.3% each) and generalized rash (2 patients; 1.6%). TEAEs were managed with dose interruption or reduction in 85 patients (66%). Doses were reduced in 25 patients (19.4%), 4 (3.1%) of whom subsequently increased their dose as allowed per protocol. Dose reductions occurred most commonly with diarrhea (9 patients; 7.0%) followed by febrile neutropenia and lipase increases (each 3 patients and 2.3%).

No clinically meaningful safety differences were observed between 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 disease progression. Of the remaining eight, three (2.3%) were deemed unrelated to treatment: a 61-year-old female with cardiac disorders and respiratory, thoracic, and mediastinal disorders died of cardiopulmonary arrest and respiratory failure; a 79-year-old patient with ongoing cardiopulmonary disease died from cardiac failure; and a 62-year-old patient with diabetes and cardiopulmonary and thrombotic disease died from 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: drug reaction with eosinophilia and systemic symptoms, sepsis syndrome (DRESS)/ toxic epidermal necrolysis (TEN). However, both events were confounded by concomitant administration of medications associated with severe and fatal DRESS and TEN. One additional treatment-related death due to 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.26,27 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.28,29 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% (2 CR, 59 PR) 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 1 study (IPI-145-02, NCT01476657).22,23 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 immune-oncology therapies,29,30 immune-related toxicities including pneumonitis, transaminase elevations, colitis, and rash were observed, requiring treatment discontinuation in 31% of patients. Prophylaxis for *Pneumocystis,* HSV, and HZV infections was required per protocol. Serious opportunistic infections occurred in < 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 < 2 years) after their first treatment regimen. Among FL patients, 27 patients (33%) experienced early progression (< 2 years after initial diagnosis) following 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 (e.g., high FLIPI risk and elevated LDH) 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 above), 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). Though these three new treatment options are important for both physicians and patients, evaluating them side by side for the treatment of FL is challenging, as cross-trial comparisons are undermined by variability in patient selection and treatments. For instance, in the Phase 2 CHRONOS-1 study, copanlisib demonstrated an ORR of 59%. While 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.31 Also, the AE profile of copanlisib, specifically including hyperglycemic effects mediated through PI3K-α isoform inhibition,32,33 and hypertension, merits consideration before use in an elderly patient population with a high prevalence of these co-morbidities. Idelalisib, in a phase II trial in patients with disease refractory to both rituximab and chemotherapy, demonstrated an ORR of 57%.34 The AE profile was similar to duvelisib, except for higher incidence of grade 3 or higher aminotransferase increase with idelalisib (13% vs 5.4%). While many new therapies are being investigated for patients with RR indolent lymphoma (lenalidomide and rituximab, cellular therapies, bi-specific antibodies, and other small molecules), treatment options beyond the PI3K inhibitors are still limited. RIT is rarely 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 FL patients who relapsed after or whose disease proved refractory to a rituximab-containing regimen, based upon the results of the GADOLIN study.35 Given that bendamustine-rituximab is increasingly utilized as first-line treatment for FL in the US, duvelisib monotherapy may offer an alternative for the considerable number of patients whose disease is refractory to or who are unable to tolerate bendamustine. Patients previously treated with bendamustine had an ORR of 39% per IRC. While this was nominally lower than what was seen in patients not previously exposed to bendamustine, it nevertheless suggests 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 currently lacking sufficient treatment options.

**REFERENCES**

1. National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program. https://seer.cancer.gov/statfacts/html/nhl.html. Accessed April 24, 2018.
2. Bello C, Zhang L, Naghashpour M. Follicular Lymphoma: Current Management and Future Directions. Cancer Control. 2012;19(3):187-95.
3. LymphomaInfo.net. B-Cell lymphoma. 2015 [cited 2016 January 26, 2016]; Available from: http://www.lymphomainfo.net/nhl/b-cell.html.
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. 2004; 104:3064-3071.
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. Journal of Clinical Oncology. 2015;33(23):2516-22.
10. Sehn LH. Introduction to a review series: the paradox of indolent B-cell lymphoma. Blood. 2016; 127: 2045-2046.
11. MacDonald D, Prica A, Assouline S, et al. Emerging therapies for the treatment of relapsed or refractory follicular lymphoma. *Current Oncology*. 2016; 23:407-
12. Vanhaesebroeck B, Guillermet-Guibert J, Graupera M, Bilanges B. The emerging mechanisms of isoform-specific PI3K signalling. Nat Rev Mol Cell Biol. 2010;11:329-41.
13. Okkenhaug K, Vanhaesebroeck B. PI3K in Lymphocyte Development, Differentiation, and Activation. Nat Rev Immunol. 2003;3: 317-30.
14. Fruman DA, Rommel C. PI3Kdelta inhibitors in cancer: Rationale and serendipity merge in the clinic. Cancer Discov. 2011;1:562-72.
15. Courtney KD, Corcoran RB, Engelman JA. The PI3K Pathway as Drug Target in Human Cancer. J Clin Oncol. 2010; 28 :1075-1083.
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. 2014;124(21):328.
17. Gyori D, Chessa T, Hawkins PT, et al. Class (I) phosphoinositide 3-kinases in the tumor microenvironment. Cancers 2017, 9, 24.
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. 2018; 131(8):888-898.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. 2014 Feb;24:71-81.
19. 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. 2017;8:747.
20. 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. 2014 Feb;24:71-81.
21. COPIKTRA label, revised September 2018. https://www.accessdata.fda.gov/drugsatfda\_docs/label/2018/211155s000lbl.pdf
22. 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. 2018 Feb 22;131(8):877-887. doi: 10.1182/blood-2017-05-786566. Epub 2017 Nov 30.
23. 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. 2018 Nov;93(11):1311-1317. doi: 10.1002/ajh.25228. Epub 2018 Aug 31. PMID: 30033575.
24. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. Journal of Clinical Oncology. 2007 February 10, 2007; 25(5):579-86.
25. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Cancer Therapy Evaluation Program, common terminology for adverse events, version 30. Bethesda, MD: National Cancer Institute, 2009 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\_4.03\_2010-06-14\_QuickReference\_5x7.pdf).
26. Hitz F, Ketterer N, Lohri A, et al. Diagnosis and treatment of follicular lymphoma. Swiss Medical Weekly. 2011.
27. Cheson BD. Current Approaches to Therapy for Indolent non-Hodgkin’s Lymphomas McMahon Publishing; 2002.
28. Federico M, Vitolo U, Zinzani PL, et al. Prognosis of follicular lymphoma: a predictive model based on a retrospective analysis of 987 cases. Blood. 2000 2000;95(3):783-89.
29. Coutré SE, Barrientos JC, Brown JR, de Vos S, Furman RR, Keating MJ, et al. Management of adverse events associated with idelalisib treatment: expert panel opinion, Leuk Lymphoma. 2015;56(10):2779-86. doi: 10.3109/10428194.2015.1022770. Epub 2015 May 19.
30. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 2015; 12:2375–2391. doi: 10.1093/annonc/mdv383
31. Dreyling M, Santoro A, Mollica L, et al. Phosphatidylinositol 3-kinase inhibition by copanlisib in relapsed or refractory indolent lymphoma. J Clin Oncol. 2017 Dec 10;35(35):3898-3905.
32. Greenwell IB, [Ip A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ip%20A%5BAuthor%5D&cauthor=true&cauthor_uid=29179250), [Cohen JB](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cohen%20JB%5BAuthor%5D&cauthor=true&cauthor_uid=29179250). Oncology (Williston Park). PI3K Inhibitors: Understanding Toxicity Mechanisms and Management. 2017 Nov 15;31(11):821-8.
33. 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. 2016 Oct;27(10):1928-40. doi: 10.1093/annonc/mdw282.
34. Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014 Mar 13;370(11):1008-18. doi: 10.1056/NEJMoa1314583. Epub 2014 Jan 22. PMID: 24450858.
35. 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. 2016 Aug;17(8):1081-1093. doi: 10.1016/S1470-2045(16)30097-3. Epub 2016 Jun 23. PMID: 27345636.

# LEGENDS

**Figure 1. Subgroup Analysis of Overall Response Rate per IRC – Full Analysis Set)**

**Figure 2. Best Percent Change in SPD of Nodal Target Lesions per IRC – Full Analysis Set**

**Figure 3.**

**3a. Duration of Response per IRC Assessment – Full Analysis Set**

**3b. Progression-Free Survival per IRC Assessment – Full Analysis Set**

**3c. Overall Survival – Full Analysis Set**

**Table 1. Patient Demographics and Disease Characteristics**

**Table 2. Summary of Efficacy in Full Analysis Set**

**Table 3. All-Grade TEAEs (>10%) or ≥ Grade 3 TEAEs (>5%) in Full Analysis Set**

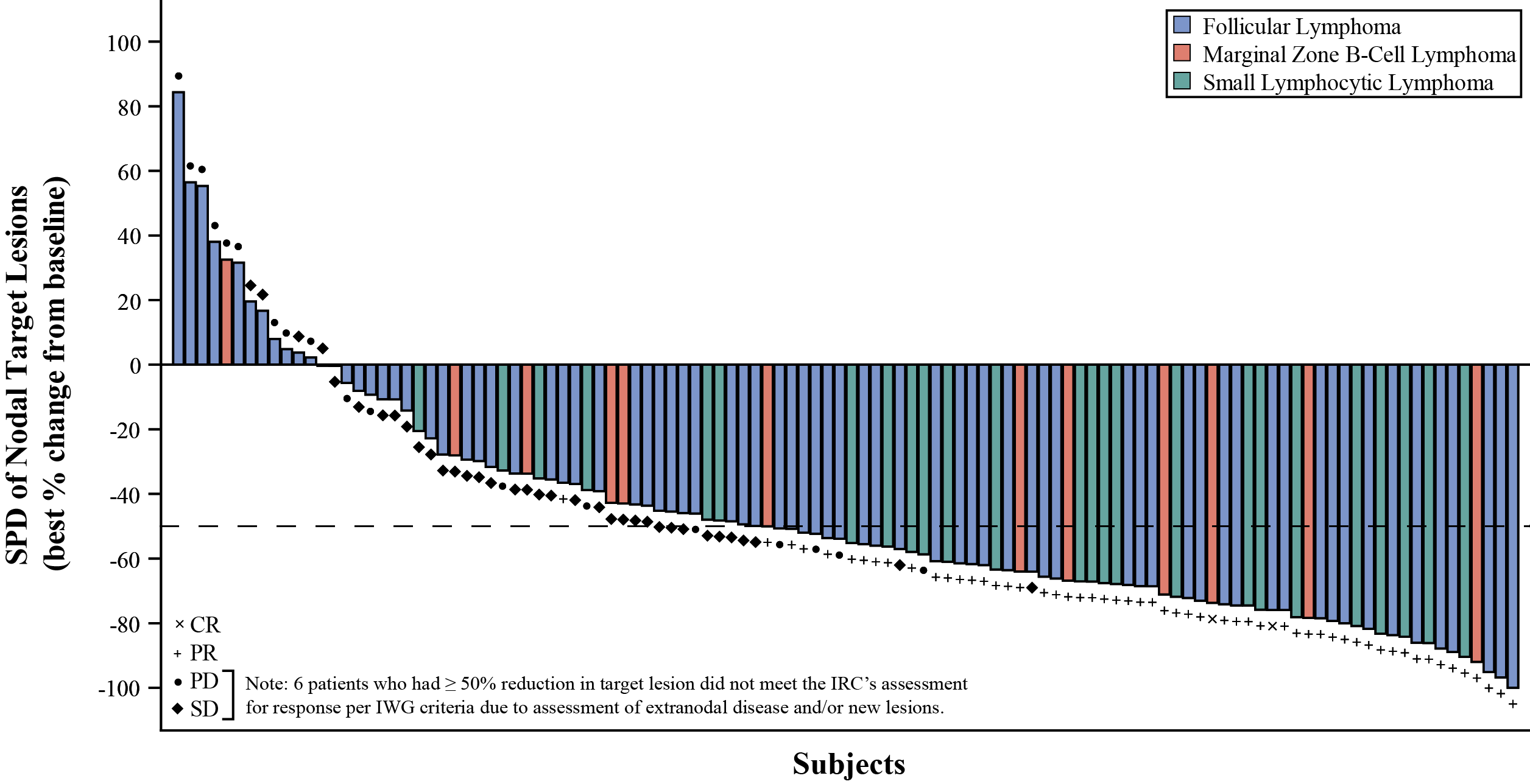
# 

**Figure 1. Subgroup Analysis of Overall Response Rate per IRC – Full Analysis Set**



**CI:** confidence interval; **FL**: follicular lymphoma; **IRC**: independent review committee; **MZL**: marginal zone lymphoma; **SLL**: small lymphocytic lymphoma

**Figure 2. Best Percent Change in SPD of Nodal Target Lesions per IRC – Full Analysis Set**



**CR**: complete response; **IRC**: independent review committee; **PD**: progressive disease; **PR**: partial response; **SD**: stable disease; **SPD:** sum of the product of the longest perpendicular dimensions.

**Figure 3.**

**3a. Duration of Response per IRC Assessment – Full Analysis Set**



**3b. Progression-Free Survival per IRC Assessment –Full Analysis Set**



**CI:** confidence interval; **IRC**: independent review committee

**3c. Overall Survival – Full Analysis Set**



**CI:** confidence interval; **NE**: not estimable

|  |  |
| --- | --- |
| **Table 1. Patient Demographics and Disease Characteristics** | |
| Characteristic | N=129 |
| Age, years |  |
| Median | 65.0 |
| Range | 30 – 90 |
| Race, n (%) |  |
| 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, n (%) |  |
| Male | 88 (68.2) |
| Female | 41 (31.8) |
| Time since NHL diagnosis, months |  |
| Median | 54.15 |
| Range | 3.9 – 324.0 |
| Stage at entry, n (%) |  |
| I-II | 19 (14.7) |
| III-IV | 109 (84.5) |
| Missing | 1 (0.8) |
| ECOG performance status, n (%) |  |
| 0-1 | 122 (94.6) |
| 2 | 7 (5.4) |
| Histologic Subtypes |  |
| 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, n (%) |  |
| Low (score = 0-1) | 11 (13.3) |
| Intermediate (score = 2) | 17 (20.5) |
| High (score >2) | 54 (65.1) |
| Missing | 1 (1.2) |
| Elevated LDH at Baseline, n (%) |  |
| Yes | 86 (66.7) |
| No | 42 (32.6) |
| Missing | 1 (0.8) |
| No. of prior anticancer regimens, n (%) |  |
| Median | 3.0 |
| Range | 1 – 18 |
| Time since completion of last therapy, months |  |
| Median | 3.5 |
| Range | 0 – 121 |
| Prior therapy, n (%) |  |
| Rituximab | 129 (100) |
| Alkylating Agent/Purine Analogue | 129 (100) |
| Alkylating Agent | 127 (98.4) |
| Combination of Rituximab and Alkylating Agent | 122 (94.6) |
| Bendamustine | 82 (63.6) |
| Anthracycline | 78 (60.5) |
| R-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 Analogue Therapy, months |  |
| Median | 7.7 |
| Range | 1 – 141 |
| Prior therapy to which the disease was refractory, n (%) |  |
| Rituximab | 127 (98.4) |
| Alkylating Agent/Purine Analogue | 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) |
| R-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 ≥ 2 Regimens | 99 (76.7) |
| Bulky diseasea at Baseline, n (%) | 51 (39.5) |
| **ECOG**: Eastern Cooperative Oncology Group; **FLIPI**: Follicular Lymphoma International Prognostic Index; **LDH**: lactate dehydrogenase; **NHL**: non-Hodgkin’s lymphoma; **R**: rituximab; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, prednisone; **R-CVP:** rituximab, cyclophosphamide, vincristine, prednisone.  a Bulky disease: longest diameter of nodal target lesion ≥ 5 cm. | |

|  |  |  |
| --- | --- | --- |
| **Table 2. Summary of Efficacy in Full Analysis Set** | | |
|  | Response by IRC | Response by Investigator |
| Overall Population | N=129 | N=129 |
| Response | No. of patients (%) | No. of patients (%) |
| ORR (CR + PR) | 61 (47.3) | 77 (59.7%) |
| 95% Exact Binomial CI | 38.4 – 56.3 | 50.7 – 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 – 10.5 | 6.5 – 12.5 |
| Median PFS, months | 9.5 | 10.0 |
| 95% CI | 8.1 – 11.8 | 8.3 – 11.7 |
| Median OS, months | 28.9 | - |
| 95% CI | 21.4 – 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 – 53.5 | 41.7 – 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 – 84.1 | 67.3 – 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 lymphoma | n=18 |  |
| ORR (CR + PR) | 7 (38.9) | 9 (50.0%) |
| 95% Exact Binomial CI | 17.3, 64.3 | 26.0, 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) |
| **CI**: confidence interval; **CR**: complete response; **DOR**: duration of response; **IRC**: independent review committee; **IWG**: International Working Group; **NE**: not evaluable; **ORR**: overall response rate; **OS**: overall survival; **PD**: progressive disease; **PFS**: progression-free survival; **PR**: partial response; **SD**: stable disease; **TTR**: time to response.  \* No evidence of disease at baseline and no post-baseline assessment of PD in one patient with a single extranodal target lesion (nasopharynx) evaluated as CR by the investigator. | | |

|  |  |  |
| --- | --- | --- |
| **Table 3. All-Grade TEAEs (>10%) or ≥ Grade 3 TEAEs (>5%) in Full Analysis Set** | | |
|  | All Grades | ≥ Grade 3 |
|  | N=129 | N=129 |
|  | No. of patients (%) | No. of patients (%) |
| Patients with at Least 1 TEAE | 128 (99.2) | 114 (88.4) |
| Diarrhoea | 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 |
| Anaemia | 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 |
| Oedema peripheral | 22 (17.1) | 3 (2.3) |
| Alanine aminotransferase 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) |
| Hypokalaemia | 17 (13.2) | 4 (3.1) |
| Constipation | 15 (11.6) | 0 |
| Asthenia | 15 (11.6) | 3 (2.3) |
| Aspartate aminotransferase 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) |
|  | | |
| **TEAE**, treatment-emergent adverse event | | |

# ACKNOWLEDGMENTS

Infinity Pharmaceuticals and Verastem Oncology provided financial support. We would like to thank the study investigators, coordinators, nurses, and patients and their families for their contributions. Sven DeVos, Carole Miller, and Pier Luigi Zinzani served as consultants to Verastem Oncology for this research. Steven Mousterakis and Justin McLaughlin, formerly of Infinity Pharmaceuticals, and Paul Guttry of Acumen Medical Communications provided graphical and editorial support.