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ORIGINAL ARTICLE

Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma

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Background: Copanlisib is a pan-class I phosphatidylinositol 3-kinase inhibitor with predominant activity against the α- and δ-isoforms.

Patients and methods: This phase II study evaluated the response rate of copanlisib administered intravenously on days 1, 8, and 15 of a 28-day cycle, in patients with indolent or aggressive malignant lymphoma. Archival tumor tissues were used for immunohistochemistry, gene-expression profiling, and mutation analysis.

Results: Thirty-three patients with indolent lymphoma and 51 with aggressive lymphoma received copanlisib. Follicular lymphoma (48.5%) and peripheral T-cell lymphoma (33.3%) were the most common histologic subtypes. Most patients (78.6%) had received prior rituximab and 54.8% were rituximab-refractory. Median duration of treatment was 23 and 8 weeks in the indolent and aggressive cohorts, respectively (overall range 2–138). Eighty patients were evaluated for efficacy. The objective response rate was 43.7% (14/32) in the indolent cohort and 27.1% (13/48) in the aggressive cohort; median progression-free survival was 294 days (range 0–874) and 70 days (range 0–897), respectively; median duration of response was 390 days (range 0–825) and 166 days (range 0–786), respectively. Common adverse events included hyperglycemia (57.1%; grade ≥3, 23.8%), hypertension (54.8%; grade ≥3, 40.5%), and diarrhea (40.5%; grade ≥3, 4.8%), all generally manageable. Neutropenia occurred in 28.6% of patients (grade 4, 11.9%). Molecular analyses showed enhanced antitumor activity in tumors with upregulated phosphatidylinositol 3-kinase pathway gene expression.

Conclusion: Intravenous copanlisib demonstrated promising efficacy and manageable toxicity in heavily pretreated patients with various subtypes of indolent and aggressive malignant lymphoma. Subtype-specific studies of copanlisib in patients with follicular, peripheral T-cell, and mantle cell lymphomas are ongoing.

This trial is registered with ClinicalTrials.gov number NCT01660451 (Part A).

Key words: copanlisib, treatment, malignant lymphoma, PI3K inhibitor

Introduction

Non-Hodgkin's lymphoma comprises a heterogeneous group of malignant lymphomas, with both indolent and aggressive subtypes [1]. The B-cell receptor (BCR) signaling pathway is critical for the development, proliferation, and survival of malignant B-cells. Drugs targeting BCR pathway kinases, including the Bruton's tyrosine kinase inhibitor ibrutinib [2] and the phosphatidylinositol 3-kinase (PI3K)-δ isoform inhibitor idelalisib [3], have proved to be effective treatment options in patients with refractory follicular or relapsed mantle cell lymphoma.

However, fatal and/or serious toxicities have been associated with idelalisib use [3, 4] and, recently, frequent serious adverse events, including hepatic and gastrointestinal toxicity, colitis, opportunistic infections, autoimmune toxicities, and pneumonitis, have raised safety concerns around idelalisib in combination with standard therapies [5–7]. Therefore, new approaches, such as inhibitors of multiple PI3K isoforms, have been developed to both mitigate toxicity issues and improve efficacy [8–10].

Copanlisib (BAY 80-6946; Bayer AG, Berlin, Germany) is an intravenous pan-class I PI3K inhibitor with predominant activity against the PI3K-α and PI3K-δ isoforms [11]. A first-in-human phase I study established the maximum tolerated dose of copanlisib as 0.8 mg/kg administered on days 1, 8, and 15 of a 28-day cycle [12]. In an expansion cohort including non-Hodgkin's lymphoma patients, severe toxicities were low, and there were early signs of efficacy, including complete response (CR) or partial response (PR) in all six patients with relapsed or refractory follicular lymphoma (FL), and one of three patients with diffuse large B-cell lymphoma (DLBCL) [12].

This open-label, uncontrolled, phase II study evaluated the efficacy and safety of intravenous copanlisib administered intermittently in heavily pretreated patients with relapsed or refractory, indolent or aggressive malignant lymphoma (ClinicalTrials.gov identifier: NCT01660451; Part A). Biomarker analyses were carried out to identify a possible gene signature profile that may associate with response.

Patients and methods

Study design and patient eligibility

The study population comprised two cohorts of 30 patients each with either indolent lymphoma or chronic lymphocytic leukemia (CLL), or aggressive malignant lymphoma, relapsed or refractory to two or more prior lines of therapy. Following early signs of clinical activity, the protocol was amended to enroll additional patients with aggressive lymphoma [mantle cell lymphoma (MCL) and T-cell lymphoma]. Separate extension studies for relapsed or refractory, indolent lymphoma (NCT01660451, Part B) and DLBCL (NCT02391116) are ongoing. The study protocol and amendments were approved by all relevant institutional review boards and ethics committees. All patients gave written, informed consent.

The primary efficacy variable was objective response rate (ORR), defined as the proportion of patients who achieved a CR, an unconfirmed CR (uCR), or a PR [13], or CR or PR for patients with CLL [14]. The database cut-off date was 4 November 2013 for the primary analysis set, and 1 October 2015 including expansion patients. Secondary variables included progression-free survival, overall survival, and duration of response. Additional variables included time to response, lesion size, biomarkers, and safety.

The indolent cohort consisted of histologically confirmed grade 1, 2, or 3a FL, marginal zone lymphoma, lymphoplasmacytic lymphoma/Waldenström macroglobulinemia, or CLL. Aggressive lymphomas included histologically confirmed grade 3b FL, transformed indolent lymphoma, DLBCL, mediastinal large B-cell lymphoma, MCL, unspecified peripheral T-cell lymphoma (PTCL), anaplastic large-cell lymphoma primary systemic type, or angio-immunoblastic T-cell lymphoma. Additional inclusion criteria and exclusion criteria are described in the supplementary materials, available at *Annals of Oncology* online.

Eligible patients received 0.8 mg/kg copanlisib intravenously over a 1-h infusion on days 1, 8, and 15 of a 28-day cycle until disease progression, worsening of Eastern Cooperative Oncology Group performance status of ≥3, or unacceptable toxicity. Details of plasma glucose requirements pre-infusion, management of post-infusion hyperglycemia, and permitted dose reductions are described in the supplementary materials, available at *Annals of Oncology* online.

Dose reductions to 0.6 and 0.4 mg/kg were permitted if clinically significant toxicities were observed; re-escalation was not permitted. Treatment was discontinued if the 0.4 mg/kg dose was not tolerated.

Assessments

Tumor assessments were carried out at screening and every two cycles thereafter during year 1, every three cycles during year 2, and every six cycles during year 3. Radiologic evaluation of efficacy was carried out by central blinded independent review; in patients with CLL, treatment response was determined by investigator assessment. Patients were followed off-study for overall survival at 3-month intervals for up to 3 years. Safety was evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Measurements of glycated hemoglobin, plasma glucose, and blood pressure are described in the supplementary materials, available at *Annals of Oncology* online. Archival formalin-fixed paraffin-embedded tumor tissues were evaluated for biomarkers, for which detailed methods are described in the supplementary materials, available at *Annals of Oncology* online.

Statistical methods

Pre-specified primary evaluation was to reject the null hypothesis of a true ORR of ≤5% in the indolent or aggressive lymphoma cohorts, separately. ORR was evaluated using a one-sided exact binomial test (significance level of 5%) and was designed to have 95% power per cohort, if the true ORR was 30%, resulting in a requirement of 30 assessable patients per cohort. Exact binomial Clopper–Pearson confidence intervals (CI) with confidence level of 90% were provided for ORR. Time-to-event variables were analyzed using Kaplan–Meier methodology. In order to study promising lymphoma histologies in more detail, the aggressive cohort was expanded with an additional 17 patients, beyond those recruited for the primary evaluation. Data from these patients were included in a descriptive analysis of the study. Detailed methods are described in the supplementary materials, available at *Annals of Oncology* online.

Results

Patients

Eighty-four patients received copanlisib: 33 in the indolent cohort and 34 in the aggressive cohort for the primary analysis, and 17 additional patients with aggressive lymphoma (four patients with MCL and 13 with PTCL) enrolled into an expansion cohort (supplementary Figure S1, available at *Annals of Oncology* online). The majority had advanced-stage disease at study entry (Ann Arbor stage III/IV, 73.7% indolent, 88.2% aggressive) and had received a median of three lines of systemic anticancer therapy (Table 1).

Table 1. Baseline demographics and disease characteristics

	Primary analysis set			
	Indolent cohort (*n*=33)	**Aggressive cohort (*n*=34)**	**Aggressive cohort, all (*n*=51)**	**Total[a] (*N*=84)**
Sex, *n* (%)				
Male	15 (45.5)	17 (50.0)	29 (56.9)	44 (52.4)
Female	18 (54.5)	17 (50.0)	22 (43.1)	40 (47.6)
Median age, years (range)	68.0 (46–89)	68.0 (22–90)	63.0 (22–90)	66.5 (22–90)
Median time from initial diagnosis to start of study treatment, months (range)	119.8 (20–244)	29.7 (6–212)	24.0 (6–281)	47.6 (6–281)
Median time since first progression, months (range)	68.5 (10–177)	11.5 (0–100)	11.2 (0–100)	19.7 (0–177)
Median time since most recent progression to start of study treatment, months (range)	5.1 (1–31)	3.9 (0–18)	4.1 (0–21)	4.1 (0–31)
Most recent histology of tumor, *n* (%)				
Indolent lymphoma or CLL	33 (100)	0	0	33 (39.3)
CLL	13 (39.4)	0	0	13 (15.5)
FL	16 (48.5)	0	0	16 (19.0)
Grade 1, 2, or 3a[b]	15 (45.5)	0	0	15 (17.9)
MZL	3 (9.1)	0	0	3 (3.6)
SLL	1 (3.0)	0	0	1 (1.2)
Aggressive lymphoma	0	34 (100)	51 (100)	51 (60.7)
DLBCL	0	15 (44.1)	15 (29.4)	15 (17.9)
FL, grade 3b	0	1 (2.9)	1 (2.0)	1 (1.2)
MCL	0	7 (20.6)	11 (21.6)	11 (13.1)
Mediastinal large B-cell lymphoma	0	1 (2.9)	1 (2.0)	1 (1.2)
PTCL	0	4 (11.8)	17 (33.3)	17 (20.2)
Anaplastic large-cell lymphoma	0	0	3 (5.9)	3 (3.6)
Angio-immunoblastic TCL	0	1 (2.9)	4 (7.8)	4 (4.8)
PTCL[c]	0	3 (8.8)	10 (19.6)	10 (11.9)
Transformed indolent FL	0	6 (17.6)	6 (11.8)	6 (7.1)
Stage at study entry, *n* (%)[d]				
I	1 (3.0)	0	1 (2.0)	2 (2.9)
II	4 (12.1)	3 (8.8)	5 (9.8)	9 (10.7)
III	5 (15.2)	7 (20.6)	12 (23.5)	17 (20.2)
IV	9 (42.4)	24 (70.6)	33 (64.7)	42 (50.0)
Prior systemic anticancer therapy lines, median (range)	4 (2–10)	3 (2–9)	3 (1–9)	3 (1–10)

[a]Total includes all patients from the 'Indolent' and 'Aggressive, all' cohorts

[b]Data missing for one patient.

[c]Includes eight patients with PTCL, not otherwise specified.

[d]Data missing for 14 patients with indolent lymphoma.

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PTCL, peripheral T-cell lymphoma; SLL, small lymphocytic lymphoma; TCL, T-cell lymphoma.

The majority of patients had received chemotherapy with or without immunotherapy or immunotherapy monotherapy (supplementary Table S1, available at *Annals of Oncology* online). Twenty-three patients (69.7%) in the indolent cohort were refractory to one or more regimens with rituximab and 15 (45.5%) were refractory to one or more regimens with bendamustine.

Copanlisib treatment

Median treatment duration was 13.9 weeks overall (range 2.0–137.9): 22.7 weeks (5.7 cycles) in the indolent cohort and 8.0 weeks (2.0 cycles) in the aggressive cohort. Patients with indolent or aggressive lymphoma received a median number of 15 (range 1–101) and six (range 1–95) copanlisib infusions, respectively; patients received a median of 90.5% of the planned dose overall. Fifty patients (59.5%) had dose interruptions or delays because of adverse events, and 11 (13.1%) had dose reduction because of adverse events (supplementary Results, available at *Annals of Oncology* online); interruptions or delays had a median duration of 1 week (range 0.1–1.7).

Efficacy

Sixty-six patients were included in the per protocol analysis set for the primary efficacy analysis. The ORR was 43.8% (90% CI 28.7–59.7) in the indolent cohort and 29.4% (90% CI 16.9–44.8)

Table 2. Response evaluation by independent assessment (per protocol set)

n (%)	Indolent cohort (*n*=32)[a]	Aggressive cohort, primary analysis set (*n*=34)	Aggressive cohort, all (*n*=48)[b]
Best response			
Complete response	2 (6.3)	0	2 (4.2)
Unconfirmed complete response	1 (3.1)	4 (11.8)	2 (4.2)
Partial response	11 (34.4)	6 (17.7)	9 (18.8)
Stable disease	15 (46.9)	6 (17.7)	11 (22.9)
Progressive disease	1 (3.1)	10 (29.4)	16 (33.3)
Not available/not evaluable[c]	2 (6.3)	8 (23.5)	8 (16.7)
Objective response rate	14 (43.8)	10 (29.4)	13 (27.1)
Disease control rate[d]	29 (90.6)	16 (47.1)	24 (50.0)

[a]One patient was excluded as they did not have any measurable lesion as per Cheson criteria at baseline.

[b]Three patients were excluded because: baseline computed tomography or magnetic resonance imaging of all suspected disease sites and tumor evaluations were not taken within 28 days before starting study treatment (one patient); no measurable lesion was observed (one patient); and no post-baseline tumor assessment was available and discontinuation was not caused by a drug-related toxicity, death, or progression by clinical judgment before disease was re-evaluated (one patient).

[c]Includes patients without post-baseline tumor assessment.

[d]Disease control rate was defined as the proportion of patients with a complete response, an unconfirmed complete response, a partial response, or stable disease.

in the aggressive cohort, statistically confirming the hypothesis of an ORR >5% ($P < 0.0001$ in each cohort) (Table 2). A waterfall plot of best change in target lesion size from baseline per investigator assessment indicated that 66.7% of patients (20/30) in the indolent cohort (Figure 1A) and 42.5% (17/40) in the aggressive cohort (Figure 1B) had ≥50% reduction in lesion size.

CRs/uCRs were observed in three of 15 FL patients (20.0%) and PRs in a further three patients (20.0%); the ORR was 40% (supplementary Table S2, available at *Annals of Oncology* online). PRs were observed in five of the 13 patients with CLL (ORR 38.5%), two of the three patients with marginal zone lymphoma (ORR 66.7%), and one patient with small lymphocytic lymphoma (ORR 100%). In the initial set of patients with aggressive lymphoma, five of seven with MCL and two of four with PTCL had CR/uCR or PR, prompting additional enrollment, expanding the response analysis to 48 patients. The ORR for the aggressive lymphoma expansion cohort was 27.1% (90% CI 16.8–39.6). Objective responses were achieved in patients with DLBCL (one PR; ORR 6.7%), PTCL (two CRs, one PR; ORR 21.4%), MCL (two uCRs, five PRs; ORR 63.6%), and transformed FL (both PRs; ORR 33.3%) (supplementary Table S2, available at *Annals of Oncology* online).

Median time to response was 52 days (range 0–109) in the indolent cohort and 51 days (range 0–117) in the aggressive cohort, and was generally observed at the first response assessment (supplementary Figure S2, available at *Annals of Oncology* online). Median progression-free survival was 294 days (range 0–874) in the indolent cohort and 70 days (range 0–897) in the aggressive cohort (Figure 2A). At 12 months, progression-free survival was 45% and 13% in the indolent and aggressive cohorts, respectively. The median duration of response was 390 days (range 0–825) and 166 days (range 0–786 days) in the indolent and aggressive cohorts, respectively (Figure 2B). Median overall survival was 657 days in the indolent cohort (range 0–958) and 183 days in the aggressive cohort (range 0–1017) (Figure 2C). At 12 months, overall survival was 69% and 42% in patients with indolent and aggressive lymphoma, respectively.

Biomarkers

Loss of or low tumor PTEN protein expression was detected in six of 16 patients in the indolent cohort (including 2/10 with FL) and four of 26 patients in the aggressive cohort (supplementary Table S3, available at *Annals of Oncology* online). High expression of PI3K and/or BCR pathway genes occurred in nine of 15 patients in the indolent cohort (including 4/10 with FL) and seven of nine patients in the aggressive cohort.

In the indolent cohort, 13 of 18 patients (including 6/11 with FL) had upregulated PI3K pathway gene expression (supplementary Table S3, available at *Annals of Oncology* online). Upregulation of PI3K pathway gene expression was observed in 10 of 11 patients with either a CR or a PR, or ≥50% best decrease in target lesion size from baseline, but only three of seven patients with <50% best decrease in target lesion size (Figure 1A). In the aggressive cohort, nine of 26 patients had upregulation of PI3K pathway gene expression (supplementary Table S3, available at *Annals of Oncology* online), including three of seven patients with ≥50% best reduction in target lesion size (of whom two had CR/uCR) and six of 13 patients with <50% best decrease in target lesion size (Figure 1B).

Results from DNA next-generation sequencing are described in the supplementary materials, available at *Annals of Oncology* online. An unfavorable tumor microenvironment gene signature was more frequently expressed in patients with indolent or aggressive lymphoma who were less responsive to copanlisib, with <50% best decrease in target lesion size (Figure 1A and B).

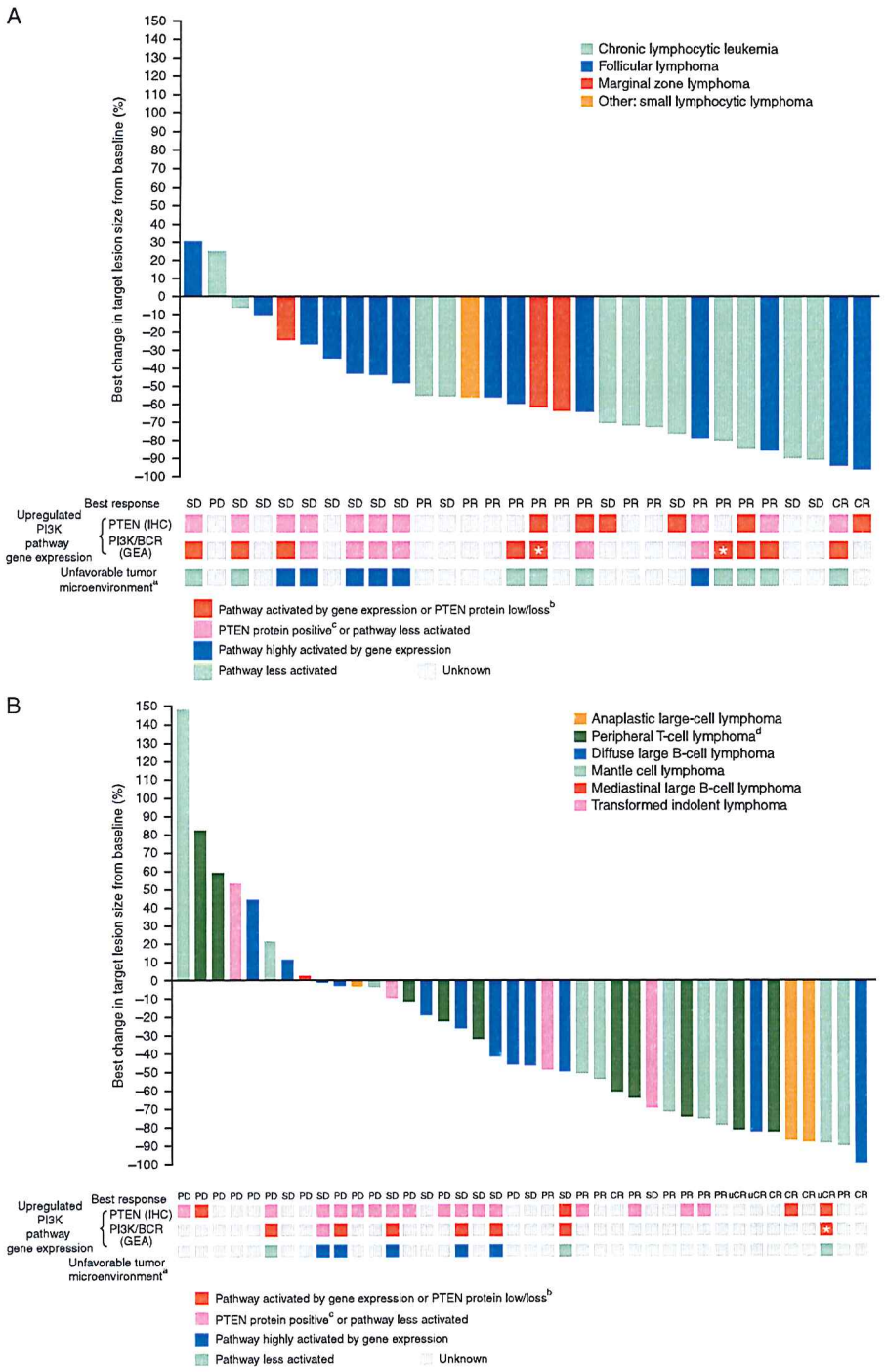

Figure 1. Percent best change in target lesion size from baseline (investigator assessment) in the indolent (A) and aggressive (B) cohorts with corresponding status of baseline upregulation of PI3K/PTEN pathway gene expression and tumor microenvironment (full analysis set). * indicates *NOTCH1* mutation by next-generation sequencing. [a]Unfavorable tumor microenvironment gene-expression signature was defined as high (greater than the median value) weighted gene-expression scores combining genes expressed in stromal, inflammatory, and immune response pathways. [b]Upregulation of PI3K/PTEN pathway gene expression was defined as PTEN protein loss (0% of tumor cells stained positive for PTEN by IHC) or low PTEN protein expression (1%–4% of tumor cells stained positive), and/or a high PI3K/BCR gene-expression signature (defined by a weighted gene-expression score greater than the median value). [c]Positive PTEN protein expression was defined as ≥5% of cells staining positive for PTEN by IHC. [d]Includes peripheral T-cell lymphoma, peripheral T-cell lymphoma not otherwise specified, and angioimmunoblastic T-cell lymphoma. BCR, B-cell receptor; CR, complete response; GEA, gene-expression analysis; IHC, immunohistochemistry; PD, progressive disease; PR, partial response; SD, stable disease; uCR, unconfirmed complete response.

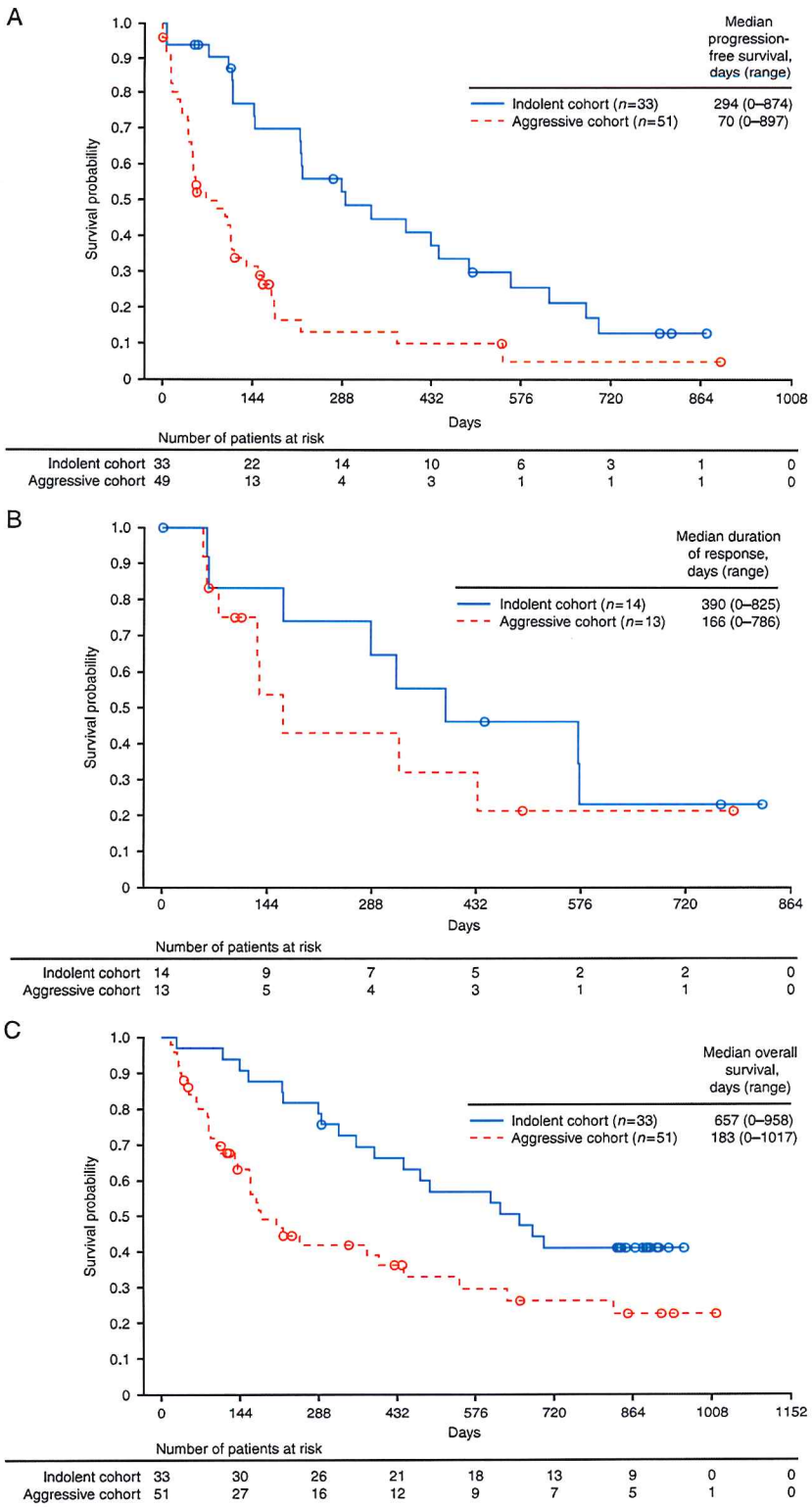

Figure 2. Progression-free survival (full analysis set) (A), duration of response (per protocol set) (B), and overall survival (full analysis set) (C) in patients in the indolent or aggressive cohorts receiving copanlisib.

Safety

Treatment-emergent adverse events (TEAEs) are shown in Table 3. Drug-related TEAEs are shown in supplementary Table S4, available at *Annals of Oncology* online. The most common TEAEs were hyperglycemia (59.5%), hypertension (54.8%), fatigue (48.8%), and diarrhea (40.5%). In most cases, grade 3 was the worst grade of TEAE (overall 60.7%; 51/84). Serious grade 3, 4, and 5 TEAEs were reported in 31.0% (26/84), 4.8% (4/84), and 11.9% (10/84) of patients, respectively. Serious grade 3 or 4 TEAEs occurring in two or more patients included: grade 3 lung infection (10.7%; 9/84); grade 3 diarrhea and grade 3 febrile neutropenia (3.6% each; 3/84); and grade 4 decreased neutrophil count, grade 3 hyperglycemia, grade 3 pneumonitis (one infectious and one possibly infectious), grade 3 pancreatitis, grade 3 cardiac disorders—other, and grade 3 infection/infestations—other (2.4% each; 2/84). There was one case of serious grade 3 hypertension and one case of serious grade 3 acute coronary syndrome. Serious drug-related TEAEs were recorded in 32.1% of patients (supplementary Table S5, available at *Annals of Oncology* online).

There were 10 deaths (Table 3), four of which were considered possibly drug-related (supplementary Table S5, available at *Annals of Oncology* online), including one case of meningitis caused by opportunistic infection with *Cryptococcus neoformans* in a patient with CLL occurring 8 days after one infusion of copanlisib.

Hyperglycemic and hypertension events were all grade ≤3 and transitory (supplementary Table S6, available at *Annals of Oncology* online). Seventeen patients received insulin to manage post-infusion hyperglycemia [grade 2, 35.3% (6/17); grade 3, 64.7% (11/17)], of whom nine had blood glucose ≤160 mg/dl. Increases in mean glycated hemoglobin from baseline to end of treatment were <0.5% in both indolent and aggressive cohorts (supplementary Table S6, available at *Annals of Oncology* online). Seventeen patients received post-dose antihypertensive treatment for grade 3 hypertension.

All-grade hematologic toxicities included decreased neutrophil count (34.5%; grade 3/4, 29.8%), anemia (28.6%; grade 3/4, 14.3%), and decreased platelet count (17.9%; grade 3/4, 11.9%), and infections and infestations were reported in 64.3% of patients (grade 1/2, 39.3%; drug-related all-grade, 29.8%). Infections of grade ≥3 occurring in two or more patients included lung infection (14.3%; 12/84) and skin infection, urinary tract infection, and other (2.4% each; 2/84). There were three reports of pneumonitis overall, including one grade 3 opportunistic infection with *Pneumocystis jirovecii* and one grade 1 non-infectious event. Diarrhea was mostly mild (grade 1, 22.6%; grade 2, 13.1%; grade ≥3, 4.8%) and was manageable with a standard symptomatic treatment such as loperamide. There were no reported cases of colitis or intestinal perforation.

TEAEs leading to permanent treatment discontinuation were reported in 25.0% of patients (Table 3). No patient discontinued because of hyperglycemia or hypertension.

Discussion

In this exploratory phase II study in heavily pretreated patients with relapsed or refractory, indolent or aggressive lymphoma, or CLL, copanlisib monotherapy was shown to be effective, confirming the early signal of activity reported in a lymphoma expansion cohort in the phase I study [12]. The ORR was 43.8% in the indolent cohort (CR/uCR 9.4%) and 27.1% in the aggressive cohort (CR/uCR 8.3%). A median duration of response of 12.8 months and median progression-free survival of 9.7 months were seen in the indolent cohort. The two largest subtypes of patients in the indolent cohort (FL and CLL) had ORRs of 40% (CR/uCR) and 38.5%, respectively. These results in the indolent cohort are similar to or slightly lower than the ORR and progression-free survival results reported by Flinn et al. [15] and Gopal et al. [16] with idelalisib in similar patient populations, although lower than those reported by Byrd et al. [17] for ibrutinib in patients with CLL and small lymphocytic lymphoma. Such cross-study comparisons are inconclusive due to the small numbers of patients, although the CR/uCR rate of 20% seen here in FL, as well as two CRs from six FL patients in the phase I study [12], are promising. A larger study in patients with indolent lymphoma is ongoing (NCT01660451, Part B).

In the aggressive cohort, the ORR ranged from 6.7% in DLBCL patients to 63.6% in MCL patients. Responses to ibrutinib have been reported to be higher in patients with activated B-cell (ABC) DLBCL compared with germinal center B-cell-like differentiation (GCB) DLBCL [18], but such subtyping of DLBCL was not available here. Based on expression of PI3K-α and PI3K-δ in DLBCL lymphoma tissues, together with heightened activity of copanlisib compared with selective PI3K-δ or PI3K-α inhibition in ABC DLBCL models [9, 10], exploration of copanlisib activity in ABC or GCB subtypes of DLBCL is ongoing (NCT02391116), and a rationale for combination with ibrutinib has been proposed [9, 10]. Objective responses have not been reported in studies with DLBCL patients treated with idelalisib.

The ORR of 63.6% (including two uCRs) in MCL patients was favorable compared with reports of idelalisib (ORR 40%) [19] or ibrutinib (ORR 67%) [20]. Copanlisib activity in MCL is consistent with expression of PI3K-α and PI3K-δ, with increased PI3K-α expression in later-stage disease [8]. In PTCL patients, the ORR was 21.4% and included two CRs, which was similar to that seen in a phase I study in PTCL patients with the PI3K-δ,γ inhibitor duvelisib [21]. Therefore, further study with copanlisib in relapsed or refractory MCL and PTCL may be warranted.

The safety profiles for PI3K inhibitors warrant careful scrutiny following the recent safety concerns for the oral agent idelalisib [5–7]. Hyperglycemia and hypertension were the most common TEAEs seen with copanlisib, were consistent with its target profile and route of administration, and were predicted [12]. Both were transient and manageable, and followed a similar pattern as previously reported [12], with blood pressure peaking 1–2 hours after the start of infusion and plasma glucose levels peaking 5–8 hours after the start of infusion, followed by a decline to baseline levels. No patients discontinued because of either adverse event. No hyperglycemic or hypertension events of grade ≥4 were reported, and serious events of grade 3 were reported in two patients and one patient, respectively, who all had baseline risk factors requiring planned hospitalization to adjust dosing. Cardiac events were infrequent and low, and glycated hemoglobin levels did not increase compared with baseline.

Infections are common for patients with hematologic malignancies such as CLL, and drugs inhibiting PI3K-δ or Bruton's

Table 3. Summary of TEAEs irrespective of causality (safety analysis set)[a]

n (%)	Grade 1 or 2 (*n*=84)	Grade 3 or 4 (*n*=84)	Total (*N*=84)
Patients with ≥1 TEAEs	7 (8.3)	67 (79.8)	84 (100)[b]
Patients with any TEAE leading to permanent discontinuation of study drug	3 (3.6)	18 (21.4)	21 (25.0)[c]
Patients with any TEAE leading to dose reduction	3 (3.6)	8 (9.5)	11 (13.1)
Patients with any TEAE leading to dose interruption	11 (13.1)	39 (46.4)	50 (59.5)
TEAEs occurring in ≥10% of patients overall[d]			
Hyperglycemia	29 (34.5)	21 (25.0)	50 (59.5)
Hypertension	12 (14.3)	34 (40.5)	46 (54.8)
Fatigue	31 (36.9)	10 (11.9)	41 (48.8)
Diarrhea	30 (35.7)	4 (4.8)	34 (40.5)
Decreased neutrophil count	4 (4.8)	25 (29.8)	29 (34.5)
Nausea	26 (31.0)	2 (2.4)	28 (33.3)
Anemia	12 (14.3)	12 (14.3)	24 (28.6)
Oral mucositis	18 (21.4)	1 (1.2)	19 (22.6)
Lung infection	5 (6.0)	10 (11.9)	17 (20.2)
Fever	15 (17.9)	1 (1.2)	16 (19.0)
Decreased platelet count	5 (6.0)	10 (11.9)	15 (17.9)
Headache	15 (17.9)	0	15 (17.9)
Urinary tract infection	12 (14.3)	2 (2.4)	14 (16.7)
Dyspnea	11 (13.1)	3 (3.6)	14 (16.7)
Constipation	13 (15.5)	0	13 (15.5)
Skin and subcutaneous disorders - other	12 (14.3)	0	12 (14.3)
Anorexia	11 (13.1)	1 (1.2)	12 (14.3)
Vomiting	10 (11.9)	1 (1.2)	11 (13.1)
Abdominal pain	8 (9.5)	2 (2.4)	10 (11.9)
Musculoskeletal and connective tissue disorders - other	10 (11.9)	0	10 (11.9)
Cough	10 (11.9)	0	10 (11.9)
Infections and infestations - other	7 (8.3)	3 (3.6)	10 (11.9)
Bronchial infection	8 (9.5)	1 (1.2)	9 (10.7)
Upper respiratory infection	8 (9.5)	1 (1.2)	9 (10.7)
Clinical laboratory			
Increased alanine aminotransferase[e]	19 (23.2)	3 (3.7)	22 (26.2)
Increased aspartate aminotransferase[e]	21 (25.6)	2 (2.4)	23 (27.4)
Increased alkaline phosphatase[e]	29 (35.4)	1 (1.2)	30 (35.7)
Adverse events of interest			
Pneumonitis	1 (1.2)	2 (2.4)	3 (3.6)

[a]October 2015 data set including all patients.
[b]There were 10 deaths ≤30 days following the last infusion of the study drug, including infections and infestations in five patients (meningitis, pneumonia, lower respiratory tract infection, pyelonephritis, and septic shock), general disorders in two patients (deterioration in general physical health and multi-organ dysfunction syndrome), and acute respiratory failure, circulatory collapse, and progressive disease in one patient each.
[c]Adverse events leading to permanent discontinuation of study drug included grade 3 fatigue, lung infection, pneumonitis, and maculo-papular rash in two patients each (2.4%), and grade 4 lipase increase, serum amylase increase, autoimmune disorder, and meningitis in one patient each (1.2%).
[d]Common Terminology Criteria for Adverse Events version 4.0.
[e]Two patients missing.
TEAE – treatment-emergent adverse event.

tyrosine kinase may exacerbate the rate and severity of infection [7, 22]. Copanlisib treatment decreased neutrophil count in 34.5% of patients (29.8% grade ≥3), yet serious febrile neutropenia was infrequent (three patients), as were opportunistic infections (two patients) and pneumonitis (three patients). Higher rates of pneumonitis have been reported with idelalisib in patients with relapsed lymphoma [11% (grade ≥3, 7%) and 12.5% (grade ≥3, 10%)] [16, 19]. Similarly, the incidence of pneumonitis here was low (3.6%; one grade 1 non-infectious, one grade 3 infectious, one grade 3 possibly infectious).

High rates of hepatic and gastrointestinal toxicity have been seen with idelalisib [22]. With idelalisib trials, the incidence of elevated aminotransferases ranged from 48% to 60% (all grade), with grade ≥3 ranging from 8% to 13% in phase II [15, 16, 19]. Here, elevated alanine aminotransferase and aspartate aminotransferase were incidental findings in 25.6% of patients, almost all of which were grade

1 (23.2% and 24.4%, respectively; grade 3, 3.7% and 2.4%, respectively). Diarrhea was the most common adverse event reported in a phase II study of idelalisib (all-grade, 43%; grade ≥3, 13%) [15, 16, 19]. Late-onset idelalisib-induced diarrhea has been reported, a possible symptom of autoimmune colitis [23]. In one study, 86% of patients (12/14) treated with idelalisib for ≥3 months with idelalisib-induced diarrhea had colitis with intra-epithelial lymphocytosis, crypt cell apoptosis, and neutrophilic infiltration of crypt epithelium [24]. Here, diarrhea was reported in 40.5% of patients (grade ≥3, 4.8%) and there were no reports of colitis. Only one case of colitis was reported with copanlisib in the phase I study [12]. This differentiation may reflect the intermittent administration of intravenous copanlisib versus oral agents dosed continuously.

Tumor gene expression and mutation analyses showed that consistent with the known low prevalence of *PIK3CA* mutations in lymphoma [25, 26], no mutations in *PIK3CA*, *PIK3CB*, *PIK3CD*, or *PIK3CG*, or *PTEN*, were detected. Upregulation of PI3K pathway gene expression was frequently observed in indolent and aggressive lymphoma types. Analysis of gene-expression data using response rate and progression-free survival (data not shown) as clinical outcomes demonstrated increased copanlisib antitumor activity in cases with activated PI3K/BCR signaling, which, together with low expression of unfavorable tumor microenvironment genes, is consistent with the proposed mechanism of action of copanlisib. These preliminary results are therefore currently under further evaluation in an extension cohort of patients with indolent lymphoma.

Overall, our data suggest that intravenous copanlisib may provide an effective therapeutic option for patients with relapsed or refractory, indolent or aggressive lymphoma whose disease has progressed after standard therapy. Moreover, the safety profile of intravenous intermittently dosed copanlisib is distinct and manageable, and potentially advantageous, with a lower incidence of fatal and/or severe hepatic and gastrointestinal toxicity compared with oral PI3K inhibitors. An extension study of copanlisib in patients with indolent lymphoma is ongoing, along with studies of copanlisib as monotherapy and in combination with standard chemotherapy in patients with indolent lymphoma (NCT02369016, NCT02367040, and NCT02626455) and aggressive lymphoma (NCT02391116).

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Disclosure

MD: Participated in advisory boards for and on a speaker bureau for Bayer. DC: Received research funding from Amgen, AstraZeneca, Bayer, Celgene, Merrimack, MedImmune, Merck Serono, and Sanofi. CT: Received honoraria from and participated on a board of directors or advisory board for AbbVie, Bayer HealthCare, Celgene, and Janssen; acted as a consultant for Janssen; and received research funding from Roche. FH, MG, and KK: Employees of Bayer AG. JG-V, IG, LL, CP, and BHC: Employees of Bayer HealthCare. MN: Employee of Bayer SA. PLZ: Participated in advisory boards for Roche, Janssen, Celgene, Gilead, Servier, Bayer, TG Pharmaceuticals, and Takeda. All remaining authors have declared no conflicts of interest.

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Supplementary methods

Inclusion and exclusion criteria

Marginal zone lymphoma included nodal or splenic marginal zone B-cell lymphoma or mucosa-associated lymphoid tissue lymphoma. Patients with aggressive lymphoma relapsed or refractory to prior immunotherapy-based regimens, and not qualifying for a high-dose regimen followed by autologous transplant, were also eligible. Exclusion criteria included: a previous (<5 years) or concurrent cancer; known lymphomatous involvement within the central nervous system; uncontrolled hypertension; type 1 or type 2 diabetes mellitus with fasting blood glucose >125 mg/dL; and concomitant use of CYP3A4 inducers or inhibitors.

Copanlisib administration

Patients fasted for 8 hours before and 2 hours following the first copanlisib dose; a low-carbohydrate meal was permitted 3 hours following the start of the first infusion, and before subsequent infusions if no hyperglycemia of National Cancer Institute Cancer Terminology Criteria for Adverse Events grade 2 occurred after the first infusion. Plasma glucose had to be ≤125 mg/dL before the start of the first infusion and ≤125 mg/dL (fasting) or ≤180 mg/dL (non-fasting) for subsequent infusions. Rapid short-acting insulin was recommended for hyperglycemia following copanlisib dosing on cycle 1 day 1. For subsequent doses, the decision to use an intermediate- or long-acting insulin preparation or an oral antihyperglycemic agent (e.g. metformin) was at the discretion of the investigator.

Dose reductions to 0.6 mg/kg and 0.4 mg/kg were permitted if clinically significant toxicities were observed; re-escalation was not permitted. Treatment was discontinued if the 0.4 mg/kg dose was not tolerated.

Laboratory assessments

Glycated hemoglobin was evaluated at screening and on day 1 of odd-numbered cycles from cycle 3 onwards. Plasma glucose was assessed on cycle 1 day 1 pre-dose and at 3, 4, 6, and 8 hours after the start of copanlisib infusion. Blood pressure was measured pre-dose and at 0.5, 1, 1.5, 2, 3, 4, and 6 hours following the start of infusion on cycle 1 day 1 and at the end of each infusion from cycle 1 day 8 onwards.

Biomarker assessments

Biomarker analyses were retrospective and exploratory; all assays were performed centrally. Formalin-fixed paraffin-embedded tumor tissues were collected where available, and with informed consent. Biomarker investigations focused on genes known to be frequently dysregulated in lymphoma and/or involved in phosphatidylinositol 3-kinase (PI3K) and B-cell receptor (BCR) signaling, and included PTEN protein expression by immunohistochemistry, mRNA gene-expression profiling, and next-generation sequencing for mutations.

Immunohistochemistry for PTEN protein expression was performed on archival tumor tissue samples using an anti-PTEN antibody (rabbit clone 138G6) in accordance with standard methods and validated protocols from Mosaic Laboratories (Lake Forest, CA, USA). Tissues were stained with 3,3'-diaminobenzidine chromogen (Dako, Agilent Technologies, Santa Clara, CA, USA). PTEN protein levels were evaluated and scored by pathology review. Pathology scoring included determination of the percentage of tumor cells staining positive for PTEN at each intensity level (intensity scale of 0–3+). Total percentage positivity was defined as the total percentage of tumor cells staining positive for PTEN at any intensity level (1–3+). PTEN protein loss, low, or positive was defined as 0%, 1–4%, or ≥5% of tumor cells, respectively, staining positive at any intensity level (1+, 2+, or 3+) for PTEN by

immunohistochemistry. PTEN loss or low (0% or 1–4% PTEN of tumor cells staining positive at any intensity of 1+, 2+, or 3+) was used as a cut-off for PTEN-negative. This cut-off was exploratory and numerically defined based on none or 95% of tumor cells showing no staining, which will need to be validated in future studies.

Next-generation sequencing was performed by Foundation Medicine (Cambridge, MA, USA) using the Foundation One® panel, testing for mutations in 315 genes as well as select rearrangements known to frequently occur in cancer. RNA gene-expression analysis of tumor samples was performed using Affymetrix Gene ST 1.0 arrays (AltheaDx Inc., San Diego, CA, USA). Gene-set enrichment analysis was performed to determine whether there was a statistically significant association of copanlisib response with the gene sets including PI3K and BCR signaling pathway components, among other pathways and tumor microenvironment signatures [1]. Hypothesis-free single-gene multivariate analysis including logistic regression, Cox proportional hazards models, two-way filtering-based modeling, and hypothesis-driven gene-set enrichment analysis was performed to identify genes and pathways associated with copanlisib clinical activity. Weighted gene-expression scores reflecting the overall expression level for each pathway based on gene sets were calculated using logistic regression and Cox proportional hazards models to assess association with response. Median gene-expression scores were used as a cut-off to define high and low levels for each pathway.

Statistical analysis

Efficacy analyses were conducted on the per protocol set, defined as all patients who received the study drug, were evaluable for objective response rate (having one or more post-baseline tumor assessments), and had no major protocol deviation affecting the primary efficacy evaluation. Safety analyses were conducted on the safety set, defined as all patients receiving

one or more infusions of copanlisib. All analyses were performed by or under the supervision of the sponsor's study statistician and statistical analyst. Statistical evaluation was performed using Statistical Analysis Software package, release 9.2 or higher (SAS Institute Inc., Cary, NC, USA). Variables were summarized using descriptive statistics including mean, standard deviation, median, minimum, and maximum, as well as first and third quartiles. Frequency tables were generated for categorical data. Time-to-event data were evaluated using Kaplan-Meier methodology.

Supplementary results

Copanlisib treatment

Adverse events leading to dose interruptions or delays in five or more patients included decreased neutrophil count (15.5%; 13/84), lung infection (7.1%; 6/84), and fever (6.0%; 5/84, of which four events were grade 1). Adverse events leading to dose reductions included grade 3 febrile neutropenia, grade 4 decreased neutrophil count, and hypertension (one grade 1 and one grade 2) in two patients each.

Biomarkers

DNA next-generation sequencing of 17 samples (seven indolent lymphoma and 10 aggressive lymphoma) did not reveal mutations in the class I PI3K catalytic isoform genes *PIK3CA*, *PIK3CB*, *PIK3CD*, or *PIK3CG*, or in PTEN (data not shown). Samples from one patient each with chronic lymphocytic leukemia, marginal zone lymphoma (Figure 1A), and mantle cell lymphoma (Figure 1B) had mutated *NOTCH1* (P2514fs*4, Q2440*, and R2431fs*4, respectively) and high upregulation of PI3K pathway gene expression and/or loss of/low PTEN protein expression.

Safety

Seventeen patients received insulin to manage post-infusion hyperglycemia (grade 2, 35.3% [6/17]; grade 3, 64.7% [11/17]), of whom nine had blood glucose values ≤160 mg/dL. Increases in mean glycated hemoglobin from baseline to end of treatment were <0.5% in both indolent and aggressive lymphoma cohorts (supplementary Table S4). Seventeen patients received post-dose antihypertensive treatment for grade 3 hypertension.

Supplementary reference

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Supplementary figure legends

Figure S1. Patient disposition. [a]Full analysis set. CLL – chronic lymphocytic leukemia.

Figure S2. Time to response in patients with indolent or aggressive lymphoma receiving copanlisib (per protocol set).

Table S1. Prior anticancer therapy

	Primary analysis set		
	Indolent cohort (*n*=33)	**Aggressive cohort (*n*=34)**	**Aggressive cohort, all (*n*=51)**
Type of prior systemic anticancer therapy, *n* (%)			
Immuno- / chemotherapy	28 (84.8)	27 (79.4)	33 (64.7)
Immunotherapy	20 (60.6)	6 (17.6)	12 (23.5)
High-dose chemotherapy and autologous transplant	6 (18.2)	6 (17.6)	12 (23.5)
Non-conventional	4 (12.1)	6 (17.6)	6 (11.8)
Radioimmunotherapy	1 (3.0)	2 (5.9)	2 (3.9)
Prior rituximab, *n* (%)	30 (90.9)	29 (85.3)	36 (70.6)
Median time since last anticancer therapy			
Months (range)	9.1 (0.5–41.4)	3.3 (0.3–60.2)	2.5 (0.3–60.2)
Time >6 months, *n* (%)	17 (51.5)	9 (26.5)	11 (21.6)
Refractory against ≥1 regimen (alone or in combination) with:			
Rituximab, *n* (%)	17 (51.5)	16 (47.1)	21 (41.2)
Bendamustine, *n* (%)	9 (27.3)	2 (5.9)	5 (9.8)
Rituximab and bendamustine[a], *n* (%)	6 (18.2)	2 (5.9)	2 (3.9)

[a]Patient received both drugs, but not necessarily in the same regimen.

Table S2. Response evaluation by histology of lymphoma (per protocol set)[a]

n (%)	Complete response	Unconfirmed complete response	Partial response	Stable disease	Progressive disease	Not available/ not evaluable	Objective response rate
Indolent lymphoma or CLL (*n*=32)	2 (6.3)	1 (3.1)	11 (34.4)	15 (46.9)	1 (3.1)	2 (6.3)	14 (43.8)
FL (*n*=15)[b]	2 (13.3)	1 (6.7)	3 (20.0)	8 (53.3)	0	1 (6.7)	6 (40.0)
CLL (*n*=13)[c]	0	0	5 (38.5)	6 (46.2)	1 (7.7)	1 (7.7)	5 (38.5)
MZL (*n*=3)	0	0	2 (66.7)	1 (33.3)	0	0	2 (66.7)
SLL (*n*=1)	0	0	1 (100)	0	0	0	1 (100)
Aggressive lymphoma (*n*=48)	2 (4.2)	2 (4.2)	9 (18.8)	11 (22.9)	16 (33.3)	8 (16.7)	13 (27.1)
DLBCL (*n*=15)	0	0	1 (6.7)	6 (40.0)	4 (26.7)	4 (26.7)	1 (6.7)
PTCL (*n*=14)	2 (14.3)	0	1 (7.1)	5 (35.7)	5 (35.7)	1 (7.1)	3 (21.4)
MCL (*n*=11)	0	2 (18.2)	5 (45.5)	0	3 (27.3)	1 (9.1)	7 (63.6)
Transformed indolent FL (*n*=6)	0	0	2 (33.3)	0	3 (50.0)	1 (16.7)	2 (33.3)
FL (*n*=1)[d]	0	0	0	0	0	1 (100)	0
Mediastinal large B-cell lymphoma (*n*=1)	0	0	0	0	1 (100)	0	0

[a]October 2015 data set including all patients.

[b]Grades 1, 2, and 3a.

[c]Independent assessment not conducted for patients with CLL; results based on investigator assessment.

[d]Grade 3b.

CLL – chronic lymphocytic leukemia; DLBCL – diffuse large B-cell lymphoma; FL – follicular lymphoma; MCL – mantle cell lymphoma; MZL – marginal zone lymphoma; PTCL – peripheral T-cell lymphoma; SLL – small lymphocytic lymphoma.

Table S3. Baseline status of tumor biomarkers

	Indolent cohort	Aggressive cohort	Total[a]
PTEN expression status by IHC			
n	16	26	42
High PTEN expression, *n* (%)	10 (62.5)	22 (84.6)	32 (76.2)
Low/loss of PTEN expression, *n* (%)	6 (37.5)	4 (15.4)	10 (23.8)
PI3K/BCR pathway gene-expression analysis			
n	15	9	24
Low expression, *n* (%)	6 (40.0)	2 (22.2)	8 (33.3)
High expression, *n* (%)	9 (60.0)	7 (77.8)	16 (66.6)
Combined activation of PI3K/BCR pathway (PTEN IHC and PI3K/BCR gene-expression analysis)			
n	18	26	44
No activation detected, *n* (%)	5 (27.8)	17 (65.4)	22 (50.0)
Activation, *n* (%)	13 (72.2)	9 (34.6)	22 (50.0)
Unfavorable tumor microenvironment gene signature			
n	15	9	24
Low expression, *n* (%)	9 (60.0)	3 (33.3)	12 (50.0)
High expression, *n* (%)	6 (40.0)	6 (66.7)	12 (50.0)

[a]Total values based on total number of tumor samples assessed and evaluable for each analysis.

BCR – B-cell receptor; IHC – immunohistochemistry; PI3K – phosphatidylinositol 3-kinase.

Table S4. Summary of TEAEs attributed as possibly drug-related

n (%)	Grade 1 or 2 (*n*=84)	Grade 3 or 4 (*n*=84)	Total (*N*=84)
Patients with ≥1 drug-related TEAEs	13 (15.5)	64 (76.2)	81 (96.4)[a]
Patients with any drug-related TEAE leading to permanent discontinuation of study drug	3 (3.6)	11 (13.1)	14 (16.7)
Patients with any drug-related TEAE leading to dose reduction	3 (3.6)	7 (8.3)	10 (11.9)
Patients with any drug-related TEAE leading to dose interruption	3 (3.6)	30 (35.7)	33 (39.3)
Drug-related TEAEs occurring in ≥10% of patients overall[b]			
Hyperglycemia	28 (33.3)	20 (23.8)	48 (57.1)
Hypertension	12 (14.3)	32 (38.1)	44 (52.4)
Diarrhea	23 (27.4)	4 (4.8)	27 (32.1)
Decreased neutrophil count	4 (4.8)	20 (23.8)	24 (28.6)
Fatigue	17 (20.2)	6 (7.1)	23 (27.4)
Nausea	14 (16.7)	1 (1.2)	15 (17.9)
Lung infection	3 (3.6)	8 (9.5)	13 (15.5)
Oral mucositis	12 (14.3)	1 (1.2)	13 (15.5)
Anemia	7 (8.3)	4 (4.8)	11 (13.1)

[a]There were four deaths ≤30 days following the last infusion of the study drug.

[b]Common Terminology Criteria for Adverse Events version 4.0.

TEAE – treatment-emergent adverse event.

Table S5. Summary of serious TEAEs attributed as possibly drug-related

n (%)	Grade 1 or 2 (*n*=84)	Grade 3 or 4 (*n*=84)	Total (*N*=84)
Patients with ≥1 drug-related serious TEAEs	1 (1.2)	22 (26.2)	27 (32.1)[a]
Drug-related serious TEAEs occurring in ≥3 patients overall[b]			
Lung infection	0	8 (9.5)	10 (11.9)
Diarrhea	0	3 (3.6)	3 (3.6)
Febrile neutropenia	0	3 (3.6)	3 (3.6)

[a]There were four grade 5 drug-related serious TEAEs, including cryptococcosis in one patient with chronic lymphocytic leukemia, lung infection in two patients with aggressive lymphoma, and acute respiratory failure in one patient with aggressive lymphoma.

[b]Common Terminology Criteria for Adverse Events version 4.0.

TEAE – treatment-emergent adverse event.

Table S6. Summary of blood pressure, blood glucose, and glycated hemoglobin values

	Indolent cohort (*n*=33)		Aggressive cohort (*n*=51)	
	n	**Mean (SD)**	***n***	**Mean (SD)**
Diastolic blood pressure, mmHg				
Baseline	33	71.6 (11.2)	51	72.9 (11.1)
Cycle 1 day 1	33	70.6 (10.2)	51	74.7 (11.8)
Cycle 1 day 8	32	70.6 (7.1)	49	72.2 (10.8)
Cycle 1 day 15	32	71.2 (9.7)	47	70.3 (10.4)
Cycle 2 day 1	32	71.2 (8.5)	37	69.9 (9.9)
Systolic blood pressure, mmHg				
Baseline	33	122.8 (16.1)	51	119.2 (14.4)
Cycle 1 day 1	33	122.2 (13.4)	51	120.5 (15.1)
Cycle 1 day 8	32	124.3 (14.3)	49	123.9 (15.4)
Cycle 1 day 15	32	120.4 (17.0)	47	119.5 (14.6)
Cycle 2 day 1	32	122.7 (18.0)	37	117.1 (11.9)
Blood glucose, mg/dL				
Baseline	32	95.4 (12.3)	49	97.7 (17.0)
Cycle 1 day 8	31	101.5 (19.4)	47	101.7 (22.6)
Cycle 1 day 15	30	101.7 (17.8)	45	103.5 (19.0)
Cycle 1 day 22	26	96.3 (15.7)	35	106.4 (22.0)
Cycle 2 day 1	29	93.3 (10.8)	35	94.9 (16.0)
Serum glycated hemoglobin, %				
Baseline	28	5.44 (0.71)	48	5.36 (0.52)
Cycle 3 day 1	18	5.73 (1.00)	14	5.65 (0.48)
Cycle 5 day 1	12	5.59 (0.68)	7	5.54 (0.67)
End-of-treatment visit	16	5.91 (1.07)	18	5.74 (0.81)

SD – standard deviation.