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Long-term safety and efficacy of the PI3K inhibitor copanlisib in patients with relapsed or refractory indolent lymphoma: 2-year follow-up of the CHRONOS-1 study

Martin Dreyling[1] | Armando Santoro[2] | Luigina Mollica[3] | Sirpa Leppä[4] | George Follows[5] | Georg Lenz[6] | Won Seog Kim[7] | Arnon Nagler[8] | Maria Dimou[9] | Judit Demeter[10] | Muhit Özcan[11] | Marina Kosinova[12] | Krimo Bouabdallah[13] | Franck Morschhauser[14] | Don A. Stevens[15] | David Trevarthen[16] | Javier Munoz[17] | Liana Rodrigues[18] | Florian Hiemeyer[19] | Ashok Miriyala[20] | Jose Garcia-Vargas[20] | Barrett H. Childs[20] | Pier Luigi Zinzani[21]

[1]Department of Medicine III, University Hospital, LMU, Munich, Germany

[2]Humanitas Clinical and Research Center, Rozzano, Italy

[3]Maisonneuve-Rosemont Hospital Research Centre, Montréal, Canada

[4]Department of Oncology, Helsinki University Hospital Comprehensive Cancer Center and University of Helsinki, Helsinki, Finland

[5]Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

[6]Translational Oncology, University Hospital Münster, Münster, Germany

[7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

[8]Chaim Sheba Medical Center, Tel Aviv University, Tel HaShomer, Tel Aviv-Yafo, Israel

[9]School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

[10]First Department of Internal Medicine, Semmelweis University, Budapest, Hungary

[11]Department of Internal Medicine, Division of Hematology, Ankara University, Ankara, Turkey

[12]Kemerovo Regional Clinical Hospital, Kemerovo, Russian Federation

[13]Department of Hematology, University Hospital of Bordeaux, Hôpital Haut-Lévêque, Pessac, France

[14]Univ. Lille, CHU Lille, EA 7365 - GRITA - Groupe de Recherche sur les formes Injectables et les Technologies Associées, Lille, France

[15]Norton Cancer Institute, Louisville, Kentucky

[16]Comprehensive Cancer Care and Research Institute of Colorado, LLC, Englewood, Colorado

[17]Banner MD Anderson Cancer Center Clinic, Gilbert, Arizona

[18]Bayer SA, São Paulo, Brazil

[19]Pharmaceutical Division, Bayer AG, Berlin, Germany

[20]Bayer HealthCare Pharmaceuticals, Inc., Whippany, New Jersey

[21]Institute of Hematology "Seràgnoli", University of Bologna, Bologna, Italy

Correspondence
Martin Dreyling, Klinikum der Universität München-Grosshadern, Medizinische Klinik und Poliklinik III, München, Germany.
Email: martin.dreyling@med.uni-muenchen.de

Abstract

Safety profiles of oral PI3K inhibitors have resulted in US FDA black box warnings regarding fatal/serious toxicities. The approved intravenous PI3K inhibitor copanlisib has

M.D. and A.S. contributed equally to this study.

low incidence of severe toxicities and no black box warnings, but chronic treatment effects were unknown. We provide an update on safety and efficacy of copanlisib with a minimum 2-year follow-up of the CHRONOS-1 study. A total of 142 patients with histologically confirmed indolent B-cell lymphoma who had relapsed after or were refractory to ≥2 prior treatments received intravenous copanlisib 60 mg on days 1, 8, and 15 (28-day cycle). The primary efficacy endpoint was objective response rate (ORR) after ≥4 cycles (independent assessment). The predominant histology was follicular lymphoma (n = 104). The ORR was 60.6% (seven additional complete responses since primary analysis). Secondary endpoints of median duration of response, progression-free survival, and overall survival were 14.1 months (median follow-up, 16.1 months), 12.5 months (median follow-up, 14.0 months), and 42.6 months (median follow-up, 31.5 months), respectively. Median safety follow-up was 6.7 months; 26% of patients received treatment for >1 year. Common treatment-emergent adverse events (TEAEs) (all grade/grade 3/grade 4) were transient hyperglycemia (50.0%/33.1%/7.0%), diarrhea (35.2%/8.5%/0%), transient hypertension (29.6%/23.9%/0%), and neutropenia (28.9%/9.2%/14.8%). Serious AEs were largely unchanged, with no new cases of pneumonitis (4.2%), diarrhea (2.8%), or grade 5 events. Note, TEAEs showed no evidence for increased incidence or worsening following longer exposure in patients treated >1 year. Long-term follow-up of patients with relapsed/refractory indolent B-cell lymphoma treated with intravenous copanlisib demonstrated durable, enhanced responses without evidence of worsening TEAEs, as reported for orally administered PI3K inhibitors.

1 | INTRODUCTION

Indolent B-cell lymphomas are often incurable due to frequent relapse following an initial response to first-line therapy and eventual development of refractory disease, representing a significant challenge for treatment and a high unmet need.[1] Several phosphatidylinositol 3-kinase (PI3K) inhibitors are either approved or in development to target the aberrant PI3K signaling that underlies tumor progression in several types of cancer, including lymphoma.[2-7] Clinical benefit has been reported in patients with indolent lymphoma[2,5,6]; however, data on the long-term effectiveness of PI3K inhibitors remain limited. In addition, several orally administered agents targeting the PI3K pathway have demonstrated adverse events (AEs), such as autoimmune dysfunction and opportunistic infections,[8] with reports of more severe late-onset toxicities such as diarrhea and ulcerative colitis.[9,10] Such PI3K-associated toxicities have caused the US Food and Drug Administration (FDA) to include warning statements as part of the prescribing information for orally administered PI3K inhibitors.[11,12] Hence, there is an unmet need for long-term treatment options that are both safe and effective in this patient population with advanced and difficult-to-treat lymphoma.

Copanlisib (Bayer AG, Berlin, Germany) is an intravenous pan-class I PI3K inhibitor with predominant and potent activity against the PI3K-α and PI3K-δ isoforms.[13,14] Copanlisib is indicated in the US for the treatment of patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies.[15] Clinically

significant activity was demonstrated in a population of patients with relapsed or refractory indolent B-cell lymphoma who had received at least two prior therapies in a large phase 2, multicenter, open-label study (CHRONOS-1; NCT01660451, Part B). The primary efficacy endpoint of that study was objective response rate (ORR); 84 of 142 patients achieved an objective response, giving an ORR of 59.2%.[2] At the time of the primary analysis, the minimum follow-up from the date of the last patient initiating treatment was only 4 months, with an overall median duration of safety follow-up of 24 weeks. There were low rates of severe hepatic transaminitis, diarrhea, pneumonitis, and colitis (0.7%) and infrequent opportunistic infections, fatal infections, or other fatal AEs.[2] Based largely on these results, copanlisib was approved by the US FDA without the so-called black box warning.

To gain a better understanding of the safety and efficacy associated with long-term use of an intravenous PI3K inhibitor, including patients treated for 1 year or more, we report here the safety and efficacy from a 2-year follow-up of patients treated with copanlisib in the CHRONOS-1 study.

2 | METHODS

Detailed methods of the CHRONOS-1 study have been reported previously.[2] Briefly, this was an open-label, single-arm, phase 2 study evaluating the efficacy and safety of single-agent copanlisib in patients with

histologically confirmed indolent B-cell lymphoma who had relapsed after or were refractory to at least two prior lines of treatment (clinicaltrials.gov; NCT01660451, Part B). Eligibility criteria included patients aged ≥18 years with histologically confirmed indolent B-cell lymphoma, including FL grades 1 to 3a, marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and Waldenström macroglobuline-mia/lymphoplasmacytoid lymphoma (WM/LPL), who had previously received rituximab and an alkylating agent or regimen. Patients were also required to have at least one bidimensionally measurable lesion[16] and an Eastern Cooperative Oncology Group performance status (ECOG PS) of ≥2.

Copanlisib was administered at a fixed dose of 60 mg via a 1-hour intravenous infusion on an intermittent schedule, on days 1, 8, and 15 of a 28-day cycle until progression or unacceptable toxicity.

The primary efficacy variable was ORR after 4 or more cycles of treatment, defined as the proportion of patients who had a best response rating of complete response or partial response according to central radiologic review. Secondary efficacy variables included duration of response (DoR), progression-free survival (PFS), overall survival (OS), best change in target lesions, and disease control rate.

Tumors were assessed by computed tomography scan or magnetic resonance imaging at screening and every 2 cycles during year 1, every 3 cycles during year 2, and every 6 cycles during year 3. Response was determined by independent radiologic review.[16] For patients with WM, very good partial response and minor response categories were omitted from the response categories published by the Sixth International Workshop on Waldenström's Macroglobuline-mia.[17] A safety follow-up visit was scheduled to occur within 30 to 35 days after the last study treatment, followed by scheduled visits every 3 months. The AEs were reported per the Medical Dictionary for Regulatory Activities version 20.1, and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Prophylaxis for opportunistic infection was not mandated.

All patients who received treatment comprised the full analysis set and were included in analyses, unless otherwise specified. Prespecified evaluation of the primary efficacy variable was performed using a one-sided exact binomial test (α = 2.5%), rejecting the null hypothesis of an ORR of ≤40%. Estimates were calculated, and exact 95% confidence intervals (CI) were determined using the Clopper–Pearson method. Kaplan–Meier estimates were used to describe time-to-event variables. Median follow-up of efficacy variables was calculated using the method of Schemper et al.[18] Statistical evaluations were completed using Statistical Analysis System 9.2 software or higher (SAS Institute, Cary, NC, USA) and R version 3.2.3/3.3.0 (The R Foundation, Vienna, Austria).

Each patient provided written, informed consent. Study methodologies conformed to the standards set by the Declaration of Helsinki and were approved by the appropriate ethics committee at each study site. All authors had a role in analyzing the data and had access to the primary clinical trial data.

3 | RESULTS

3.1 | Patients and treatment

The full analysis set comprised 142 patients who received treatment with copanlisib, of whom 141 had indolent lymphoma. Patient demographics and baseline characteristics are presented in Table 1. The median age at baseline was 63 years (range 25-82) and 50.0% of patients were male. Patients received a median of three prior lines of therapy (range 2-9); all patients had received rituximab and alkylating agents, with 80.3% of patients refractory to any prior therapy and 60.6% refractory to the last regimen. In total, 19 patients (13.4%) received prior high-dose chemotherapy or autologous stem cell transplant. No patients received allogeneic stem cell transplant prior to or during the study, though eight patients (5.6%) received allogeneic stem cell transplant during follow-up.

Detailed study results of the primary analysis have been reported previously.[2] At the time of the primary analysis, 46 patients were still receiving treatment, whereas 11 (7.7%) remained on treatment at the extended database cut-off. Overall, the reasons for discontinuation of treatment were radiological progressive disease (31.7%; 45/142), AEs not associated with disease progression (26.8%; 38/142), study withdrawal by patient (14.1%; 20/142), AEs associated with clinical disease progression (10/142; 7.0%), clinical progressive disease (8/142; 5.6%), physician decision (5/142; 3.5%), sponsor decision, protocol deviation, protocol violation, and death (1/142 each; 0.7%).

3.2 | Safety profile

The median duration of copanlisib treatment was 26 weeks (range 1-192). This corresponded to a median of 6.5 treatment cycles (range 0.3-48.0). Patients received a median of 95.1% of the planned dose (range 51.0-102.8). In total, 70 patients (49.3%) received copanlisib for up to 6 months, 35 patients (24.6%) received copanlisib for between 6 months and 1 year, and 37 patients (26.1%) received copanlisib for more than 1 year, including seven patients (4.9%) who received treatment for more than 3 years. The median duration of safety follow-up was 6.7 months (range 0.2-44.1).

Treatment-emergent AEs (TEAEs) of any grade were reported for 140/142 patients (98.6%), which remained unchanged with the longer follow-up since the primary analysis. The most common TEAEs of any grade were transient hyperglycemia (50.0%), diarrhea (35.2%), transient hypertension (29.6%), neutropenia (28.9%), pyrexia (26.8%), and fatigue (26.1%) (Table 2). Newly occurring worst-grade events of any grade did not increase more than 5% vs the primary analysis set. Drug-related TEAEs were reported in 127/142 patients (89.4%), one additional patient than reported at the primary analysis, and are presented in Supporting Information, Table S1.

Grade 3 TEAEs were experienced by 77 patients (54.2%) and grade 4 events were experienced by 41 patients (28.9%), an addition of two and three patients, respectively, compared with the primary analysis (Table 2). The most common grade 3 TEAEs were

hyperglycemia (33.1%) and hypertension (23.9%), and the most common grade 4 TEAEs were neutropenia (14.8%) and hyperglycemia (7.0%). Overall, there were four additional cases of grade 3 diarrhea (total 12 patients [8.5%]), two new cases of grade 3 bronchitis (total 2 patients [1.4%]), and two additional cases of grade 4 neutropenia (total 21 patients [14.8%]) compared with the primary analysis. No

TABLE 1 Patient demographics and baseline characteristics

	Total (N = 142)[2]
Males, n (%)	71 (50.0)
Median age, years (range)	63 (25–82)
Race, n (%)	
White	120 (84.5)
Asian	15 (10.6)
Not reported	7 (4.9)
Histology of tumor, n (%)[a]	
FL (grades 1-3a)[b]	104 (73.2)
MZL	23 (16.2)
SLL	8 (5.6)
WM/LPL	6 (4.2)
DLBCL[c]	1 (0.7)
Ann Arbor Conference classification of disease stages at study entry, n (%)	
I	3 (2.1)
II	25 (17.6)
III	32 (22.5)
IV	82 (57.7)
Mean serum LDH at baseline, units/L (SD)[d]	298.4 (185.9)
Baseline ECOG PS, n (%)	
0	80 (56.3)
1	57 (40.1)
2	5 (3.5)
Median time from most recent progression, weeks (range)	8.3 (1–73)
Median number of prior anti-cancer therapy lines (range)	3 (2–9)
Prior therapy, n (%)	
Rituximab	142 (100)
Alkylating agents	142 (100)
High-dose chemotherapy/ autologous stem cell transplant	19 (13.4)
Refractory,[e] n (%)	114 (80.3)
Rituximab	100 (70.4)
Rituximab and any other treatment[f]	79 (55.6)

(Continues)

TABLE 1 (Continued)

	Total (N = 142)[2]
Refractory to last regimen, n (%)	86 (60.6)
Rituximab	80 (56.3)
Alkylating agents[g]	61 (43.0)
Rituximab and alkylating agents[g]	61 (43.0)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOS PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; LDH, lactate dehydrogenase; MZL, marginal zone lymphoma; SD, standard deviation; SLL, small lymphocytic lymphoma; WM/LPL, Waldenström macroglobulinemia/lymphoplasmacytoid lymphoma.
[a]Histology was determined based on investigator assessment.
[b]Grade of FL was not available for three patients.
[c]The patient with DLBCL was initially assessed by the investigator as having indolent lymphoma, which was later confirmed by both the investigator and central pathology review to be DLBCL; however, the patient received treatment and was included in the full analysis set.
[d]n = 35.
[e]A patient was considered refractory to an anti-cancer therapy if they had a best response of progressive disease, stable disease, or unknown for ≥1 anti-cancer regimen or if the response lasted <6 months.
[f]Excluding transplant/radiotherapy or non-conventional therapy.
[g]Since completion of the primary analysis, the WHO Drug Dictionary has been updated to include cisplatin as an alkylating agent; therefore, one additional patient who received cisplatin as the last regimen was included in the alkylating agents group who did not qualify at the time of the primary analysis.

grade 4 diarrhea was reported. There were increased incidences of one patient each for the following grade 3 TEAEs: hyperglycemia, hypertension, neutropenia, pneumonia, and anemia. Of TEAEs of special interest, one additional case of grade 3 pneumonitis was reported, totaling two events (1.4%) overall (Table 2). Likewise, laboratory findings of elevated liver enzymes (any grade) were less than 5% (Table 2).

Serious AEs (SAEs) were reported in 79 patients (55.6%), compared with 71 patients (50.0%) at the time of the primary analysis. The most common all-grade SAEs occurring in at least three patients were pneumonia (16/142; 11.3%), pyrexia (9/142; 6.3%), hyperglycemia (7/142; 4.9%), and pneumonitis (6/142; 4.2%) (Supporting Information, Table S2). Of SAEs of grade ≥3, there was one new or additional case each of the following grade 3 events: cholecystitis, pneumonitis, *Klebsiella* bacteremia, afferent loop syndrome, disorientation, abdominal pain, and pulmonary embolism; and one additional case each of the following grade 4 events: chronic lymphocytic leukemia and sepsis.

Overall, rates of pneumonitis (9/142 [6.3%], all grade) and colitis (1/142 [0.7%], grade 4) remained low and were unchanged from the primary analysis. The one grade 4 event of colitis occurred early in treatment (day 28-34) in a patient with a history of diverticulosis; the patient responded to antibiotics with no recurrence at a reduced dose.

No new treatment-emergent mortality was observed in the extended analysis compared with the primary analysis; 6/142 patients (4.2%) experienced grade 5 events during treatment or within 35 days following permanent discontinuation, with three events (2.1%)

TABLE 2 Summary of TEAEs and incidence of most common TEAEs

n (%)	June 2016 data cut-off (N = 142)			February 2018 data cut-off (N = 142)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
TEAE	140 (98.6)	75 (52.8)	38 (26.8)	140 (98.6)	77 (54.2)	41 (28.9)
TEAEs occurring in ≥10% of the total population						
Non-hematologic toxicities						
Hyperglycemia	69 (48.6)	46 (32.4)	10 (7.0)	71 (50.0)	47 (33.1)	10 (7.0)
Diarrhea	48 (33.8)	8 (5.6)	0	50 (35.2)	12 (8.5)	0
Hypertension	42 (29.6)	33 (23.2)	0	42 (29.6)	34 (23.9)	0
Pyrexia	36 (25.4)	6 (4.2)	0	38 (26.8)	6 (4.2)	0
Fatigue	36 (25.4)	3 (2.1)	0	37 (26.1)	3 (2.1)	0
Nausea	33 (23.2)	1 (0.7)	0	33 (23.2)	1 (0.7)	0
Cough	24 (16.9)	0	0	27 (19.0)	0	0
Upper respiratory tract infection	19 (13.4)	2 (1.4)	0	21 (14.8)	2 (1.4)	0
Pneumonia	18 (12.7)	12 (8.5)	2 (1.4)	20 (14.1)	13 (9.2)	2 (1.4)
Vomiting	18 (12.7)	0	0	20 (14.1)	0	0
Constipation	17 (12.0)	0	0	18 (12.7)	0	0
Decreased appetite	15 (10.6)	0	0	15 (10.6)	0	0
Bronchitis	13 (9.2)	0	0	16 (11.3)	2 (1.4)	0
Back pain	12 (8.5)	0	0	15 (10.6)	1 (0.7)	0
Hematologic toxicities						
Neutropenia	36 (25.4)	12 (8.5)	19 (13.4)	41 (28.9)	13 (9.2)	21 (14.8)
Anemia	20 (14.1)	6 (4.2)	0	25 (17.6)	7 (4.9)	0
Thrombocytopenia	19 (13.4)	7 (4.9)	0	20 (14.1)	7 (4.9)	0
TEAEs of special interest						
Pneumonitis[a]	10 (7.0)	1 (0.7)	0	9 (6.3)	2 (1.4)	0
Colitis	1 (0.7)	0	1 (0.7)	1 (0.7)	0	1 (0.7)
Laboratory toxicities						
ALT increased[b]	4 (2.8)	1 (0.7)	0	6 (4.2)	1 (0.7)	0
AST increased[b]	2 (1.4)	0	0	3 (2.1)	0	0

Note: AEs were classified by using the Medical Dictionary for Regulatory Activities (MedDRA; version 20.1) and graded by using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03).

Abbreviations: AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

[a]One patient initially diagnosed with pneumonitis at the primary cut-off was later confirmed to have infection and the MedDRA entry was corrected accordingly by the investigator, totaling nine patients with any-grade pneumonitis.

[b]Missing values for 1 patient.

considered treatment related (lung infection, respiratory failure, and embolism [0.7% each]).

Of the 142 patients who were treated with copanlisib, 38 patients (26.8%) discontinued due to an AE not associated with disease progression, of which the majority (15%) occurred within the first 6 months of treatment and were highest in the first 3 cycles of treatment. The most common TEAEs leading to permanent discontinuation included pneumonitis in five patients (3.5%), neutropenia in four patients (2.8%), and diarrhea, hyperglycemia, and thrombocytopenia in three patients (2.1%) each. A total of 30 patients (21.1%) discontinued due to an AE attributed to copanlisib.

The TEAEs leading to dose reductions were recorded in 40 patients (28.2%), most commonly hyperglycemia (n = 12), neutropenia (n = 8), hypertension (n = 6), and pneumonitis (n = 4). Dose reduction to 45 mg occurred in 41 patients (28.9%) for a median of 6.0 weeks (range 0-64.0). Dose interruptions or delays were experienced by 116/142 patients (81.7%), an additional 11 patients since the primary analysis. Thirty-four patients experienced one interruption or delay, 24 patients experienced two interruptions or delays, and 20 patients experienced three interruptions or delays; the remaining 38 patients experienced four or more interruptions or delays. The median time of interruption or delay was 1.0 week (range 0-2.9); 96.6% of interruptions/delays lasted 1 week or less. The TEAEs leading to dose interruptions were recorded in 97 patients (68.3%), most commonly neutropenia (n = 28), hypertension (n = 11), pneumonia (n = 11), bronchitis (n = 10), diarrhea (n = 8), and pyrexia (n = 7).
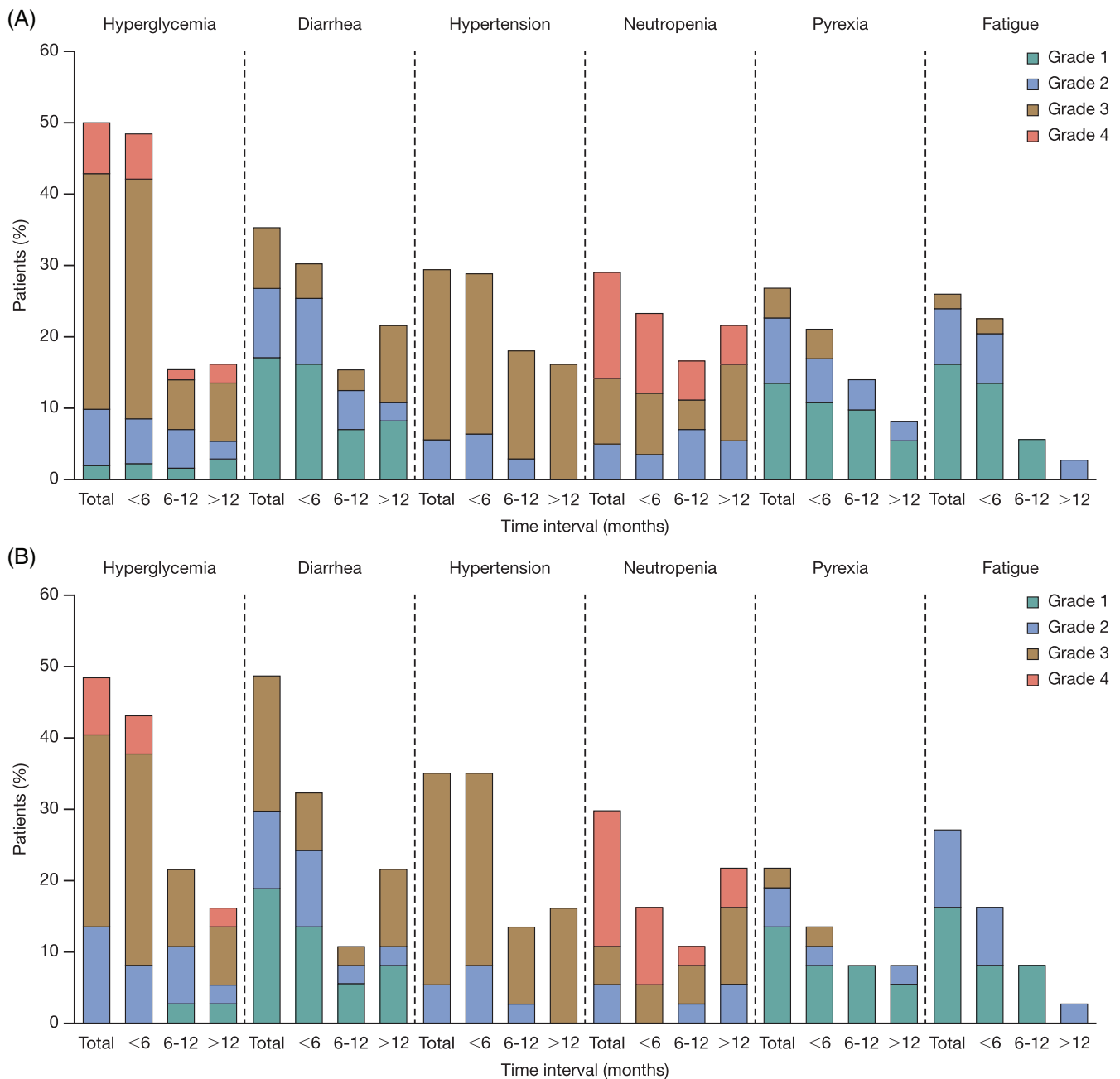
FIGURE 1 Time of onset for the most common TEAEs for A, all patients (total, N = 142; <6 months, n = 142; 6-12 months, n = 72; >12 months, n = 37); and B, patients treated for >12 months (n = 37). The >12-month category includes patients with up to 44.3 months (192 weeks) of treatment. TEAE, treatment-emergent adverse event

Because of reports of delayed or late-onset AEs associated with continuously dosed oral PI3K inhibitors, in addition to the overall incidence of AEs as commonly reported (Table 2), we further evaluated the incidence and severity of AEs over the course of treatment. Specifically, we determined the incidence of new or worsening AEs within specific time intervals: patients treated up to 6 months (n = 142), between 6 and 12 months (n = 72), and >12 months (n = 37). The assumption was that if there were cumulative toxicity or late-onset AEs, then AEs would occur at a higher incidence or higher grade following longer treatment. As shown in Figure 1A for AEs with overall incidence of ≥25% and in Supporting Information, Table S3 for all

AEs >10%, the highest incidence of AEs was seen early in the <6-months interval, with reduction in incidence and grade in the 6-12 months and >12-months intervals. The possible exception was grade 3 diarrhea, which was reported in 10.8% of patients treated for >12 months compared with 4.9% of patients treated for <6 months (it should be noted, however, that the treatment interval in the >12-month group was as long as 192 weeks compared to the earlier 6-month intervals). There were no reports of grade 4 diarrhea and only one case of colitis in this study (grade 4, <6-month interval).

For the 37 patients who received copanlisib for more than 1 year, there was no evidence for higher incidences of new or worsening
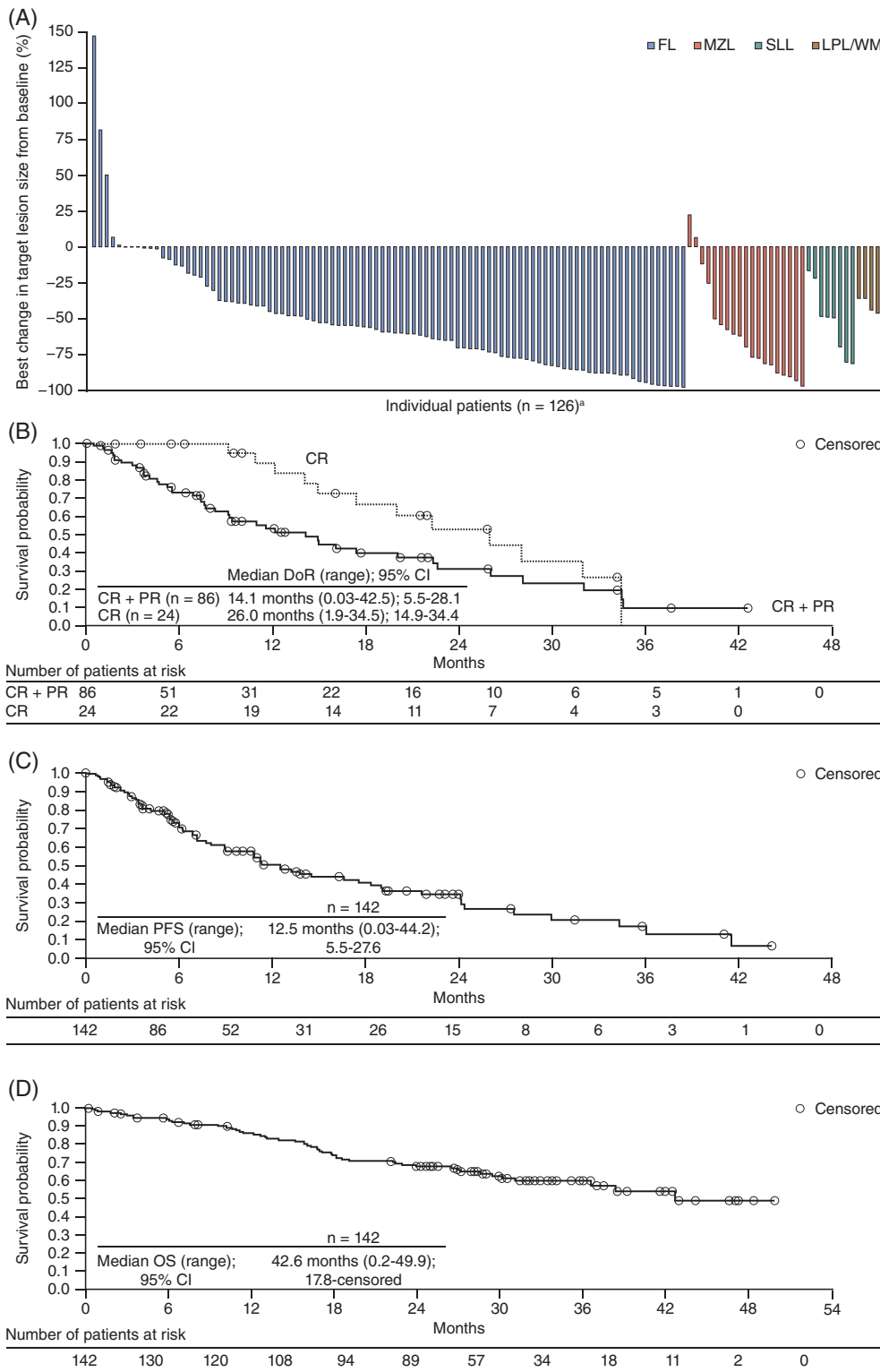
FIGURE 2 A, percentage best change from baseline of lesion size in target lesions per investigator assessments and secondary efficacy endpoints of B, DoR; C, PFS; and D, OS at the February 2018 cut-off date (full analysis set). [a]Each bar represents one patient; of the full analysis (n = 142), the best change in target lesions for the investigator onsite assessment could not be determined in 15 patients (10.6%), and the change in lesions (increase of 250%) is not shown for one patient classified by the investigator as having FL but who was reclassified by independent assessment as having DLBCL. CI, confidence interval; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; OS, overall survival; PFS, progression-free survival; PR, partial response; SLL, small lymphocytic lymphoma; WM/LPL, Waldenström macroglobulinemia/ lymphoplasmacytoid lymphoma

TEAEs occurring after 12 months of treatment compared with those occurring in the first 6 months of treatment in the same group of patients (Figure 1B and Supporting Information, Table S4). The incidences of worst grade 3 and grade 4 hyperglycemia and hypertension were lower in the 6-12 months and >12-months intervals for patients treated for more than 1 year compared with the incidences occurring during <6 months of treatment. Grade 3 hyperglycemia was reported in 11/37 patients (29.7%) in the first 6 months of treatment and in 3/37 patients (8.1%) after 1 year; grade 4 hyperglycemia was reported in two patients (5.4%) in the first 6 months and one patient (2.7%) after 1 year of treatment. Grade 3 hypertension was experienced by 10/37 patients (27.0%) in the first 6 months of treatment and by 6/37 patients (16.2%) after 1 year; none of the 37 patients had grade 4 hypertension. There was one additional worst grade 3 diarrhea event

at the later time interval; 3/37 patients (8.1%) in the first 6 months and 4/37 patients (10.8%) after 1 year of treatment. There was no grade 4 diarrhea reported in any interval. Similarly, elevations in liver enzymes were not seen (Supporting Information, Table S4). For the patients receiving treatment for more than 1 year, no grade 3 or grade 4 upper respiratory tract infection occurred after 6 months of treatment, and no grade 3 or grade 4 fatigue was reported at any time. Grade 3 pneumonitis was reported in 1/37 patients (2.7%; occurring after 1 year of treatment), and no cases of colitis were reported at any time interval for the patients treated in excess of 1 year. No fatal AEs were reported in patients who received copanlisib for more than 1 year.

3.3 | Efficacy

Per independent central review, 24 patients (16.9%) achieved complete response and 62 patients (43.7%) achieved partial response, resulting in an ORR of 60.6% (86/142) (Supporting Information, Table S5), compared with 17 patients with complete responses and an ORR of 59.2% (84/142) at the time of the primary analysis. Stable disease was observed in 41 patients (28.9%) and progressive disease occurred in three patients (2.1%). Complete responses were observed in 21 patients with FL (complete response rate of 20.2%; 21/104) and partial responses were observed in 40 patients (38.5%; 40/104), resulting in an ORR of 58.7% (61/104). In the subset of patients with MZL, three patients achieved a complete response (complete response rate of 13.0%; 3/23) and 15 patients achieved a partial response (65.2%; 15/23), resulting in an ORR of 78.3% (18/23). The seven additional complete responses were observed in six patients with FL and one patient with MZL. One additional partial response was observed in a patient with MZL who had stable disease at the primary analysis. The overall disease control rate remained unchanged at 85.9% (122/142).

Response rates were consistent across subgroups (Supporting Information, Figure S1), including by patient age, tumor size, the number of prior lines of therapy, and whether patients were refractory to their last therapy. Median time to response was 1.8 months (range 1.3-17.3). Median time to complete response was 4.7 months (range 1.5-20.9).

Of those evaluated for lesion size, 116/126 patients (92.1%) experienced a reduction in target lesion size from baseline following treatment with copanlisib (Figure 2A). A reduction of at least 50% was experienced by 79/126 patients (62.7%), compared with 74/125 patients (59.2%) at the time of the primary analysis.

Median DoR was 14.1 months (range 0.03-42.5), with a median follow-up of 16.1 months; median duration of complete response was 26.0 months (range 1.9-34.5) (Figure 2B). There were 72 progressions, and median PFS was 12.5 months (range 0.03-44.2) (Figure 2C), with a median follow-up of 14.0 months; the PFS rate at 2 years was 34%. Fifty-two patients died, and median OS was 42.6 months (range 0.2-49.9) (Figure 2D), with a median follow-up of 31.5 months; the OS rate at 2 years was 69%. Although patients with WM/LPL had the lowest ORR (16.7%) of any subset, tumor shrinkage was seen in all patients with measurable disease (Figure 2A).

For the 41 patients (28.9%) who had stable disease as best response, the median duration of stable disease was 7.2 months (range 1.3-23.0).

4 | DISCUSSION

Long-term follow-up data from the large multicenter CHRONOS-1 study of copanlisib demonstrated continued safety and enhanced efficacy in patients with relapsed or refractory indolent B-cell lymphoma. In the 2-year follow-up of the primary analysis, an overall ORR of 60.6% was achieved, compared with 59.2% at the time of the primary analysis,[2] and indicated some deepening of responses with time on treatment, principally partial response to complete response. Six patients who initially had a partial response at the primary analysis achieved complete response at the later cut-off, and one patient who initially had stable disease achieved a partial response at the later cut-off. Indeed, the median time to complete response (4.7 months) was more than twice the median time to first response (1.8 months). The ORR in patients with FL remained at 58.7%, while the ORR in patients with MZL increased to 78.3%. The proportion of patients with a primary response of progressive disease was low (2.1%). The ORR was consistent across the various subgroups, including patients aged <65 years or ≥65 years and patients who were or were not refractory to last treatment.

The median DoR overall was 14.1 months and was greater than 2 years for patients with complete responses. Median PFS was greater than 1 year. Median OS was demonstrated to be more than 3.5 years with copanlisib treatment.

These efficacy data for copanlisib suggest favorable response rates, generally consistent with or better than those reported for other PI3K inhibitors to date. A 20-month follow-up of the oral PI3K-δ inhibitor idelalisib reported an ORR of 56% in refractory indolent B-cell lymphoma[19] (ORR of 57% at the primary evaluation).[5] The median DoR (13.9 months) and median PFS (11.0 months)[19] were similar to those observed with copanlisib. The PI3K-δ and -γ inhibitor duvelisib achieved an ORR of 47.3% and median PFS of 9.5 months in patients with indolent refractory lymphoma.[6] The PI3K-δ inhibitor umbralisib demonstrated an ORR of 36.7% in patients with hematological malignancies,[20] while an ORR of 25% was reported in a phase 2 study of the oral pan-PI3K inhibitor buparlisib (median PFS of 9.8 months in patients with FL).[21]

Overall, the most common TEAEs of any grade reported with long-term treatment with copanlisib were transient hyperglycemia (50.0%), diarrhea (35.2%), transient hypertension (29.6%), neutropenia (28.9%), and pyrexia (26.8%), remaining consistent with the primary analysis and with previous reports of copanlisib.[2,22,23] Events continued to be transient and manageable. Hyperglycemia has also been reported as a common TEAE with other PI3K inhibitors[21,24-26] and is believed to be an on-target effect of PI3K-α inhibition due to its well-described role in insulin signaling.[27] The incidence and severity of hyperglycemia with copanlisib were similar to those reported with the orally administered α-selective PI3K inhibitor alpelisib.[28] Although hyperglycemia with the latter agent is presumably more prolonged due to daily administration, hyperglycemia observed with copanlisib

administered intravenously once weekly is transient and returns to baseline within 24 hours.[29] Interestingly, the incidences of hyperglycemia and hypertension appeared to decrease in later use compared with the earlier time points. Whether this reflects improved patient management or the development of tolerance cannot be determined at this time. In general, in later treatment intervals and for the patients treated for more than 1 year with copanlisib, the most commonly reported events showed no evidence for increased incidence or worsening severity following longer exposure, suggesting that worst-grade TEAEs tended to occur earlier in treatment. In addition, there was no evidence of new or unexpected TEAEs in patients exposed to copanlisib for longer duration. The safety profile that was observed from this extended analysis remains consistent with the known safety profile of copanlisib.

Of particular interest was whether there was an occurrence of late-onset worst-grade or severe toxicities with longer exposure to copanlisib. An additional four patients experienced grade 3 diarrhea (total incidence of grade 3 diarrhea was 8.5%). In the 37 patients treated with copanlisib for more than 1 year, four patients experienced grade 3 diarrhea with an onset after 12 months of treatment, although it is important to note that some patients in this subgroup had received treatment for more than 3 years. Overall, there were no cases of grade 4 diarrhea. Rates of individual severe toxicities also remained low, with all-grade SAEs of pneumonitis (4.2%), hyperglycemia (4.9%), and diarrhea (2.8%) unchanged at the extended cut-off date; there was one additional patient with all-grade SAE of lung infection. Colitis (one case overall) or other severe gastrointestinal toxicities or hepatic transaminase elevations remained low, suggesting a lack of late-onset toxicities of concern for patients receiving extended treatment with copanlisib. Higher rates of diarrhea and other severe gastrointestinal toxicities have been reported with other PI3K inhibitors that are approved for the treatment of B-cell lymphoma. This includes a phase 2 study of duvelisib with a similar median duration of treatment (6.7 months)[6] as well as a phase 2 study of idelalisib with a longer median duration of treatment (11.1 months).[19] In addition, higher rates of colitis, ulcerative colitis, and other severe gastrointestinal toxicities have been reported for idelalisib[9] and for duvelisib.[6] The low rate of severe gastrointestinal toxicities such as colitis or severe liver enzyme elevations reported with copanlisib may be attributable to lower exposure of the gastrointestinal tract to copanlisib due to the intermittent dose schedule and intravenous route of administration vs continuously administered oral agents such as idelalisib[9] or duvelisib.[30]

In conclusion, long-term follow-up of copanlisib demonstrated sustained and enhanced efficacy over time, including additional durable complete responses. The AEs remained transient and manageable over time, including in those patients treated with copanlisib for more than 1 year. No new or unexpected TEAEs were reported in patients exposed to copanlisib for longer duration. In addition, the lack of late-onset toxicities and severe gastrointestinal toxicities suggests that the approved intravenous route of administration and the intermittent dose schedule for copanlisib benefit tolerability. Studies are currently investigating copanlisib in combination with standard of care treatments in relapsed indolent non-Hodgkin lymphoma (NCT02367040 and NCT02626455).

CONFLICT OF INTEREST

M.D.: honoraria: Celgene, Janssen, Roche; scientific advisory boards: Acerta, Bayer, Celgene, Gilead, Janssen, Novartis, Roche, Sandoz; speaker's honoraria: Bayer, Celgene, Gilead, Janssen, Roche; institutional support: Celgene, Janssen, Roche. A.S.: speaker's bureau: AbbVie, Amgen, ArQule, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Eisai, Gilead, Lilly, MSD, Novartis, Pfizer, Roche, Sandoz, Servier, Takeda; advisory boards: Bayer, Bristol-Myers Squibb, Eisai, Gilead, MSD, Pfizer, Servier; consultancy: ArQule. L.M.: nothing to disclose. S.L.: consultancy: Celgene, Janssen, Merck, Novartis, Roche, Takeda; honoraria: Merck, Roche, Takeda; research funding: Bayer, Celgene, Janssen, Roche, Takeda. G.F.: advisory board and lecturing: AbbVie, Bayer, Janssen, Roche. G.L.: grants, personal fees, and nonfinancial support: AstraZeneca, Bayer, Celgene, Gilead, Janssen, MorphoSys, Roche; grants: Agios, Verastem; personal fees and nonfinancial support: Bristol-Myers Squibb, Novartis. W.S.K.: nothing to disclose. A.N.: nothing to disclose. M.D.: nothing to disclose. J.D.: consulting or advisory role: Amgen, Angelini, Aramis Pharma, Bristol-Myers Squibb, Celgene, Novartis, Pfizer, Roche. M.Ö.: grants: AbbVie, Amgen, Archigen, Bayer, Bristol-Myers Squibb, Celgene, Janssen, M.S.D., Novartis, Roche, Takeda; medical congress accommodation: AbbVie, Bristol-Myers Squibb, Roche, Takeda; honoraria: Amgen, Takeda. M.K.: research funding: AbbVie, Astellas Pharma, Bayer, CSL Behring GmbH, PRA, Takeda. K.B.: nothing to disclose. F.M.: lectures and advisory boards: Celgene, Roche; advisory boards: Bayer, Bristol-Myers Squibb, Epizyme, Gilead, Janssen; lectures: Janssen. D.A.S.: nothing to disclose. D.T.: nothing to disclose. J.M.: speaker's bureau: AstraZeneca, Bayer, Gilead/Kite Pharma, Pharmacyclics/Janssen; advisory boards: Alexion, Bayer, Bristol-Myers Squibb, Genentech, Gilead/Kite Pharma, Juno/Celgene, Kyowa Kirin, Pfizer, Pharmacyclics/Janssen. L.R.: employment: Bayer SA. F.H.: employment: Bayer AG. A.M.: employment: Bayer HealthCare Pharmaceuticals, Inc. J.G.V.: employment: Bayer HealthCare Pharmaceuticals, Inc. B.H.C.: employment: Bayer HealthCare Pharmaceuticals, Inc. P.L.Z.: consultancy: EUSA Pharma, MSD, Sanofi, Verastem; speaker's bureau: Bristol-Myers Squibb, Celgene, Celltrion, EUSA Pharma, Gilead, Immune Design, Janssen, Kyowa Kirin, MSD, Portola, Roche, Servier, Verastem; advisory boards: Bristol-Myers Squibb, Celgene, Celltrion, EUSA Pharma, Gilead, Immune Design, Janssen, Kyowa Kirin, MSD, Portola, Roche, Sandoz, Servier, Verastem.

AUTHOR CONTRIBUTIONS

M.D. participated in the literature review and data collection, analysis, and interpretation. A.S., L.M., S.L., G.F., G.L., W.S.K., A.N., M.D., J.D., M.Ö., M.K., K.B., F.M., D.A.S., D.T., J.M., and P.L.Z. participated in data

collection, analysis, and interpretation. L.R., F.H., A.M., J.G.V., and B.H.C. participated in the literature review, study design and protocol development, and data analysis and interpretation. All authors participated in writing and/or critically reviewing the manuscript and approved this version for submission.

ORCID

Pier Luigi Zinzani 🔵 https://orcid.org/0000-0002-2112-2651

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.