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# Copanlisib in combination with rituximab and bendamustine for transplant-ineligible relapsed/refractory diffuse large B-cell lymphoma patients: Results from the phase II multicentre FIL Copa-BR trial from Fondazione Italiana Linfomi (FIL)

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**Summary**

Treatment options for relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) patients ineligible for autologous stem cell transplant (ASCT) or chimeric antigen receptor (CAR)-T-cell therapy remain limited. The PI3K inhibitor copanlisib has shown activity as a single agent in DLBCL. This phase II, single-arm, multicentre trial evaluated copanlisib with rituximab and bendamustine (copa-BR) in ASCT- and CAR-T-ineligible R/R DLBCL. Patients received six cycles of copa-BR, followed by up to 12 cycles of copanlisib maintenance. The primary end-point was 12-month progression-free survival (PFS). Thirty-seven patients (aged 68–87 years, R/R after 1–2 prior lines) were enrolled. The overall response rate was 24.3%, with complete responses in 13.5%. After a median follow-up of 20 months, the 12-month PFS and overall survival rates were 25.1% and 44.5% respectively. Grade ≥3 toxicities included neutropenia (56.8%), infections (27.0%, including 6 death due to COVID-19 infection with 25% fatality) and thrombocytopenia (16.2%). Due to limited efficacy, poor tolerability and emerging alternative treatments, the trial was terminated prematurely. Copa-BR showed limited activity and an unfavourable safety profile, discouraging further investigation of this combination in ASCT- and CAR-T-ineligible R/R DLBCL.

**KEYWORDS**
bendamustine, copanlisib, diffuse large B-cell lymphoma, relapsed/refractory, rituximab

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For affiliations refer to page 8.

# INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin lymphoma (NHL) accounting for 30%–40% of newly diagnosed lymphomas.[1] Cyclophosphamide, doxorubicin, vincristine and prednisone with rituximab (R-CHOP) represent the standard treatment in first-line but approximately one-third of the patients relapse or are refractory.[2–6] Those with no response or early relapse after R-CHOP have a dismal prognosis with a 2-year overall survival (OS) of less than 20%.[7] For those patients, treatment included high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT).[8,9] In addition, chimeric antigen receptor (CAR) T cells are now used in second or in third line with excellent results showing a 2-year progression-free survival (PFS) ranging from 31% to 48%.[10–14] Patients ineligible for or failing transplantation or CAR-T cells have limited treatment options. The immunochemotherapy regimen rituximab plus bendamustine (BR) has been shown to be effective in treating relapsed/refractory (R/R) DLBCL, with an overall response rate (ORR) of up to 63%, but short lasting with a median PFS of a few months.[15–18] More recently, in a phase 2 randomized trial, the addition of polatuzumab vedotin to BR (pola-BR) improved median PFS compared to BR alone (9.2 vs. 3.7 months).[19] However, real-world data with pola-BR reported inferior results.[20–22] Thus, there is an urgent need for effective treatments for R/R DLBCL patients ineligible to or failing ASCT and/or CAR-T cells.

The signalling of B-cell receptor (BCR) plays a crucial role in the development of lymphoma. Several drugs target the kinases involved in the BCR pathway, such as Bruton tyrosine kinase (BTK) or the phosphatidylinositol 3-kinase (PI3K). PI3Ks activate intracellular pathways controlling vital cellular functions, activating the mTOR pathway via protein kinase B (AKT). PI3K/AKT pathway abnormalities are common in cancers like DLBCL.[23,24] Copanlisib is an inhibitor of PI3K mainly directed against α-and δ- isoforms found in malignant B cells, which inhibits important cell-signalling pathways, such as BCR and NFκB signalling in lymphoma cell lines.[23] Initially, copanlisib was studied as a single agent in patients with R/R indolent and aggressive NHLs in the CHRONOS-1 study. The study showed manageable toxicities and durable responses in indolent NHLs, and a certain activity on aggressive NHLs consisting of 27% of ORR and a median PFS of 2 months.[24,25] In a phase II study, copanlisib confirmed its activity in R/R DLBCL with 25% of ORR and enhanced efficacy in activated B-cell subtype by cell of origin classification, with an ORR of 37.5% and 25% of complete remission (CR) in this subset.[26] Further clinical trials were developed exploring combinations with chemoimmunotherapy to potentially enhance efficacy. A recent randomized double-blind phase III trial showed that copanlisib plus rituximab had significantly higher ORR and PFS compared to placebo plus rituximab in indolent NHL.[27] In addition, a safety run-in of the combination of copanlisib plus BR in indolent NHLs showed a favourable safety profile.[28]

Based on the efficacy results of copanlisib single-agent and the preliminary safety data of the combination with BR—a known treatment platform for R/R DLBCL—we designed a multicentre single-arm phase II trial aimed at improving the efficacy of BR with the addition of copanlisib (copa-BR) in R/R DLBCL.

# METHODS

## Study design

FIL Copa-BR was a multicentre, open-label, single-arm phase II trial, sponsored by the Fondazione Italiana Linfomi (FIL), aimed to investigate the efficacy and safety of copa-BR in patients with R/R DLBCL, ineligible to ASCT or CAR-T cells or relapsed after these regimens.

## Patients

Eligible patients were aged ≥18 years, with R/R DLBCL, including de novo DLBCL or DLBCL transformed by indolent lymphoma, double or triple hit lymphoma (DHL/THL), high-grade B lymphoma (HGBL) NOS and follicular lymphoma grade 3B. A new biopsy at relapse was recommended but not mandatory. Prior study entry or archival biopsies were centrally reviewed. Patients were enrolled if failed 1 to maximum 3 prior lines of therapy, that must have included R-CHOP or R-CHOP-like immunochemotherapy, and were considered not eligible to ASCT or CAR-T cells (or relapsed after that). Patients should present an ECOG performance status ≤2 and acceptable organ and bone marrow function (see Supplemental Materials for inclusion and exclusion criteria).

## Procedures

The treatment schedule included an induction phase followed by a maintenance phase. The induction phase included six courses of copa-BR according to the scheme: copanlisib 60 mg intravenous (iv) administered on days 1,8,15, in association with rituximab 375 mg/m$^2$ iv on day 1, and bendamustine 90 mg/m$^2$ iv days 1,2, q28 days (for details on drugs, see Supplemental Materials). For patients with at least a stable disease (SD), a maintenance phase with copanlisib single agent (60 mg/day iv day 1, 15 q28 days) was planned after the induction phase, starting 28 days after cycle 6 and up to 1 year (12 courses) (Figure 1).

Response was evaluated, according to Cheson Response Assessment Revised Criteria, with intermediate computed tomography (CT) scan after cycle 2 and 4 and with CT scan and positron emission tomography (PET/CT) scan after cycle 6.[29]

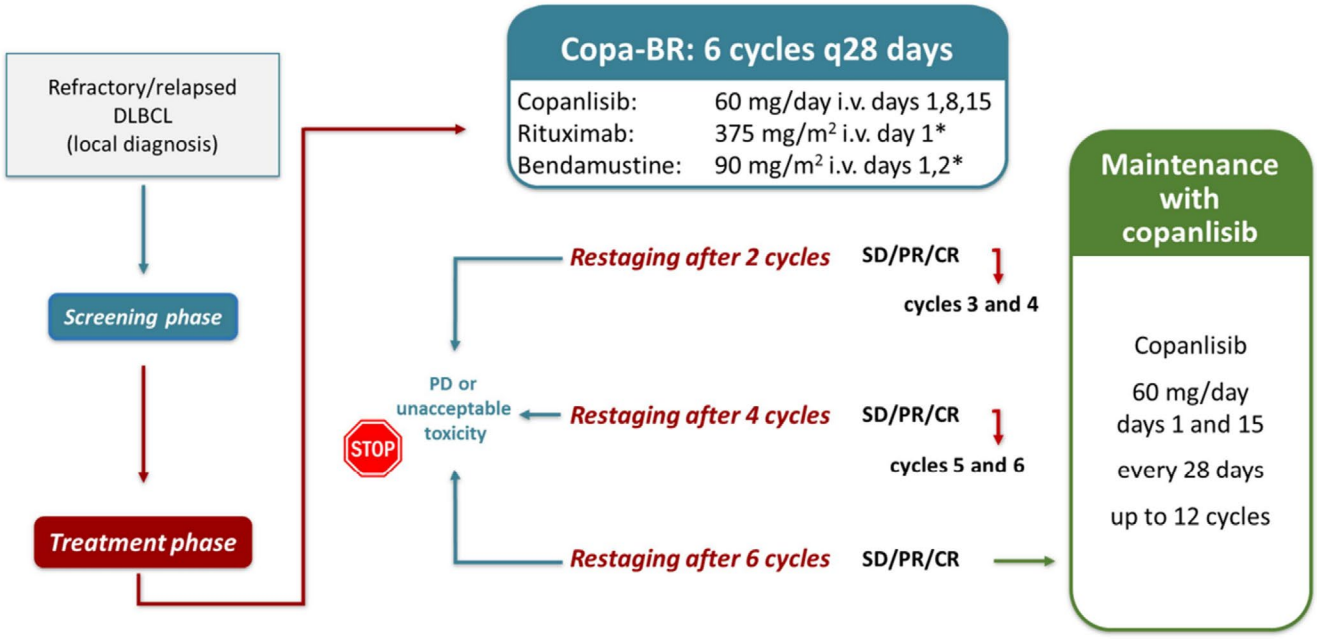


**FIGURE 1** Study design and treatment schedule. *During cycle 1, rituximab could be administered on day 2: in this case, bendamustine would be administered on days 2–3. In the case of a frail patient or a patient with high tumour burden, copanlisib could be administered on day 1, rituximab on day 2 and bendamustine on days 3–4, at physician discretion. CR, complete response; PR, partial response; SD, stable disease.

During maintenance, CT scan was planned every 4 months and PET/CT at the end of treatment (EOT). At each response assessment, patients who achieved at least an SD could proceed with the treatment plan.

Adverse events (AEs) were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and quality of life (QOL) using the EORTC QLQ-C30.[30] The cumulative incidence of first severe, life-threatening, fatal (CTCAE grade 3, 4 and 5) and/or serious AEs from the study drug infusion and at any time during therapy and follow-up was calculated; the cumulative incidence was calculated using the method of Gooley, considering death from any cause as a competing event.[31]

## Statistical analysis

The primary end-point of the study was 12-month PFS (12-m PFS) with an expected improvement from 20% to 35% by adding copanlisib to BR combination. Based on that, a sample size of 81 patients was required (see supplemental materials for details).

Secondary end-points were OS, ORR, best ORR reached, CR, duration of response (DOR).

For patients who achieved the maintenance phase, the conversion rate from SD/partial response (PR) to PR/CR was evaluated. Another secondary end-point was safety.

PFS and OS were calculated using Kaplan–Meier survival analysis. PFS was defined as the time from treatment initiation to the time of disease progression, death or to the date of last follow-up visit for event-free patients. OS was defined as the time from treatment initiation to the date of death from any cause or to the date of last follow-up visit.

All eligible patients are included in time-to-event analyses. All patients who received at least one dose of study drugs (whether eligible or not) are included in safety analyses.

Analyses were performed using 'Stata/SE 17.0 (College Station, TX, USA)'.

# RESULTS

## Patients

Between November 2019 and July 2022, 45 patients with R/R DLBCL were screened and 37 patients were enrolled in the trial and received the investigational treatment (Figure 2).

Demographics and disease characteristics are summarized in Table 1. The median age at the time of enrolment was 76 years (range: 68–87), 19 patients (51%) were female, 25 (68%) with stage IV and 23 (62%) at high-intermediate or high risk by International Prognostic Index (IPI) score (score 3–5). All patients had DLBCL histology, including 28 (76%) de novo DLBCL and 9 (24%) DLBCL transformed by indolent lymphomas. Biopsy specimens for the external pathology review were available for 29/37 patients, and centrally reviewed diagnoses resulted as follows: previous diagnoses were confirmed in 86.2% of the cases ($n = 25/29$ diagnosis). The median number of prior systemic treatments was 1 (range: 1–2). Thirteen patients (35%) were refractory to the last treatment. None of the patients previously received ASCT or CAR-T cells.

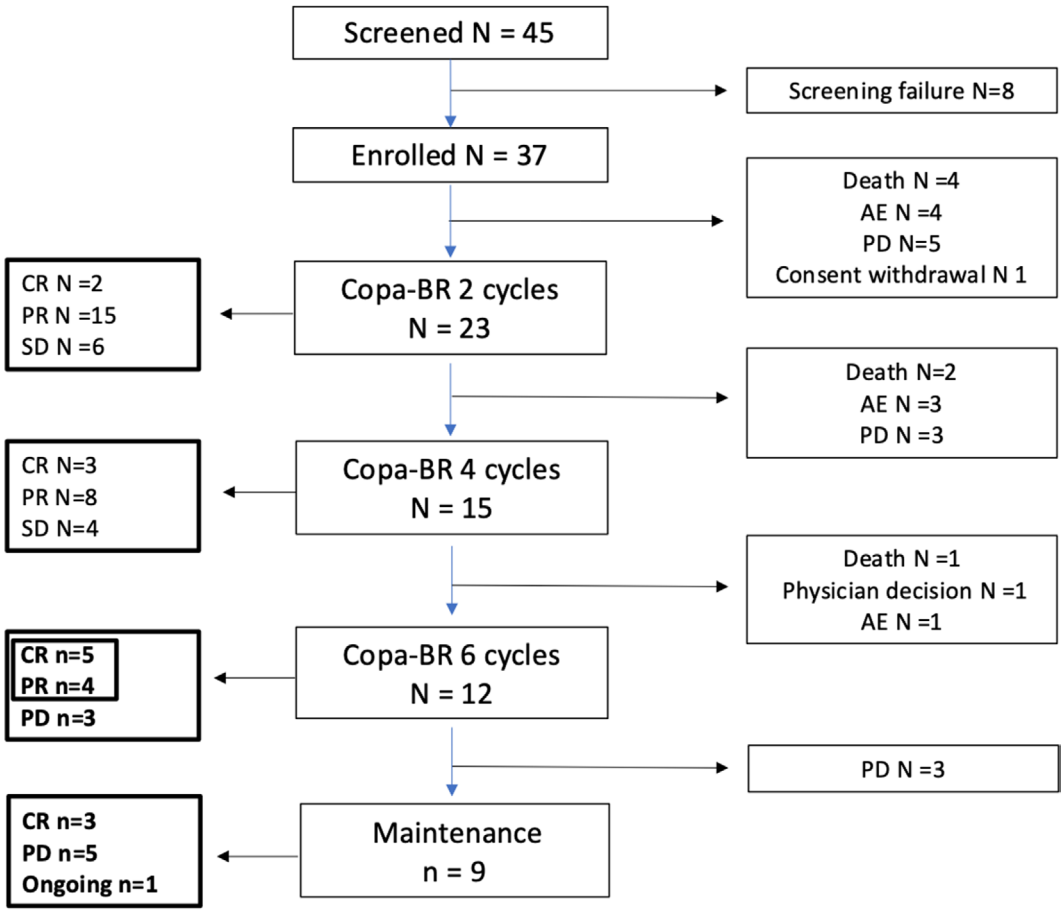


**FIGURE 2** Consort diagram. Details of events: n 8 exits after cycle one: n 2 deaths (legionella pneumophila, COVID-19), n 2 AE (cachexia, erythema, thrombocythaemia), n 2 PD, n 1 withdrawal consent. N 6 exits after cycle 2: n 2 deaths (septic shock, multiorgan failure), n 3 PD, n 1 AE (COVID-19). N 4 exits after cycle 3: n 1 death (COVID-19), n 3 AE (gastric carcinoma, cachexia, low creatinine/erythema). N 4 exits after cycle 4: n 1 death (sepsis), n 3 PD. N 4 exits after cycle 5: n 1 early progression from PR in restaging at cycle 4 (did not start cycle 5), n 1 death (COVID-19), n 1 physician decision/cachexia (PR after 4 cy, CR last contact), n 1 AE (CMV reactivation/general condition (CR after 4 cy)). N 3 exits after cycle 6: 3 PD. AE, adverse event; CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease.

## Feasibility and efficacy

Twelve of 37 patients completed the 6 courses of induction (induction completion rate 32.4%) and 9 (24.3%) entered the maintenance phase (Figure 2). Among the whole cohort, the best ORR was 51.4% (95% CI: 34.4%–68.1%) ($n = 19$) with a CR rate of 18.9% (95% CI: 8.0%–35.2%) ($n = 7$); ORR at the end of induction (EOI) was 24.3% (95% CI: 11.8%–41.2%) ($n = 9$) with CR 13.5% (95% CI: 4.5%–28.8%) ($n = 5$). During the maintenance phase, all patients in PR at the EOI subsequently progressed ($n = 4$) while four of five patients in CR at the EOI maintained the response at the last follow-up (Figure 3 and Figure S1).

After a median follow-up of 20 months (95% CI: 16–25; range: 1–26 months), the 12-m PFS was 25.1% (95% CI: 14.2%–37.5%) with a median PFS of 5.3 months (95% CI: 2.7–8.2) (Figure 4A). The median DOR among 19 patients achieving at least PR as best response was 9.2 months (95% CI: 3.9-NA). The 12-m OS was 44.5% (95% CI: 28.1%–59.7%) with a median OS of 8.8 months (95% CI: 3.8–14.6) (Figure 4B). At the time of the last follow-up, nine patients remained alive, including four in continuous response. After copa-BR failure, 13 patients received subsequent treatments. None of the patients received consolidative stem cell transplantation or CAR-T cells. Twenty-eight patients had died due to PD ($n = 12$), AEs ($n = 10$) and COVID-19 infection ($n = 6$) (Table S1).

## Safety

Thirty-one (84%) patients required a dose reduction of copanlisib. Rituximab and bendamustine dose reduction occurred in 4 (11%) and 15 (41%) patients respectively (Table 2, Figure S2). The most common reason for copanlisib and bendamustine dose reduction was cytopenias (neutropenia 56.8%), followed by infections (43.2%), gastrointestinal toxicities (18.9%) and cutaneous reactions (16.2%) (Figure S3).

Twenty-one (57%) patients required at least one treatment delay during the induction; the main reasons for treatment delay were AEs ($n = 18$, 49%).

**TABLE 1** Baseline characteristics.

| Characteristic | *n* = 37 |
|---|---|
| Demographics | |
| Median age, years (range) | 76 (68–87) |
| Sex | |
| Female | 19 (51.4) |
| Male | 18 (48.6) |
| Disease characteristics | |
| Histology | |
| De-novo DLBCL | 28 (75.7) |
| Transformed by iNHL | 9 (24.3) |
| ECOG PS | |
| 0–1 | 34 (91.9) |
| 2 | 3 (8.1) |
| B symptoms | 1 (2.7) |
| LDH > ULN | 21 (56.8) |
| Ann Arbor stage | |
| I–II | 5 (13.5) |
| III–IV | 32 (86.5) |
| Extranodal sites | |
| 0–1 | 26 (70.3) |
| >1 | 11 (29.7) |
| IPI score | |
| 0–2 | 14 (37.8) |
| 3–5 | 23 (62.2) |
| Previous treatments | |
| Lines of prior therapy | |
| 1 | 23 (62.2) |
| 2 | 14 (37.8) |
| Refractory to last therapy[a] | 13 (35.1) |

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; iNHL, indolent non-Hodgkin lymphoma; IPI, International Prognostic Index, LDH, lactate dehydrogenase.

[a]Definition of refractory: no response or progression within 6 months of last treatment.

Thirty-three patients discontinued the treatment: consent withdrawal in 1 (0.1%), AEs in 8 (21.6%), PD in 17 (45.9%) and death in 7 (18.9%) cases.

The most common all-grade and grade 3–4 AEs are summarized in Table 3 and Figure S4. Neutropenia was recorded in 62.1% of patients (grade ≥3 56.8%) while febrile neutropenia was limited to one patient (2.7%) during the induction phase.

Other haematological toxicities during the induction phase included thrombocytopenia in 45.9% of patients (grade ≥3 16.2%) and anaemia in 21.6% (grade ≥3 5.4%).

Infections were reported in 45.9% (grade ≥3 27.0%). Overall, 37 infectious events have been reported, including 24 cases of COVID-19 infections (64.9%) of whom six were fatal (25.0%), and 13 infectious events caused by other agents (35.1%) leading to death in three cases (23.1%). Eighteen patients experienced a cytomegalovirus (CMV) reactivation (49.0%) but none of them demonstrated clinical manifestations.

Other extra-haematological AEs were represented by gastrointestinal toxicity in 48.6% (grade ≥3 18.9%) and cutaneous toxicity in 48.6% (grade ≥3 16.2%) during the induction phase. After copanlisib infusion, hypertension occurred in 4 (11%) patients. Hyperglycaemia occurred in 6 (16%) cases, although it resolved spontaneously in all cases.

Since the slow recruitment, the occurrence of unexpected adverse events and the emergence of potentially more effective novel treatments, the study was interrupted prematurely by the steering committee's decision.

## DISCUSSION

The treatment of R/R DLBCL in patients ineligible for ASCT or CAR-T cells remains challenging, with a generally poor prognosis. They are typically elderly, have multiple comorbidities and exhibit poor tolerance to intensive chemotherapy regimens. Among various chemotherapy combinations, the BR platform has been favoured for its relatively good tolerance and preliminary efficacy. However, responses to BR are often short-lived, with rapid disease progression reported in the literature.[15,16]

Based on these considerations, we designed a phase II trial to evaluate whether adding copanlisib to BR (copa-BR) could improve outcomes in this patient population. Thirty-seven patients were enrolled and received treatment. The ORR at EOI was 24.3%, including a CR rate of 13.5%. After a median follow-up of 20 months, the 12-m PFS (primary end-point) was 25.1%, with a median PFS of 5.3 months. The 12-m OS rate was 44.5%, with a median OS of 8.8 months. The efficacy of copa-BR resulted in lower than expected and did not improve upon the results achieved with copanlisib monotherapy in the aggressive NHL cohort of the CHRONOS-1 study (ORR: 27.1%).[24] Nevertheless, our study cohort was particularly challenging to treat, characterised by older age (median: 76 years), higher IPI scores and one-third of patients refractory to prior therapy. Moreover, the unfavourable toxicity profile of the combination led to frequent treatment discontinuations further compromising its potential efficacy.

These results suggest that the copa-BR regimen offers limited efficacy, with a modest 12-m PFS above the null hypothesis and a small number of patients ($n = 4$) achieving durable responses during copanlisib maintenance. Unfortunately, the regimen was associated with significant toxicity. Grade 3–4 neutropenia occurred in half of the patients, although febrile neutropenia was rare (1 case). Grade 3–4 infections were frequent (45.9%), alongside frequent CMV reactivations, though without clinical signs of infection. These AEs necessitated frequent dose reductions and treatment delays, potentially impacting efficacy outcomes.

The trial was also conducted during the peak of the COVID-19 pandemic, which introduced additional

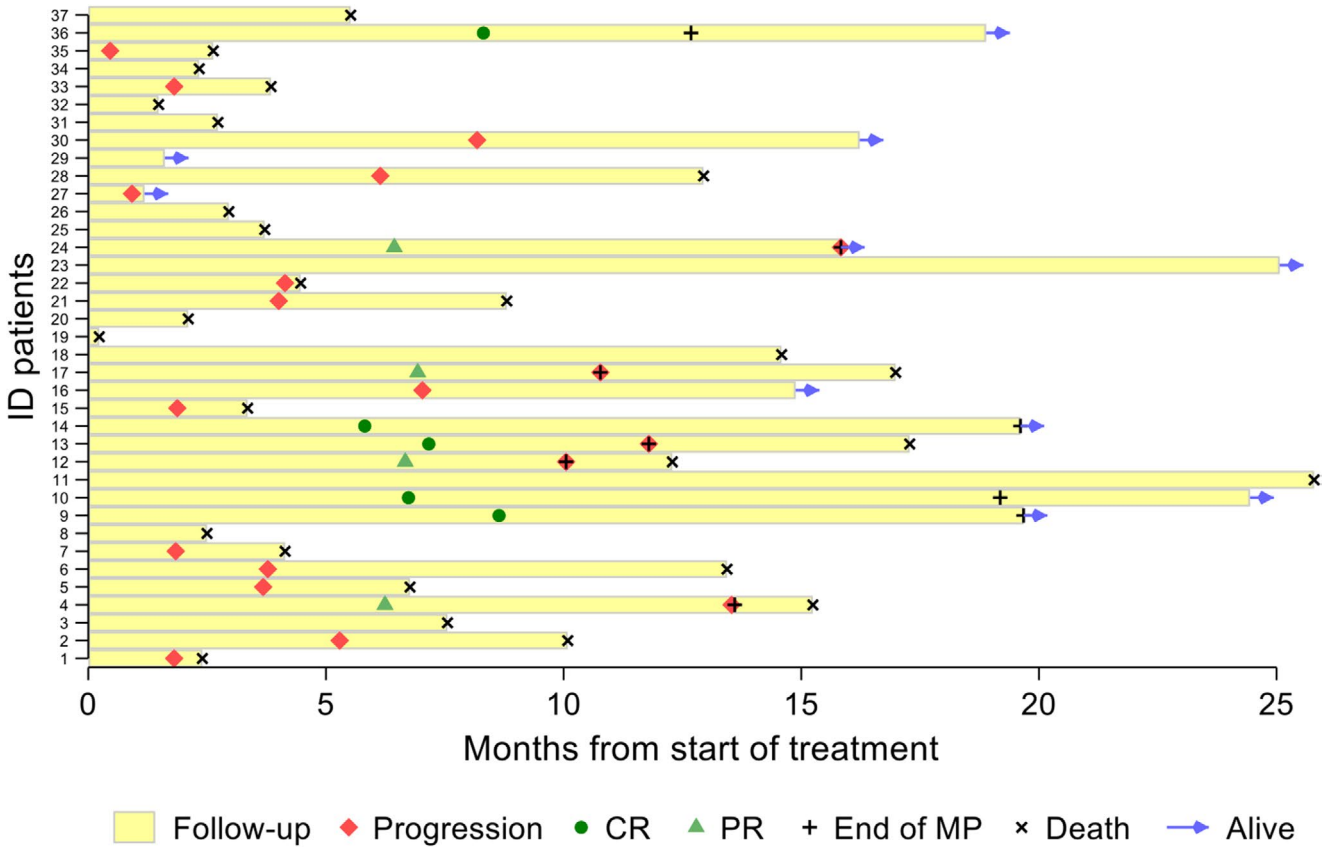


**FIGURE 3** Swimmer plot. Swimmer plot of N 37 patients included in the trial. CR, complete remission; MP, maintenance phase; PR, partial remission.

challenges. Among the 24 patients who contracted SARS-CoV-2, six died, likely impacting both PFS and OS outcomes. Immunosuppressive effects of the copa-BR regimen may have contributed to the high infection rate, though it is worth noting that patients with haematological malignancies receiving various treatments during the pandemic were universally at elevated risk of COVID-19-related morbidity and mortality.[32]

Although the preliminary evaluation of the first 37 patients enrolled did not formally meet the criteria for interrupting the study, the steering committee carefully evaluated the efficacy and safety data and decided to close the study since the unfavourable benefit–risk profile, the slow recruitment and the emerging of potentially more effective and safer treatment options for the setting under investigation.

Copa-BR did not demonstrate superior efficacy compared to historical data with BR alone for R/R DLBCL. In the phase II study by Ohmachi et al.[15] BR alone achieved an ORR of 63%, a CR rate of 37% and a median PFS of 6.7 months. Similar outcomes were reported in real-world settings, with ORRs and CRs of 50% and 28%, respectively, and a median PFS of 8.8 months.[18] Furthermore, during the accrual period for the FIL_Copa-BR trial, the pola-BR combination received FDA and EMA approval based on a randomized phase II study by Sehn et al.[19] This study demonstrated significant improvements in response and survival compared to BR in a similarly challenging population (median of two prior lines of therapy, 75% refractory to the last treatment). Of note, these positive results have been confirmed with an extended cohort analysis, although data obtained in the real-world setting showed a lower efficacy.[20–22,33]

In our study, the copa-BR combination did not show improved efficacy compared with other therapies available for transplant-ineligible R/R DLBCL. The combination of rituximab, gemcitabine and oxaliplatin (R-GEMOX) reached CR rates ranging from 34% to 50% and 12-m PFS rates of 20%–30% in transplant-ineligible R/R DLBCL.[34–36] The combination of tafasitamab plus lenalidomide (tafa-len), recently approved, showed high response rates with durable outcomes in the L-MIND trial.[37] While early real-world data suggested lower efficacy, more recent cohorts have aligned more closely with the pivotal trial's results.[38–40] Additionally, CD3xCD20 bispecific antibodies, such as glofitamab and epcoritamab, have shown promising efficacy in heavily pretreated DLBCL patients, with ORRs and CRs up to 60% and 40%, respectively, and median DOR ranging from 12 to 18 months.[41,42]

The unfavourable toxicity profile of copa-BR observed in our study reflects the safety concerns emerged in recent times for other PI3K inhibitors. A number of PI3K inhibitors other than copanlisib were previously approved for B-cell malignancies in light of their efficacy demonstrated as

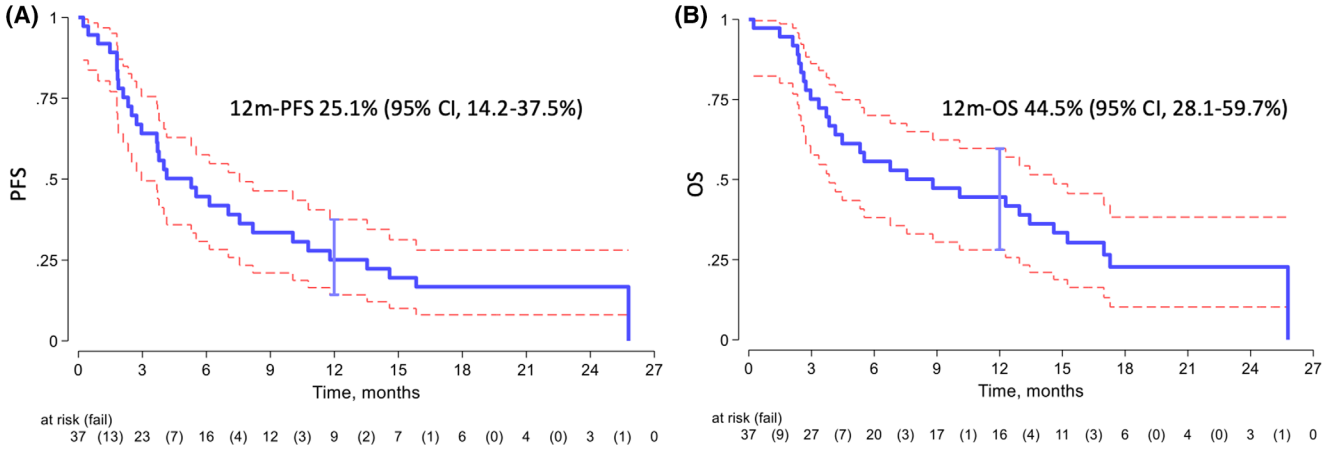


**FIGURE 4** Kaplan–Meier curves of progression-free survival (PFS) (A) and overall survival (OS) (B). (A) At a median follow-up: 20 months (95% CI, 16–25; range: 1–26 months), observed 12-m PFS was 25.1% (95% CI, 14.2%–37.5%) and median PFS was 5.3 months (95% CI, 2.7–8.2). (B) At a median follow-up: 20 months (95% CI, 16–25; range: 1–26 months), observed 12-m OS was 44.5% (95% CI, 29.0%–61.2%) and median OS was 8.8 months (95% CI, 3.8–14.6).

**TABLE 2** Causes of treatment discontinuation.

| Causes | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | Total |
|---|---|---|---|---|---|---|---|
| PD | 2 | 3 | | 4 | | 3 | 12 |
| Death | 2 | 2 | 1 | 1 | 1 | | 7 |
| Legionella pneumophila | 1 | | | | | | 1 |
| COVID-19 | 1 | | 1 | | 1 | | 3 |
| Septic Shock | | 1 | | 1 | | | 2 |
| Multiorgan failure | | 1 | | | | | 1 |
| AE | 3 | 1 | 3 | | 2 | | 9 |
| Cachexia | 1 | | 1 | | 1 | | 3 |
| Erythema | 1 | | 1 | | | | 2 |
| Thrombocytopenia | 1 | | | | | | 1 |
| COVID-19 | | 1 | | | | | 1 |
| Gastric Cancer | | | 1 | | | | 1 |
| CMV reactivation | | | | | 1 | | 1 |
| Withdrawal consent | 1 | | | | | | 1 |

Abbreviations: AE, adverse event; CMV, cytomegalovirus; PD, progression disease.

a single agent in phase II studies.[43,44] However, subsequent randomized trials testing PI3K inhibitors in combination with other therapies raised safety concerns due to higher fatal events and other serious AEs than shown in single-arm trials.[45–47] This led to FDA recommendations in 2022 that new approval of PI3K inhibitors should be supported by randomized trial data.[48] Reflecting these concerns, the sponsor recently withdrew its FDA New Drug Application for copanlisib in follicular lymphoma.[49]

Our results are consistent with findings from the CHRONOS-4 trial, a phase III study of copa-BR in indolent B-cell lymphomas.[50] This trial showed no improvement in efficacy with copa-BR over placebo-BR but reported higher rates of serious AEs, particularly infections. Pharmacokinetic and exposure–response analyses from CHRONOS-4 also revealed reduced copanlisib dose intensity due to AEs, potentially limiting its clinical benefit. These data suggest that copanlisib could only be combined with chemotherapy using extreme caution in any future study with this agent class. Additionally, CMV reactivation rates were unexpectedly high (31.9%) in CHRONOS-4, comparable to those observed in our study (45.9%), though none in our trial resulted in clinical symptoms.

In conclusion, the copa-BR combination did not demonstrate clinical benefit and was associated with significant toxicity in R/R DLBCL, discouraging further investigations of this regimen. Effective treatments for transplant- and CAR-T-cell-ineligible R/R DLBCL remain a pressing unmet need, and continued efforts are essential to improve outcomes for this challenging population.

**TABLE 3** Adverse events.

| Induction treatment | All grades, *n* (%) | Grades 3–4, *n* (%) |
|---|---|---|
| Haematological events | | |
| Anaemia | 8 (21.6) | 2 (5.4) |
| Leucopenia | 8 (21.6) | 7 (18.9) |
| Neutropenia | 23 (62.2) | 21 (56.8) |
| Thrombocytopenia | 17 (45.9) | 6 (16.2) |
| Febrile neutropenia | 1 (2.7) | 1 (2.7) |
| Extra-haematological events | | |
| Cardiac disorders | 3 (8.1) | 3 (8.1) |
| Endocrine disorders | 2 (5.4) | 1 (2.7) |
| Eye disorders | 1 (2.7) | 0 (0) |
| Gastrointestinal disorders | 18 (48.6) | 2 (5.4) |
| General disorders and administration site conditions | 15 (40.5) | 2 (5.4) |
| Infections and infestations | 17 (45.9) | 10 (27.0)[a] |
| Hepatobiliary disorders | 2 (5.4) | 2 (5.4) |
| Investigations | 4 (10.8) | 2 (5.4) |
| Metabolism and nutrition disorders | 5 (13.5) | 1 (2.7) |
| Musculoskeletal and connective tissue disorders | 4 (10.8) | 4 (10.8) |
| Nervous system disorders | 4 (10.8) | 1 (2.7) |
| Renal and urinary disorders | 3 (8.1) | 0 (0.0) |
| Respiratory/thoracic and mediastinal disorders | 4 (10.6) | 2 (5.4) |
| Skin and subcutaneous tissue disorders | 18 (48.6) | 6 (16.2) |
| Social circumstances | 1 (2.7) | 0 (0) |
| Vascular disorders | 4 (10.8) | 2 (5.4) |

[a]Including nine cases of grade 5 events.

## AUTHOR CONTRIBUTIONS

AC, MN, PMMF and UV designed the study and wrote the manuscript; LM conducted the statistical analyses; MV conducted the external pathology review; all authors have been involved in data collection, had access to the trial data, reviewed and approved the final manuscript.

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## CONFLICT OF INTEREST STATEMENT

MN—advisory board (not related to this manuscript): Abbvie; honoraria (not related to this manuscript): Abbvie, Incyte, Sobi; MS—advisory board (not related to this manuscript): Abbvie, AstraZeneca, Beigene, Gilead, Incyte, Istituto Gentili, Novartis, Roche, Servier, Sobi; honoraria for talks (not related to this manuscript): Gilead, Servier, Sobi; UV—advisory board (not related to this manuscript): AbbVie, Genmab, Gilead, Incyte, Regeneron, Sobi; honoraria for

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## DATA AVAILABILITY STATEMENT

Qualified researchers may contact the FIL board at segreteriadirezione@filinf.it to share individual-level patients' clinical data analysed for this manuscript (for the avoidance of doubt, no identifiable data, such as name, address, hospital name, date of birth or any other identifying data, will be shared and should not be requested). For each data sharing request, it is essential that a pro forma (available on request) is completed that describes the general purpose, specific aims, data items requested, analysis plan and acknowledgment of the trial management team. Requests will be reviewed based on scientific merit and ethical principles. Requestors who are granted access to the data will be required to complete a data sharing agreement that will be signed by the requester and FIL. In compliance with the domestic ethics guideline and applicable legislation, individual deidentified patients' data underlying the results reported in this article (including study protocol, statistical analysis plan and data coding) can be shared until 5 years after the publication of the present article.

## ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and according to Good Clinical Practice. The study protocol was approved by the ethics committee.

## PATIENT CONSENT STATEMENT

All patients provided written informed consent.

## CLINICAL TRIAL REGISTRATION

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## SUPPORTING INFORMATION

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

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