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Copanlisib in non-Hodgkin’s lymphoma and solid tumors: An efficacy and safety analysis

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Abstract

Introduction: Copanlisib is an intravenous pan-class I PI3K inhibitor with predominant activity against the α and δ isoforms. We conducted this review to assess the efficacy and safety of copanlisib in patients with relapsed or refractory non-Hodgkin’s lymphoma (NHL) and other solid tumors.

Methods: A systematic search of the electronic database (PubMed, Cochrane, Clinicaltrials.gov, Google scholar, and China National Knowledge Infrastructure) was conducted for relevant studies. Any clinical trial with clear outcome measures on the efficacy or safety of copanlisib in NHL or other solid tumors were eligible for inclusion. The objective response rate (ORR) and the complete response (CR) rate were used to assess the efficacy. Incidence of all grade and grade 3–4 treatment-emergent adverse events (TEAE) were calculated to evaluate the safety profile.

Results: We analyzed seven single-arm prospective clinical trials. The pooled ORR was 39.1% (95% CI: 21.0–60.7%) for NHL cohort. The pooled CR rate for NHL was 10.9% (95% CI: 6.9–16.8%). Indolent NHL had a higher rate of response than aggressive NHL (ORR 56.9% vs. 22.8%; CR rate 15.8% vs. 7.6%). The pooled incidence rate of grade 3–4 TEAE was 73.9% (95% CI: 66.4–80.3%). Most common grade 3–4 TEAE were: hyperglycemia (31.4%), hypertension (29.8%), neutropenia (18.3%), anemia (7.4%), and pneumonia (6.8%).

Conclusions: Copanlisib is effective in the treatment of relapsed or refractory NHL, with a higher rate of response in indolent NHL than aggressive NHL. Hyperglycemia and hypertension were the most common adverse events.

Keywords: Copanlisib, Review, Non-Hodgkin’s Lymphoma, Solid tumors.

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Introduction

Cancer is the second leading cause of death globally and was responsible for an estimated 9.6 million deaths in 2018. Lung, breast, and colorectal cancer account for nearly 33.4% of the overall cancer incidence. Non-Hodgkin’s Lymphoma (NHL) ranks as the thirteenth most common cancer worldwide.

Phosphoinositide 3-kinase (PI3K) signaling controls cell growth, proliferation, and differentiation, as well as survival signals, and its aberrant signaling has been shown to drive tumorigenesis. PI3Ks are divided into three classes, according to their structural characteristics and substrate specificity. Of these, the most commonly studied are the class I enzymes (comprising p110 catalytic subunit). The class I PI3K has four isoforms (α, β, γ, δ) of the catalytic subunit that share overlapping but distinct functions. The δ isoform is highly expressed in the immune system and hematopoietic lineage, and the α and β isoforms are ubiquitously expressed.

The PI3K pathway is dysregulated in many solid tumors, including, but not limited to, breast, colorectal, lung, and gynecological. The conspicuous role of this pathway has also been identified in lymphomas, particularly relapsed or refractory indolent B cell lymphoma. PI3K inhibitors may be used as a strategic therapeutic intervention in PI3K pathway-driven tumors, and this has led to the development of PI3K inhibitors gaining significant momentum. Several PI3K inhibitors such as dual PI3K/ mammalian target of rapamycin (mTOR) inhibitors, pan-PI3K inhibitors, and isoform-specific PI3K inhibitors are either under clinical investigation or have been approved for therapeutic use in lymphomas and solid tumors. In 2014, idelalisib (PI3Kδ specific inhibitor) was the first PI3K inhibitor to be approved by the US Food and Drug Administration (FDA). Currently, three PI3K inhibitors have been approved for relapsed follicu-...
lar lymphoma (FL): duvelisib (oral), idelalisib (oral), and copanlisib (intravenous)\(^\text{10}\).

Copanlisib (BAY 80-6946; Bayer AG, Berlin, Germany) is an intravenous pan-class I PI3K inhibitor. In 2017, the US FDA approved it to treat patients with relapsed FL, who have been treated with at least two prior systemic therapies. Several phase I and II clinical trials have been conducted to evaluate the efficacy and safety profile of copanlisib in lymphomas and solid tumors. Patients treated with copanlisib in these clinical trials demonstrated a varying degree of clinical response, albeit the response was not promising in some studies, especially for solid tumors. Copanlisib has also been investigated in combination with other anti-cancer agents. These newer results have further demonstrated the anti-tumor effects of the drug and the possibility of synergy to treat diverse cancer types\(^\text{10}\). The current recommended dosing regimen for copanlisib is 60 mg administered as a 1-hour intravenous infusion on days 1, 8, and 15 of a 28-day treatment cycle, on an intermittent schedule (three weeks on and one week off)\(^\text{10}\).

In this study we pooled data from published prospective single-arm clinical trials. This review assesses the clinical efficacy and safety of copanlisib for the treatment of NHL or other solid tumors. We evaluated the effectiveness with an objective response rate (ORR) and complete response (CR) rate. Safety was assessed by calculating the incidence of all grade and grade 3–4 treatment-emergent adverse events (TEAE).

**Materials and Methods**

Our review on the efficacy and safety of copanlisib in the management of relapsed or refractory NHL and other solid tumors (protocol number: PROSPERO CRD42020185267) was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) statement\(^\text{15}\). Our research question was based on the PICO (Population, Intervention, Comparison/control, Outcome) format: population- NHL or other solid tumors; intervention- copanlisib (Bay 80-6946 or Aliqopa), comparison- with or without a control group, and outcome- efficacy endpoints or adverse events.

**Literature Search Strategy**

We conducted an extensive search of PubMed, Google Scholar, Cochrane, Clinicaltrials.gov, and China National Knowledge Infrastructure (CNKI) databases until 19\textsuperscript{th} May 2020, without any restriction to language or country. We used the following keywords in varying combinations for the literature search: “Copanlisib”, “BAY 80-6946”, “Aliqopa”, “Lymphoma”, “Non-Hodgkin”, “Solid tumor”, and “PI3K inhibitor”. We used the following search strategy with no automatic filters for PubMed: ((copanlisib[All Fields]) OR (copanlisib[MeSH Terms]) OR (copanlisib[Supplementary Concept]) OR (copanlisib[Title/Abstract]) OR (BAY 80 6946[All Fields]) OR (PI3K inhibitors[All Fields]) OR (aliqopa[All Fields])) AND ((lymphoma[All Fields]) OR (solid tumor[All Fields]) OR (non-hodgkin[All Fields])). All the reviewers independently screened the title and abstract of the articles identified during the initial database search. Next, we downloaded the full texts of the potentially relevant articles and studied in greater detail. Whenever there was any confusion regarding the data on efficacy or adverse events (AE), we contacted the corresponding author of the study for clarification. When we encountered duplicate or follow-up publications of the same study, we included only the latest full-text article in our analysis. Also, we screened the references of the included articles and tracked the citing articles, to not miss any eligible study.

**Eligibility Criteria**

The inclusion criteria for our analysis were: (1) prospective clinical trials of copanlisib in any phase; (2) studies involving patients with histologically confirmed NHL or solid tumors; (3) patients’ age ≥18 years; (4) studies reporting the details on schedule and dosing of copanlisib; and (5) data on efficacy or safety of copanlisib available directly or indirectly.

The exclusion criteria for our analysis were: (1) review articles, meeting or conference abstracts, posters, editorials, case-control studies, non-human studies, pre-clinical studies; (2) copanlisib in combination with another drug; and (3) studies with inadequate raw or analyzed data.

**Data Extraction**

All reviewers independently extracted the relevant data from the eligible studies. The following data were collected: (1) name of the first author; year of publication; clinical trial registration number; country/region where the studies were conducted; sample size; age, gender, and racial characteristics of the study population; phase of the clinical trial; Eastern Cooperative Oncology Group (ECOG) performance status; Ann Arbor classification stage at study entry; (2) study design, study cohorts, types of tumor, dosing and scheduling of copanlisib, treatment regimen before copanlisib administration, statistical details of the study; (3) median duration of treatment, median number of treatment cycles, complete response (CR), partial response (PR), stable disease (SD), objective response rate (ORR), disease control rate (DCR), median progression-free survival (PFS), median duration of response (DoR), median overall survival (OS); and (4) treatment-emergent adverse events (TEAE) and drug-related TEAE, according to their grades. We entered the collected data into a standardized spreadsheet. Once completed, a reviewer who was not previously involved...
in the data extraction for that particular study rechecked, verified, and if necessary, corrected the entered data.

**Outcome Measures**

The main outcomes of our study were ORR and CR rate for the evaluation of efficacy and incidence of all grade and grade 3–4 TEAE for the evaluation of the safety of copanlisib. The additional outcomes of our study were DCR, PFS, DoR, and OS. ORR is defined as the proportion of patients who achieved a CR or a PR. DCR is defined as the proportion of patients who achieved a CR, a PR, or an SD to a therapeutic regimen in a clinical trial\(^6, 17\). OS refers to the duration from the start of the treatment to the time of death because of any cause. PFS refers to the time from the start of the treatment to either objective tumor progression or death\(^8\). DoR is the time from the start of a response to treatment until disease progression or death\(^9\). TEAE are adverse events that appear or worsen after the initiation of the therapeutic intervention. However, they may or may not be related to the intervention\(^10\).

**Assessment of the Methodological Quality**

Two reviewers independently reviewed each study to evaluate the risk of bias, using the guidelines provided by the Methodological Index for Non-Randomized Studies (MINORS) instrument\(^21\). For a non-comparative study, the instrument evaluates the study against eight items: a clearly stated aim, the inclusion of consecutive patients, prospective collection of data, endpoints appropriate to the aim of the study, unbiased assessment of the study endpoint, follow-up period appropriate to the aim of the study, loss to follow up less than 5%, and prospective calculation of the study size. The maximum score for a non-comparative study is 16, with a possible score of 0, 1, or 2 for each item. Score 0 signifies that the item is not reported in the study, 1 signifies inadequate reporting, and 2 signifies adequate reporting.

**Statistical analysis**

We performed all the statistical analyses using Comprehensive Meta-Analysis software (CMA 3.3, Biostat, Englewood). The total number of clinical responses (CR, PR, SD) and the number of patients in each study were used to calculate the efficacy endpoints (ORR, DCR) and 95% confidence interval (CI) for each study. The incidence of all grade and grade 3–4 TEAE, along with 95% CI, were calculated using: the number of patients with all grade TEAE, the number of patients with grade 3–4 TEAE, and the total number of patients in the study. Then, the pooled effect estimates were calculated.

Considering the variation in the geographical and racial distribution of the study population, types of tumor, and dosing of copanlisib, the random-effects model was applied for all pooled effect estimates. We evaluated the heterogeneity between the studies using the p-value for Q statistic and quantified with the I-squared (I\(^2\)) statistic. A p-value of <0.10 for the Q statistic suggested heterogeneity between the studies. Based on the value of I\(^2\), the level of heterogeneity was classified as high (I\(^2\) > 50%) or low (I\(^2\) < 50%). We further evaluated the heterogeneity and pooled estimate of ORR, DCR and CR rate based on the sensitivity analysis results.

Subgroup analyses were pre-specified and performed for ORR, CR rate, and DCR based on the type of lymphoma (aggressive or indolent) and the phase of the clinical trial (phase I or phase II). We tried to limit the number of subgroup analyses and refrained from performing any post hoc analyses according to the guidelines presented in the Cochrane Handbook\(^22\).

We evaluated the publication bias for ORR and grade 3–4 TEAE using Egger’s and Begg’s tests. A p-value of <0.05 suggested publication bias. We also assessed the funnel plots for both ORR and grade 3–4 TEAE to supplement the tests.

**Results**

**Study selection**

The database search identified 778 articles. After the removal of duplicates and screening of the remaining articles, 47 full-text articles were assessed for further review. Of these, only six articles fulfilled the eligibility criteria. A manual search of the references and citations of those six articles produced one additional eligible study, making a total of seven studies. We show this entire process in Fig. 1.

**Study characteristics**

All seven studies were single-arm prospective clinical trials and included 434 patients of lymphomas or other solid tumors who were treated with copanlisib monotherapy\(^23-29\). There were three phase I trials and four phase II trials. The data showed that these studies enrolled patients from multiple countries across America, Asia, Europe, and Australia, and most were whites, followed by Asians. The lymphoma cohort (N = 335) in all the trials consisted of NHL. The common NHL subtypes were: follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), marginal zone lymphoma, peripheral T-cell lymphoma, small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL), and mantle cell lymphoma. FL was the most common indolent lymphoma (70%) and DLBCL was the most common aggressive lymphoma (67%). Though the study by Dreyling et al. (2019) evaluated and reported results for indolent lymphoma, one patient was later diagnosed to have DLBCL. However, the patient continued treatment and was included in the full analysis set. At the time of enrollment, 82.7% of the NHL patients were classified as Ann-Arbor stages 3–4.
The solid tumor cohort (N = 99) in these studies consisted mostly of breast cancer, endometrial carcinoma, ovarian cancer, colon cancer, gastric/esophageal cancer, bladder cancer, and pancreatic cancer.

Before initiating copanlisib therapy, all 434 patients in these studies had undergone treatment (chemotherapy, immunotherapy, radiotherapy, or a combination of these) and had either relapsed or were refractory to the treatment. Data on ECOG performance status were available for all studies except one (Dreyling et al., 2017). The patient performance status ranged from grade 0 to grade 2, of which 42.3% had grade 0 performance status and 48% had grade 1 performance status (Additional file 1: Table S2). All patients received copanlisib as a 1-hour infusion on days 1, 8, and 15 of a 28-day cycle, with doses ranging from 0.1–1.2 mg/kg or a fixed dose of 45–60 mg. The median number of treatment cycles in the studies ranged from 1.8 to 6.5 cycles. The additional characteristics of the studies are shown in Table 1.

**Study quality assessment**

We assessed the risk of bias in each study using the 8-item MINORS instrument for uncontrolled studies.
MINORS score for each of the seven studies included in our study ranged from 11 to 16, as shown in Table 1.

**Tumor response**

Out of the seven copanlisib monotherapy trials, three studies enrolled patients with NHL, two enrolled patients with other solid tumors, and two enrolled patients in both the cohorts. The efficacy results of those trials, available in 430 patients (331 with NHL and 99 with other solid tumors) are shown in Table 2. The patients in the NHL cohorts received copanlisib 0.8 mg/kg or a fixed-dose of 60 mg, except in the study by Morschhauser et al., where 20 out of 33 patients received 0.4 mg/kg. The patients in the solid tumor cohorts received copanlisib 0.4 mg/kg or 0.8 mg/kg, except in the study by Patnaik et al., where the dosing ranged from 0.1–1.2 mg/kg.

The ORR, CR rate, and DCR data for NHL were available for analysis from five trials. The pooled ORR for NHL was 39.1% (95% CI: 21.0–60.7%, Fig. 2) with high heterogeneity ($I^2 = 90.7\%$, $p ≤ 0.001$). The pooled CR rate was 10.9% (95% CI: 6.9–16.8%) with low heterogeneity ($I^2 = 35.7\%$), which appears to be insignificant based on Q statistic ($p = 0.183$). The pooled DCR for NHL was 62.7% (95% CI 38.9–81.6%) with high heterogeneity ($I^2 = 92.3\%$, $p ≤ 0.001$). On sensitivity analyses, arbitrarily omitting any study did not lead to any significant change in the heterogeneity of ORR or DCR. Omitting the study by Dreyling et al. (2019) resulted in

**Table 1 Basic characteristics of trials included**

| Author       | Year   | ClinicalTrials.gov number | Phase | N | Male/ Female | Age in years (range) | Dosing of copanlisib | Median treatment duration in weeks (range) | Cancer type                       | MINORS score |
|--------------|--------|----------------------------|-------|---|--------------|----------------------|----------------------|------------------------------------------|-----------------------------------|--------------|
| Lenz G       | 2020   | NCT02391116                | II    | 67| 39/28        | 69 (25–93)           | 60 mg                | 6.9 (0.9–71.1)                          | Diffuse Large B-Cell Lymphoma     | 12           |
| Morschhauser F| 2020  | NCT02155582                | I     | 63| 21/42        | 61.0 (38–80)         | 0.4, 0.8 mg/kg or 45–60 mg | 7 (2–87)                              | Lymphomas or other solid tumors   | 12           |
| Santin AD    | 2020   | NCT02722858                | II    | 11| 0/11         | 68 (NA)              | 60 mg                | NA                                      | Endometrial carcinoma             | 13           |
| Dreyling M   | 2019   | NCT01660451               | Part B| 142| 71/71        | 63 (25–82)           | 60 mg                | 26 (1–192)                             | Indolent B-cell lymphomas         | 16           |
| Dreyling M   | 2017   | NCT01660451               | Part A| 84| 44/40        | 66.5 (22–90)         | 0.8 mg/kg            | 13.9 (2–137.9)                        | Indolent or aggressive lymphomas  | 15           |
| Doi T        | 2016   | NCT01404390               | I     | 10| 4/6          | 59.5 (51–65)         | 0.4 mg/kg, 0.8 mg/kg | 6.2 (1.1–21.1)                       | Solid tumors                      | 11           |
| Patnaik A    | 2016   | NCT00962611               | I     | 57| 20/37        | 65 (33–86)           | 0.1–1.2 mg/kg        | 6 (NA)                                 | Solid tumors or NHL               | 11           |

**Table 2 Efficacy results of included studies**

| Study: Author, Year | Tumor type or cohort | N | CR % | PR % | ORR % | DCR % | N for PFS & OS | Median PFS in Months (95% CI) | OS in Months (95% CI) | N for DoR | Median DoR in months (95% CI) |
|---------------------|----------------------|---|------|------|-------|-------|----------------|-----------------------------|-----------------------|-----------|-------------------------------|
| Lenz G, 2020        | Lymphoma (Aggressive)| 67 | 7.5  | 11.9 | 19.4  | 40.3  | 67             | 1.8 (1.7–2.8)              | 7.4 (3.5–10.9)         | 13        | 4.3 (1.9–11.5)                 |
| Morschhauser F, 2020| Lymphoma             | 33 | 6.1  | 15.2 | 21.2  | 36.4  | NA             | NA                         | NA                    | NA        | NA                            |
| Santin AD, 2020     | Solid tumors         | 30 | 0    | 3.3  | 3.3   | 46.7  | NA             | NA                         | NA                    | NA        | NA                            |
| Dreyling M, 2019    | Lymphoma (Indolent)  | 142| 16.9 | 43.7 | 60.6  | 85.9  | 142            | 12.5 (5.5–27.6)           | 42.6 (17.8-censored)     | 86        | 14.1 (5.3–28.1)               |
| Dreyling M, 2017    | Lymphoma (indolent)  | 32 | 9.4  | 34.4 | 43.8  | 90.6  | 33             | 9.8 (NA)                   | 21.9 (NA)              | 14        | 13 (NA)                       |
| Dreyling M, 2017    | Lymphoma (aggressive)| 48 | 8.4  | 18.8 | 27.1  | 50.0  | 51             | 2.3 (NA)                   | 6.1 (NA)               | 13        | 5.5 (NA)                      |
| Doi T, 2016         | Solid tumor          | 10 | 0    | 0    | 0    | 40    | NA             | NA                         | NA                    | NA        | NA                            |
| Patnaik A, 2016     | Lymphoma             | 9  | 11.1 | 66.7 | 77.8  | 77.8  | NA             | NA                         | NA                    | NA        | NA                            |
| Patnaik A, 2016     | Solid tumor          | 48 | 2.1  | 4.2  | 6.3   | 37.5  | NA             | NA                         | NA                    | NA        | NA                            |

**Note:** CR complete response, PR partial response, ORR objective response rate, DCR disease control rate, PFS progression free survival, OS overall survival, DoR duration of response, NA not available.
no heterogeneity in CR rate in terms of both $I^2$ and Q statistic ($I^2 = 0.0\%$, $p = 0.946$), and the pooled effect was 8.0\% (95\% CI: 4.9–12.9\%). Additional data on pooling and sensitivity analysis of the response rates are provided in Additional file 2.

Out of the four trials reporting efficacy for solid tumors, only the study by Patnaik et al. had a patient with CR. The ORR for solid tumors varied from 0\% to 6.3\%. Further efficacy analysis was not done in the solid tumor cohort, because of different tumor types and variation in the doses of copanlisib.

**PFS, DoR, and OS**

Efficacy outcome data of NHL based on PFS, DoR, and OS were only available in three studies, as shown in Table 2. The study by Dreyling et al. (2019), which consisted of patients with indolent NHL, reported the best survival outcomes with PFS of 12.5 months, OS of 42.6 months, and DoR of 14.1 months. Due to the paucity of data, further pooling of these outcome measures was not done.

### Subgroup analyses for ORR, CR rate, and DCR

Subgroup analyses were done in the NHL cohort to explore the effect of copanlisib treatment across some characteristics of the studies (NHL classification: aggressive vs indolent, phase of the clinical trial: Phase 1 vs Phase 2). The results of the subgroup analyses are displayed in Table 3. Analysis based on the phase of the clinical trials showed no significant difference between the groups. However, a significant difference was found in the response rates in the aggressive vs indolent NHL subgroup. Indolent NHL reported higher response rates than the aggressive NHL (ORR 56.9% vs 22.8%; CR rate 15.8% vs 7.6%; DCR 86.8% vs 42.5%).

### Adverse events

Seven trials, with 434 patients, were analyzed for...
adverse events of copanlisib monotherapy. The overall number of TEAE (classified by grades) in each study are shown in Table 4. The pooled incidence rate of grade 3–4 TEAE was 73.9% (95% CI: 66.4–80.3%, Fig. 3) (Heterogeneity $I^2 = 55.9\%$, $p = 0.034$). There were 46 grade 5 TEAE, of which eight were attributed to copanlisib. The copanlisib-related grade 5 TEAE were: lung infection in three patients; respiratory failure in two patients; and pneumonitis, embolism, and cryptococcal meningitis in one patient each.

The common all-grade TEAE were pooled from six trials (N = 377) due to the unavailability of specific data from the study by Patnaik et al. Common grade 3–4 TEAE were pooled from five trials (N = 366) due to the unavailability of specific data from the studies by Patnaik et al. and Santin et al. The pooled TEAE data are shown in Table 5. Most common overall TEAE were: hyperglycemia (49.6%), hypertension (39.8%), fatigue (35.5%), diarrhoea (34.8%), and nausea (30.0%). Most common grade 3–4 TEAE were: hyperglycemia (31.4%), hypertension (29.8%), neutropenia (18.3%), anemia (7.4%), and pneumonia (6.8%). Further data on adverse events are provided in Additional file 3.

### Table 4: Number of TEAE (classified by grades) across included studies

| Studies       | N  | Grade 1–2 TEAE (%) | Grade 3–4 TEAE (%) | Grade 5 TEAE (%) | Total TEAE (%) |
|---------------|----|--------------------|--------------------|------------------|----------------|
| Lenz G, 2020  | 67 | 7 (10.4)           | 44 (65.7)          | 14 (20.9)        | 65 (97.0)      |
| Morschhauser F, 2020 | 63 | 9 (14.3)           | 41 (65.1)          | 9 (14.3)         | 59 (93.7)      |
| Santin AD, 2020 | 11 | 2 (18.2)           | 9 (81.8)           | 0 (0)            | 11 (100.0)     |
| Dreyling M, 2019 | 142 | 16 (11.2)       | 118 (83.1)         | 6 (4.2)          | 140 (98.6)     |
| Dreyling M, 2017 | 84 | 7 (8.3)           | 67 (79.8)          | 10 (11.9)        | 84 (100)       |
| Doi T, 2016   | 10 | 4 (40.0)           | 6 (60.0)           | 0 (0)            | 10 (100.0)     |
| Patnaik A, 2016 | 57 | 8 (14.0)           | 42 (74)            | 7 (12)           | 57 (100)       |

### Table 5: Common TEAE after pooling from studies

| TEAE                          | Grade 3–4 TEAE (N = 366) | Overall TEAE (N = 377) |
|-------------------------------|---------------------------|------------------------|
| Hyperglycemia                 | 31.4%                     | 49.6%                  |
| Hypertension                  | 29.8%                     | 39.8%                  |
| Neutropenia                   | 18.3%                     | 22.3%                  |
| Anemia                        | 7.4%                      | 19.4%                  |
| Pneumonia                     | 6.8%                      | 9.8%                   |
| Diarrhoea                     | 5.2%                      | 34.8%                  |
| Thrombocytopenia              | 4.6%                      | 9.3%                   |
| Fatigue                       | 4.1%                      | 35.5%                  |
| Fever                         | 2.5%                      | 22.0%                  |
| Dyspnea                       | 1.9%                      | 9.8%                   |
| Nausea                        | 1.4%                      | 30.0%                  |
| Vomiting                      | 1.1%                      | 16.5%                  |
| Oral mucositis/ulceration     | 0.6%                      | 11.4%                  |
| Anorexia                      | 0.3%                      | 14.6%                  |
| Constipation                  | 0.0%                      | 17.5%                  |

*Available data from 5 studies

*Available data from 6 studies

Publication bias

There was no evidence of publication bias for ORR in the NHL cohort either by the Begg’s test ($P = 0.403$) or the Egger’s test ($P = 0.282$). The Begg’s test ($P = 0.500$) and the Egger’s test ($P = 0.347$) also did not show any
publication bias for grade 3–4 TEAE. The funnel plots of publication bias for ORR and grade 3–4 TEAE are provided in Additional file 4.

Discussion

This study assessed the efficacy and safety of a novel PI3K inhibitor, copanlisib, from the results obtained in seven single-arm prospective trials consisting of 434 patients. A multicenter, single-arm, phase II study evaluated the efficacy and safety of copanlisib in patients with relapsed or refractory, indolent or aggressive lymphoma and reported an ORR of 43.8% in the indolent cohort and 27.1% in the aggressive cohort. The results led to the US FDA approval of copanlisib in 2017. It was approved for treating patients with relapsed FL, who had been treated with at least two prior systemic therapies. Idolalisib and duvelisib are other US FDA approved PI3K inhibitors for relapsed FL and SLL/CLL. However, as they both carry boxed warnings for the AE profile, copanlisib appears to have a more favorable safety profile.

We found the pooled ORR for NHL to be 39.1% with high heterogeneity. Enrollment of patients of distinct races, across multiple centers, from different countries, and having different types of lymphoma (indolent and aggressive) may have contributed to the high heterogeneity. The phase II study by Lenz et al. reported the lowest ORR of 19.4%, while the phase I study by Patnaik et al. reported the highest ORR of 77.8%. The study by Lenz et al. enrolled patients with DLBCL, an aggressive lymphoma, which could have resulted in low ORR. The reasons for the high value of ORR in the study by Patnaik et al. could be twofold. First, only nine patients were enrolled in the NHL cohort, making the sample size small. Second, six of those nine patients had indolent FL with a 100% response to copanlisib, as opposed to only 33% response in the remaining three patients, who had DLBCL.

The pooled CR rate for NHL was 10.9% with low heterogeneity. The study by Dreyling et al. (2019) reported a higher CR rate (16.9%) than other studies and omitting this study resulted in a decrease in overall pooled effect (10.9% vs 8.0%) and no heterogeneity. This can be due to the fact that patients with only indolent NHL were enrolled in this study. In contrast, other studies either had both indolent and aggressive NHL cohorts or only had aggressive NHL cohort. Also, most patients (96.5%) in this study had a baseline ECOG performance status of grade 0 or 1. ECOG status has been found to have a significant association with chemotherapy response, with lower grades ECOG status showing a higher CR rate.

The treatment of relapsed or refractory FL depends on the first-line therapy and duration of response after initial treatment. There is no standard therapy and the relapsing nature further necessitates serial treatment. Novel approaches for relapsed or refractory FL have been studied such as: rituximab plus lenalidomide (ORR 64%, CR 20%); bruton tyrosine kinase (BTK) inhibitor ibrutinib (ORR 38%, CR 13%); bendamustine (ORR 63%, CR 12%); and obinutuzumab plus bendamustine followed by obinutuzumab maintenance (ORR 69%, CR 11%), whether as a single-agent or in combination. Our study showed an ORR of 56.9% (CR rate of 15.8%) with copanlisib monotherapy in the indolent NHL cohort, which consisted mostly of FL (70%). It was comparable to most other novel therapeutic approaches for relapsed or refractory FL, as mentioned above. Similar ORR was shown by idelalisib (57%) in a phase I study in patients with relapsed indolent lymphoma and by duvelisib (47.3%) in a phase II study in patients with refractory indolent NHL. A randomized phase III study (NCT02369016) is ongoing to expand on the use of copanlisib as a single-agent in the treatment of relapsed or refractory indolent NHL. Also, two randomized, phase III studies (NCT02367040 and NCT02626455) are ongoing to explore the combination of copanlisib with rituximab and standard immunochemotherapy (rituximab and bendamustine or rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone).

Due to being either transplant-ineligible or chemorefractory, alternative approaches are warranted for over 70% of patients with relapsed or refractory DLBCL. Currently, chimeric antigen receptor cell therapy (ORR 42%), lenalidomide (ORR 27.5%), blinatumomab (ORR 43%), and ibrutinib (ORR 37%) are being considered. We found an ORR of only 22.8% in patients with aggressive NHL cohort, which mostly had patients with DLBCL (67%). Although this response rate is lower than that of the other considered novel agents, further comparative trials may be needed to assess any significant difference in the efficacy.

Although copanlisib has demonstrated potent anti-tumor and pro-apoptotic activity in various tumor cell lines and xenograft models, the efficacy responses in terms of ORR in solid tumors ranged only between 0 to 6.3% based on three phase I and one phase II trials. Among the 99 patients with solid tumors included for analysis of efficacy, only one patient had a complete response. There were different types of tumors included in this cohort and doses varied from 0.1 to 1.2 mg/kg between the studies, therefore we could not reach any conclusion. However, a meta-analysis on other PI3K inhibitors by Li et al. concluded that the addition of PI3K inhibitors to the therapeutic regimens for advanced solid tumors significantly improved the PFS. This was especially true in patients with breast cancer and neuroendocrine tumors and those with PI3K mutations. So, further exploration regarding the addition of copanlisib to the therapeutic regimens of advanced solid tumors is needed.

Although PFS and OS are considered to be better pri-
mary endpoints for efficacy analysis, CR and ORR are increasingly being used as surrogate endpoints in hematological oncology, as they can be measured in a shorter time. A meta-analysis by Mangal et al. concluded that both ORR and CR rates were found to predict median PFS, indicating the potential of these endpoints to make timely decisions in developing new NHL therapies\(^{36}\). In our analysis, median PFS and OS for NHL were reported in three studies. Median PFS and OS were reported to be higher for the indolent NHL cohort than for the aggressive NHL cohort. However, further analysis was not done due to the paucity of data.

Concerning the safety of copanlisib, we demonstrate in our review, a significant incidence of all grade and grade 3–4 TEAE among patients with NHL and other solid tumors. Although we found the efficacy of copanlisib in terms of ORR and CR rate to be favorable, especially in the NHL cohort, the adverse events (AE) profile seems to be the Achilles’ heel. The pooled incidence rate of all grade and grade 3–4 TEAE were 96.9% and 73.9%, respectively. These incidence rates can bear clinical significance when deciding to choose between copanlisib and other drugs approved for the same indication.

Patients of NHL, who have received two or more prior therapies, have options of other PI3K inhibitors besides copanlisib. Duvelisib and idelalisib are two such PI3K inhibitors approved by the US FDA\(^ {36}\). In a phase III study of duvelisib in relapsed or refractory SLL/CLL, the proportion of the patients developing all grade and grade 3–4 TEAE were 99% and 87%, respectively\(^ {41}\). In another phase II study of duvelisib in patients with refractory indolent NHL, 99.2% and 88.4% of the patients developed one or more all grade and grade 3–4 TEAE, respectively\(^ {36}\). The estimates of both studies are very similar to our estimate of all grade TEAE. However, the studies present a much higher estimate for grade 3–4 TEAE compared to our estimate of 73.9% for copanlisib. In both studies, the most common all grade TEAE were diarrhea, neutropenia, and nausea. The most common grade ≥3 TEAE were neutropenia, diarrhea, anemia, and thrombocytopenia\(^ {36, 41}\). All the aforementioned AE also occur commonly with the use of copanlisib, as shown in our study. However, two of the most common AE of copanlisib—hyperglycemia and hypertension—were not seen with the use of duvelisib. Copanlisib and duvelisib both inhibit PI3K\(\alpha\). However, copanlisib also targets the \(\alpha\) isoform, which is responsible for the downstream effects and biological responses exerted by insulin\(^ {42}\). The on-target effect of inhibition of PI3K\(\alpha\) and its resultant disruption of insulin signaling is responsible for the resulting hyperglycemia. Hypertension is most likely observed secondarily to the role of PI3K, especially \(\gamma\) isoform, in the blood pressure homeostasis. PI3K\(\gamma\) interacts with angiotensin II and stimulates calcium channels in the smooth muscles, resulting in vasoconstriction\(^ {43}\).

There have been only a few meta-analyses that explored the safety of PI3K inhibitors in lymphoma or other solid tumors. The meta-analysis by Raphael et al. included five phase II or III clinical trials of PI3K inhibitors (buparlisib or pictilisib) in the treatment of advanced breast cancer\(^ {44}\). 98.9% of the patients treated with a PI3K inhibitor reported all grade AE and 70% reported grade ≥3 AE. This incidence of AE with the use of a PI3K inhibitor closely resembles our findings with copanlisib. Depression was a significant AE of the PI3K inhibitor (buparlisib) in the meta-analysis by Raphael et al. In contrast, depression was not observed with copanlisib in our study. The spectrum of rest of the grade ≥3 AE is in congruence with the results of our study.

Another meta-analysis evaluated the risk of AE with idelalisib and ibrutinib in relapsed or refractory CLL/SLL\(^ {45}\). In the idelalisib subgroup of the meta-analysis, 83.8% of the patients developed grade 3–4 AE and the risk was increased by 33% (Relative Risk, RR = 1.33). Owing to the lack of control arms in the included studies, we could not evaluate the RR in our study. However, the incidence rate of AE in the experimental groups in both of the previously mentioned meta-analyses, and the pooled incidence rate in our study, illustrates the likelihood of AE of the PI3K inhibitors.

It is of utmost importance to evaluate the risk-benefit ratio of copanlisib to make an informed decision about the choice of treatment. This should be based on the estimate of treatment effect, AE, toxicity profile, and the effect on the quality of life.

Several limitations existed in our study. First, our study only included single-arm phase I and II clinical trials, therefore we could not make any comparison with placebo or other treatments. Because of the lack of control arms, we also could not ensure the highest possible qualities of the studies included. Second, most studies did not have adequate data on PFS and OS, and we could not do further analysis on those outcomes. Third, the types of tumors and the dosing of copanlisib were variable, especially for the solid tumor cohort, and we could not expand on the efficacy in this cohort. Fourth, most of the trials included in this study were funded by a single pharmaceutical company. Although we attempted to include all eligible studies, it is still possible that some unpublished studies were missed. Finally, the inclusion of a few studies may limit the strength of our study. Availability of more studies could have increased the power of this study.

**Conclusions**

Our study showed that copanlisib is effective in the treatment of relapsed or refractory NHL, with a higher rate of response in indolent NHL than aggressive NHL. However, we could not reach a conclusion regarding...
the treatment of solid tumors because of the variations in the types of tumors and the dosing of copanlisib. Hyperglycemia and hypertension were the most common adverse events of copanlisib noted in our study. This analysis provides estimates on the efficacy and safety of copanlisib, which will ease the selection of this novel drug for the management of relapsed or refractory NHL.

List of abbreviations

AE: Adverse events
CNKI: China National Knowledge Infrastructure
CR: Complete response
DCR: Disease control rate
DLBCL: Diffuse large B-cell lymphoma
DoR: Duration of response
ECOG: Eastern Cooperative Oncology Group
FDA: Food and Drug Administration
FL: Follicular lymphoma
MINORS: Methodological Index for Non-Randomized Studies
mTOR: Mammalian target of rapamycin
NHL: Non-Hodgkin’s Lymphoma
ORR: Objective response rate
OS: Overall survival
PFS: Progression-free survival
PI3K: Phosphoinositide 3-kinase
PICO: Population, Intervention, Comparison/control, Outcome
PR: Partial response
PRISMA: Preferred Reporting Items for Systematic Review and Meta-analysis
SD: Stable disease
SLL/CLL: Small lymphocytic lymphoma/chronic lymphocytic leukemia
TEAE: Treatment-emergent adverse events

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