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Review

Specific Toxicity of Maintenance Olaparib *Versus* Placebo in Advanced Malignancies: A Systematic Review and Meta-analysis

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Abstract. *Background/Aim: We performed a systematic review and meta-analysis to investigate the safety of maintenance with olaparib after platinum-based chemotherapy in cancer patients. Materials and Methods. Eligible studies included randomized controlled trials (RCTs) regarding the clinical role of olaparib maintenance therapy versus placebo in BRCA-mutated, advanced cancers. Safety profile from each selected study was investigated for all-grade and G3-G4 haematological and non-haematological adverse drug events (ADEs). Results: Four RTCs that involved 1099 patients were included in the analysis. Overall incidences of all-grade and G3-4 ADEs in olaparib group were 97.6% and 41%, respectively. Patients treated with maintenance olaparib showed higher risk of all-grade and G3-G4 anaemia, all-grade neutropenia and thrombocytopenia. Moreover, all-grade and G3-G4 fatigue, all-grade vomiting, diarrhoea, nausea and decreased appetite were more common in the olaparib group compared to placebo. Conclusion: Despite an increased risk and incidence of several haematological and non-haematological toxicities, olaparib is a relatively safe agent for the treatment of advanced solid tumors. Prompt identification of ADEs is mandatory to avoid therapy discontinuation and optimize treatment.*

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Poly adenosine diphosphate-ribose polymerase (PARP) inhibitors represent an emerging therapeutic class for patients harbouring mutated breast-related cancer antigens (*BRCA*) or homologous recombination-deficient (HRD) malignancies (1). The family of PARP enzymes consists of 17 nucleoproteins divided into four main groups, the first of which includes PARP1, PARP2, and PARP3 who play a key role during DNA repair (2). PARP enzymes are involved in detecting single-strand DNA breaks (SSB) and their activation triggers DNA repair mechanisms, such as base excision repair. In HRD cells (*e.g.*, *BRCA1* and *BRCA2* mutated), this damage is converted into unrepairable double-stranded break (DSB) and leading to selective cell death (3).

Olaparib was the first PARP inhibitor introduced in clinical practice (4) and its efficacy in prolonging outcomes and manageable safety profile have allowed testing of this molecule as a maintenance treatment for several advanced malignancies (5). Olaparib is currently approved in Europe as maintenance treatment in patients affected by advanced BRCA-mutated ovarian cancer following response (defined as stable disease, partial response, or complete response) to first-line platinum-based chemotherapy. Furthermore, olaparib is approved for patients with recurrent platinum-sensitive ovarian cancer after response to platinum-based chemotherapy. The role of olaparib in other malignancies and/or in combination with antiangiogenic agents is currently under investigation and it represents a hot topic in Medical Oncology (6).

The SOLO-1 trial was the first to compare front-line olaparib maintenance therapy with placebo after response to platinum-based chemotherapy in newly diagnosed advanced ovarian cancer with BRCA mutation. This double-blind,

randomized, prospective phase III trial showed a decrease in the risk of disease progression or death by 70% with olaparib compared to placebo (HR=0.30; 95%CI=0.23 to 0.41; $p<0.001$), in the presence of an acceptable safety profile (7).

Olaparib maintenance therapy represents a therapeutic advance also in the management of pancreatic cancer. The recent results of the POLO trial – a randomized, double-blind, placebo-controlled, phase III trial evaluating olaparib maintenance after response to platinum-based chemotherapy in BRCA-mutated pancreatic cancer-, confirmed the efficacy of olaparib in extending progression-free survival (7.4 months *vs*. 3.8 months; HR=0.53; 95%CI=0.35-0.82; $p=0.004$) with a tolerable safety profile (8). Currently, there are ongoing trials aimed to evaluate efficacy and safety of maintenance of olaparib in other neoplasms such as non-small-cell lung cancer, prostate cancer, and endometrial carcinoma, administered as single-agent therapy or in combination with other anticancer agents (9).

The aim of maintenance therapy is to maintain a long-lasting remission and to delay recurrence (10), leading to a prolonged treatment administration [*e.g.*, two years in SOLO-1 trial (7)], with an acceptable safety profile and optimal quality of life. Since maintenance olaparib is now part of routine clinical practice, it is essential to investigate the overall incidence and risk of the most common side effects associated with its administration. Fatigue, haematological and gastrointestinal toxicities are the most common side effects of PARP inhibitors, although they may present different, specific, toxicity profiles (11).

The aim of this systematic review and meta-analysis is to evaluate toxicity of maintenance olaparib after platinum-based chemotherapy, focusing on the most commonly reported all-grade and high-grade (G3-G4) adverse events (ADEs) in randomized controlled clinical trials comparing olaparib *versus* placebo.

Materials and Methods

Search strategies. All phase II and phase III clinical trials published from June 15, 2008 to November 29, 2019 regarding the clinical role of olaparib maintenance therapy in advanced malignancies were retrieved by 2 different authors (ADR and AR). Keywords used for searching PubMed/ Medline, Cochrane library and EMBASE were: "Olaparib" OR "maintenance Olaparib" OR "Lynparza" OR "AZD-2281" AND "advanced cancer" OR "ovarian cancer" OR "pancreatic cancer" OR "metastatic malignancies"; only articles published in peer-reviewed journals and written in English language were considered. Furthermore, proceedings of the main international oncological meetings (American Society of Clinical Oncology, European Society of Medical Oncology, European Council of Clinical Oncology, American Association for Cancer Research), were also searched from 2005 onward for relevant abstracts.

Selection criteria. Studies selected from first analysis were then restricted to: 1) prospective phase II or III randomized controlled trials (RCT) in advanced malignancies; 2) participants enrolled in maintenance treatment with olaparib or placebo; 3) studies with available data about safety profile and adverse events.

Data extraction and quality assessment. The following data were extracted from each publication: 1) study general information (author, year, phase, carry out country, inclusion criteria); 2) primary site; 3) interventions; 4) formulation of olaparib maintenance therapy; 5) number of patients; 6) median treatment duration 7) primary and secondary outcomes; 8) side effects. Two separate authors (ADR and AR) conducted the search and identification independently.

We assessed the methodological quality of the included trials using Cochrane Collaboration tool. Studies examined were graded as having a "low risk", "high risk", or "unclear risk" of bias across the 7 specified domains. This meta-analysis was conducted according to Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (12).

Assessment of risk of bias in included studies. Risk of bias in the four selected studies was assessed independently by two authors (ADR and AR) using the tool of The Cochrane Collaboration (13) for assessing risk of bias and therefore including selection, performance, detection, attrition and reporting bias. The lists of outcomes reported in the published paper were compared to those from study protocols or trials registries. The results were summarized in both a risk of bias graph (Figure 1) and risk of bias summary (Figure 2).

Types of outcome measures. We examined nine most common hematological and non-hematological ADEs including fatigue, anemia, neutropenia, thrombocytopenia, diarrhea, vomiting, nausea, decreased appetite and abdominal pain. Toxicity outcomes were divided in two groups: hematological (anemia, neutropenia, thrombocytopenia) and non-hematological toxicities (fatigue, diarrhea, vomiting, nausea, decreased appetite and abdominal pain).

Toxicity data were obtained from safety profile or supplemental material of each study and classified according to the CTCAE (Common Terminology Criteria for Adverse Events) version (3 or 4) of the National Cancer Institute Common Toxicity Criteria (NCI-CTC) (14, 15).

Statistical analysis. All statistical analyses were performed using R studio and Review Manager 5.3. For the calculation of incidence rate (IR), the number of patients with all- and G3-4 ADEs and the total number of patients being treated with olaparib were determined from each trial. The proportions of patients with all- and G3-4 ADEs and 95%CIs were calculated.

Relative Risks (RRs) were used to analyze dichotomous variables, including all-grade and high-grade (G3-G4) events (ADEs); RRs were combined with Mantel-Haenszel method. Statistical heterogeneity between studies was examined using the Chi-square test and the I^2 statistic, and a fixed-effects model was applied to analyze quantitative data when there was no significant heterogeneity ($I^2<50\%$). In other cases, a random-effects model was adopted ($I^2>50\%$).

Results

Studies selected. In our search, 288 potentially relevant reports were identified, which were subsequently restricted to 4 after independent evaluation by 2 authors (ADR and AR) (7, 8, 16, 17). We excluded 284 records as non-pertinent reports (meta-

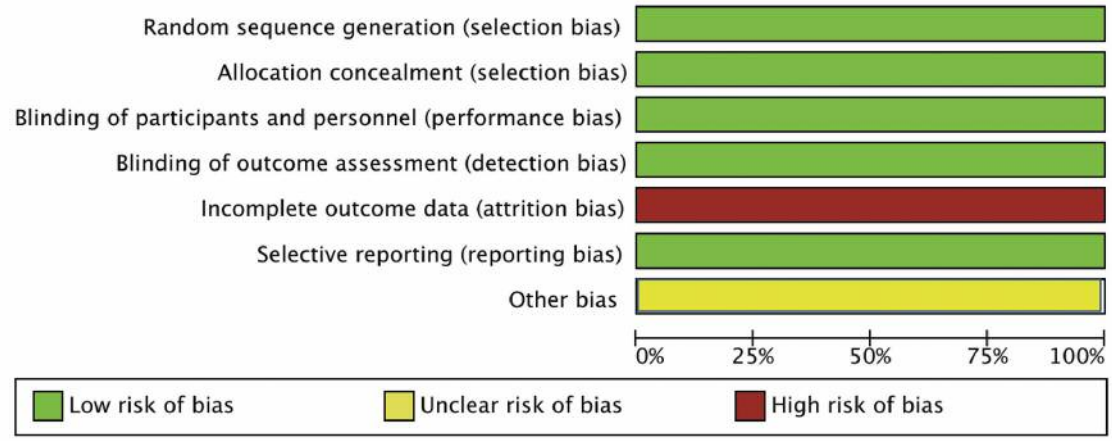

Figure 1. *Risk of bias graph: Authors' judgements on each risk of bias item presented as percentages across all included studies.*

analysis and systematic reviews, review articles, editorials, case reports, pre-clinical studies, retrospective studies, non-randomized studies, no placebo-controlled arm trials, no maintenance trials, ongoing trials/trials in progress).

All studies included in our analysis were published as full manuscripts (7, 8, 16, 17) and were judged as studies with a low risk of bias in separate reviews of 2 authors (ADR and AR). Figure 3 shows the search process.

Of the 4 eligible studies, three studies compared maintenance olaparib *versus* placebo after response to platinum-based chemotherapy in advanced or metastatic ovarian cancer (7, 8, 16). The same comparison was made in the fourth study, where maintenance Olaparib was compared to placebo after response to platinum-based chemotherapy in advanced or metastatic pancreatic cancer (17). Three trials were phase III studies (8, 16, 17), while one study was a phase II trial (7). The four studies shared several characteristics: they were all randomized, double-blind, international, multicentre, placebo-controlled trials where the PARP inhibitor olaparib was administered as maintenance therapy after partial/complete response to platinum-based chemotherapy (7, 8, 16, 17).

A total of 1099 patients were available for the meta-analysis (olaparib: 682; placebo: 417).

Olaparib dosage was as follows: 400 mg capsules twice daily in one study (7), and 300 mg tablets twice daily in the other three studies (8, 16, 17). A summary of the included RCTs is presented in Table I. All 4 trials reported ADEs according to the National Cancer Institute's CTCAE version 3 or 4 criteria (14, 15).

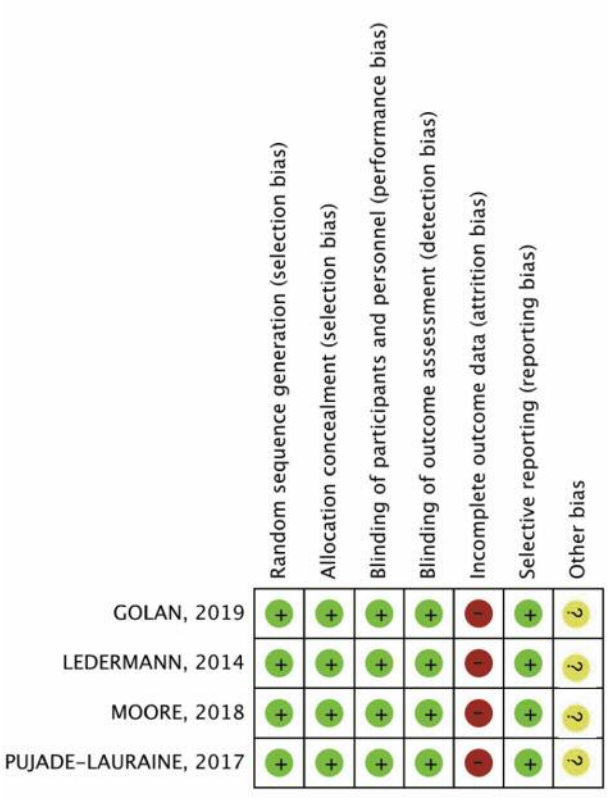

Figure 2. *Risk of bias summary: Authors' judgments on each risk of bias item for each included study.*

Incidence and RR of ADEs. As stated above, the outcomes were divided in two groups: hematological (anemia, neutropenia, thrombocytopenia) and non-hematological toxicities (fatigue, diarrhea, vomiting, nausea, decreased appetite and abdominal pain). In order to evaluate all-grade and G3-4 ADEs, data were included from all 4 RCTs comprising 1099 patients. Table II shows the pooled IRs of all outcomes included in our analysis. The incidences of all-grade and G3-4 ADEs for patients receiving maintenance

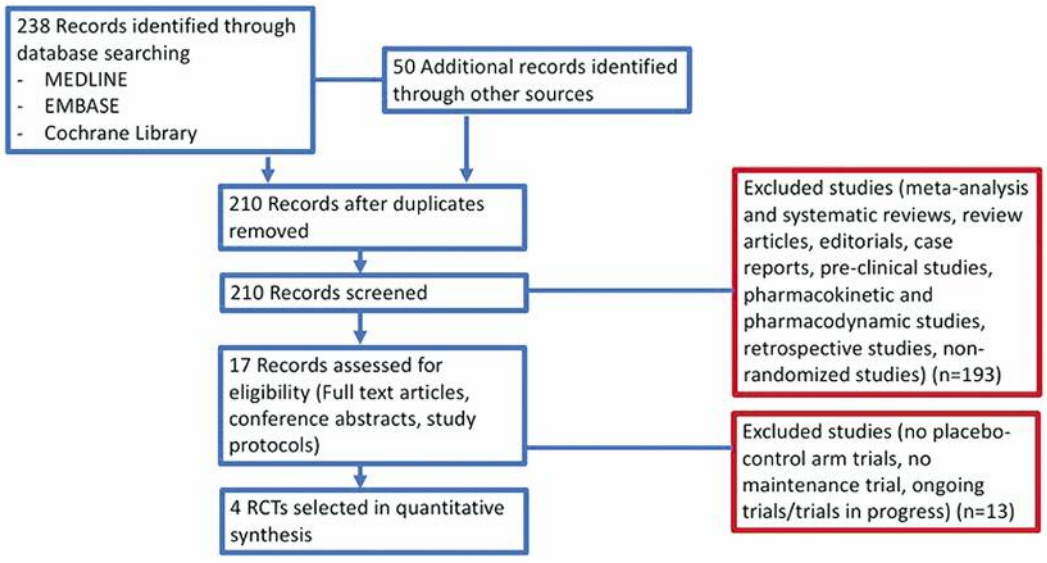

Figure 3. *Study flow diagram.*

olaparib were 97.6% and 41%, respectively. For any grade of ADEs, nausea, fatigue, anemia, vomiting and diarrhea were the most frequent clinical ADEs (70.1%, 61.4%, 35.2%, 34.9% and 30.8%, respectively). The most common G3-4 ADEs were anemia (16.3%) and fatigue (4.8%).

Haematological toxicities. We assessed 3 types of frequently occurring hematological ADEs: anemia, neutropenia and thrombocytopenia.

Patients treated with maintenance olaparib showed higher risk of G3-4 anemia (RR=8.86; 95%CI=4.12-19.07, $p<0.00001$) (Figure 4A), all-grade anemia (RR=3.39; 95%CI=2.05-5.61, $p<0.00001$ random effect model) (Figure 4B), all-grade neutropenia (RR=2.36; 95%CI=1.49-3.74, $p=0.0003$) (Figure 5B) and all-grade thrombocytopenia (RR=3.52; 95%CI=1.71-7.27, $p=0.0006$) (Figure 6B). In addition, no significant differences were observed between the incidence of G3-4 neutropenia (RR=2.33; 95%CI=0.71-7.58, $p=0.16$) (Figure 5A) and G3-4 thrombocytopenia (RR=0.67; 95%CI=0.15-2.97, $p=0.60$) (Figure 6A). All-grade and G3-G4 thrombocytopenia were reported in 2 of the 4 clinical trials and, consequently, the analysis was conducted in only 2 trials.

There was a considerable heterogeneity in all-grade anaemia analysis ($p=0.07$, $I^2=57\%$) between the two subgroups.

Non-haematological toxicities. We assessed 6 types of frequently occurring non-hematological ADEs: fatigue, diarrhea, vomiting, nausea, decreased appetite and abdominal pain. Patients treated with olaparib maintenance therapy showed higher risk of G3-G4 fatigue (RR=2.42; 95%CI=1.16-5.02, $p=0.02$) (Figure 7A), all-grade fatigue (RR=1.54; 95%CI=1.35-1.76, $p<0.00001$) (Figure 7B), all-grade vomiting (RR=2.18; 95%CI=1.70-2.80, $p<0.00001$) (Figure 7D), all-grade diarrhea (RR=1.39; 95%CI=1.12-1.73, $p=0.003$) (Figure 8B), all-grade nausea (RR=2.07; 95%CI=1.79-2.39, $p<0.00001$) (Figure 8D) and all-grade decreased appetite (RR=2.05; 95%CI=1.44-2.90, $p<0.0001$) (Figure 9B) when compared to placebo.

In addition, no significant differences were observed between the two groups regarding the incidence of G3-G4 diarrhea (RR=2.33; 95%CI=0.71-7.58, $p=0.16$) (Figure 8A), G3-G4 vomiting (RR=1.58; 95%CI=0.50-4.96, $p=0.43$) (Figure 7C), G3-G4 nausea (RR=2.52; 95%CI=0.71-8.88, $p=0.15$) (Figure 8C), G3-G4 decreased appetite (RR=4.08; 95%CI=0.51-32.71, $p=0.19$) (Figure 9A), G3-G4 abdominal pain (RR=0.74; 95%CI=0.34-1.60, $p=0.44$) (Figure 9C) and all-grade abdominal pain (RR=0.93; 95%CI=0.75-1.16, $p=0.54$) (Figure 9D) The results showed low heterogeneity; therefore a fixed effects model was used.

Discussion

Our analysis included 4 RCTs that evaluated efficacy and safety of maintenance olaparib in two malignancies with unfavourable prognosis (7, 8, 16, 17). Although maintenance olaparib was associated with an increased risk of several all-grade and G3-4 toxicities when compared to placebo, it showed a manageable safety profile, with 41% of IR for G3-4 ADEs. The analysis showed that the most common G3-4 ADEs were anemia (16.3%) and fatigue (4.8%). We did not consider the risk of developing myeloid leukaemia (AML), given the rarity of the event (5 cases of AML were reported

Table I. *Summary of the included studies*.

Author/ year	Study design	Histology	Inclusion criteria	Type of treatment	Sample size	Median age, years (range)	Median treatment duration, months
Ledermann/ 2014 (16)	Randomize, double-blind, multicentre, Phase II trial	Ovarian, fallopian tube or primary peritoneal cancer	Women ≥18 years had recurrent ovarian cancer, with high-grade (grade 2 or 3) serous features,which was platinum-sensitive	Olaparib 400 mg BID (capsules)	136	58 (21-89)	6.9
				Placebo	138	59 (33-84)	4.7
Pujade-Lauraine/ 2017 (17)	International, multicenter, double-blind, randomized, placebo-controlled, Phase III trial	Ovarian, fallopian tube or primary peritoneal cancer	Women≥18 years with confirmed, relapsed, high-grade *BRCA*-mutated serous or endometrioid ovarian cancer. Patients were also required to have platinum-sensitive disease	Olaparib 300 mg BID (tablets)	195	56 (51-63)	19.4
				Placebo	99	56 (49-63)	5.6
Moore/2018 (7)	International, multicenter, double-blind, randomized, placebo-controlled, Phase III trial	Ovarian, fallopian tube or primary peritoneal cancer	Women≥18 years with newly diagnosed advanced high-grade *BRCA*-mutated serous or endometrioid ovarian cancer. Patients were also required to have received first line platinum-based chemotherapy with complete or partial clinical response	Olaparib 300 mg BID (tablets)	260	Not reported	Not reported
				Placebo	130	Not reported	Not reported
Golan/2019 (8)	International, multicenter, double-blind, randomized, placebo-controlled, Phase III trial	Pancreatic adenocarcinoma	Patients ≥18 years with metastatic *BRCA*-mutated pancreatic cancer. Patients were also required to have received first line platinum-based chemotherapy with complete or partial clinical response	Olaparib 300 mg BID (tablets)	91	57 (37-84)	Not reported
				Placebo	60	57 (36-75)	Not reported

BID: Bis in die; BRCA: Breast related cancer antigens.

in the olaparib group and 1 case in the placebo group). Adverse events reported in the trials were usually managed by dose interruption or dose reduction, rather than discontinuation (7, 8, 16, 17).

Generally, anaemia afflicts up to 64% of patients treated for malignancies and it is characterized by a variety of etiopathogenetic mechanisms, including inflammation/chronic disease, iron deficiency, marrow aplasia/hypoplasia, and haemolytic anaemias (18). Anaemia is also the most common haematological toxicity among PARP inhibitors (11); this ADE has been associated to PARP2 inhibition during differentiation of erythroid progenitors, as observed by Farres *et al*. in mice lacking PARP2 (19), though no studies in humans have been performed so far. Dose interruptions or transfusions are often required to manage symptomatic anaemia and low haemoglobin levels (20). In the four selected studies, the

Table II. *Incidence rate of all-grade and G3-4 adverse drug events (ADEs) resulting from olaparib treatment and placebo.*

ADEs	Number of events/sample size		Incidence Rate % (95%CI)	
	Olaparib	Placebo	Olaparib	Placebo
All-grade				
Any ADE	666/682	389/417	97.6 (96.5-98.7)	93.2 (90.8-95.6)
Anemia	111/682	7/417	35.2 (31.6-38.7)	9.1 (6.3-11.8)
Neutropenia	101/682	26/417	14.8 (13.4-16.1)	6.2 (5.6-6.8)
Thrombocytopenia	56/682	8/417	8.2 (7.3-9.1)	1.9 (0.6-3.2)
Fatigue	419/682	164/417	61.4 (57.6-65.3)	39.3 (34.6-44)
Vomiting	238/682	65/417	34.9 (31.3-38.4)	15.5 (4.5-26.5)
Diarrhea	210/682	90/417	30.8 (27.3-34.2)	21.6 (17.6-25.5)
Nausea	483/682	141/417	70.1 (67.4-74.2)	33.8 (29.3-38.2)
Decreased appetite	122/682	38/417	17.8 (15-20.7)	9.1 (0.6-1.1)
Abdominal pain	161/682	104/417	23.6 (20.4-26.7)	24.9 (20.8-29.5)
Grade 3-4				
Any ADE	282/682	84/417	41 (37.6-45)	20.1 (16.3-23.9)
Anemia	240/682	38/417	16.3 (13.5-19)	1.7 (1.5-1.8)
Neutropenia	13/682	3/417	1.9 (1.7-2)	0.7 (0.1-1.5)
Thrombocytopenia	4/682	3/417	0.5 (0.4-0.6)	0.7 (0.1-1.5)
Fatigue	33/682	9/417	4.8 (3.2-6.4)	2.1 (0.1-3.5)
Vomiting	10/682	4/417	1.4 (0.5-2.3)	0.8 (0.1-1.6)
Diarrhea	13/682	3/417	1.9 (1.7-2)	0.7 (0.1-1.5)
Nausea	10/682	1/417	1.4 (0.5-2.3)	0.3 (0.1-0.5)
Decreased appetite	6/682	0/417	0.8 (0.2-1.5)	0 (0-0)
Abdominal pain	14/682	12/417	2 (0.9-3.1)	2.8 (1.2-4.4)

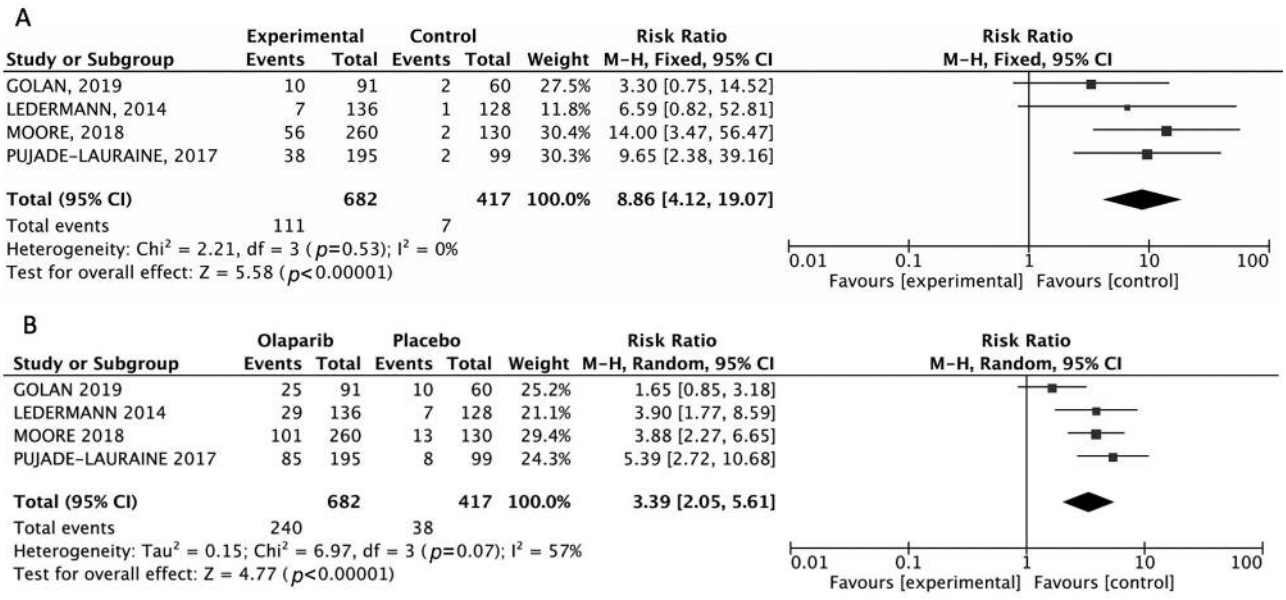

Figure 4. *Forest plot of comparison between olaparib maintenance treatment and placebo; the outcome was risk ratio of anemia (G3, G4: A; all-grade: B). CI: Confidence interval.*

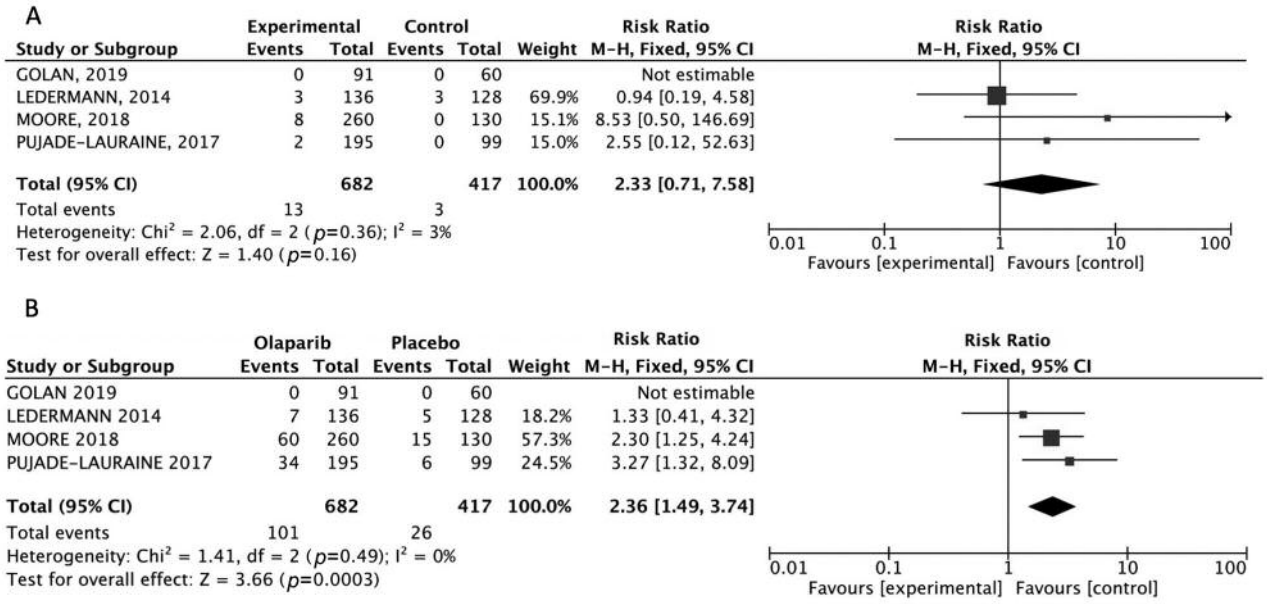

Figure 5. *Forest plot of comparison between olaparib maintenance treatment and placebo; the outcome was risk ratio of neutropenia (G3, G4: A; all-grade: B). CI: Confidence interval.*

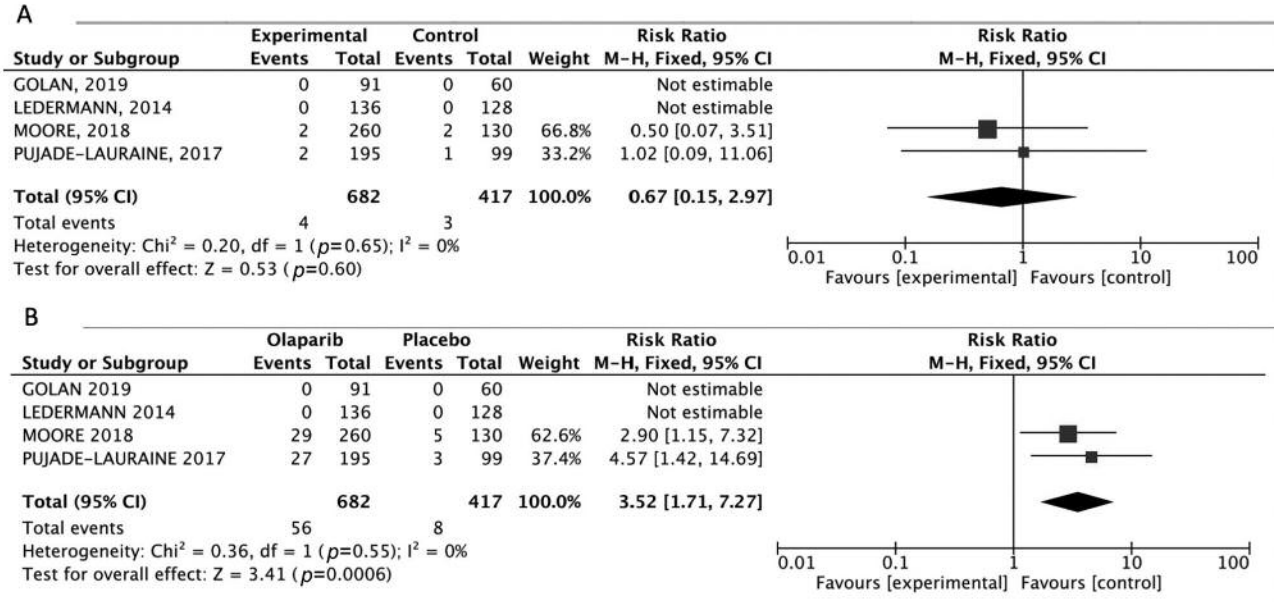

Figure 6. *Forest plot of comparison between olaparib maintenance treatment and placebo; the outcome was risk ratio of thrombocytopenia (G3, G4: A; all-grade: B). CI: Confidence interval.*

increased risk of anaemia could also have an indirect impact on treatment-associated fatigue, another very common toxicity. In fact, if fatigue represents a frequent corollary of cancer and its therapies, up to 69% of patients treated with the three approved PARP inhibitors (olaparib, niraparib and rucaparib) had experienced some grade fatigue (11). Nevertheless, there are subjective and objective dysfunctional components involved in fatigue not directly related to anticancer drugs, and pharmacological as well as non-pharmacological approaches may be efficient in reducing the symptom (21).

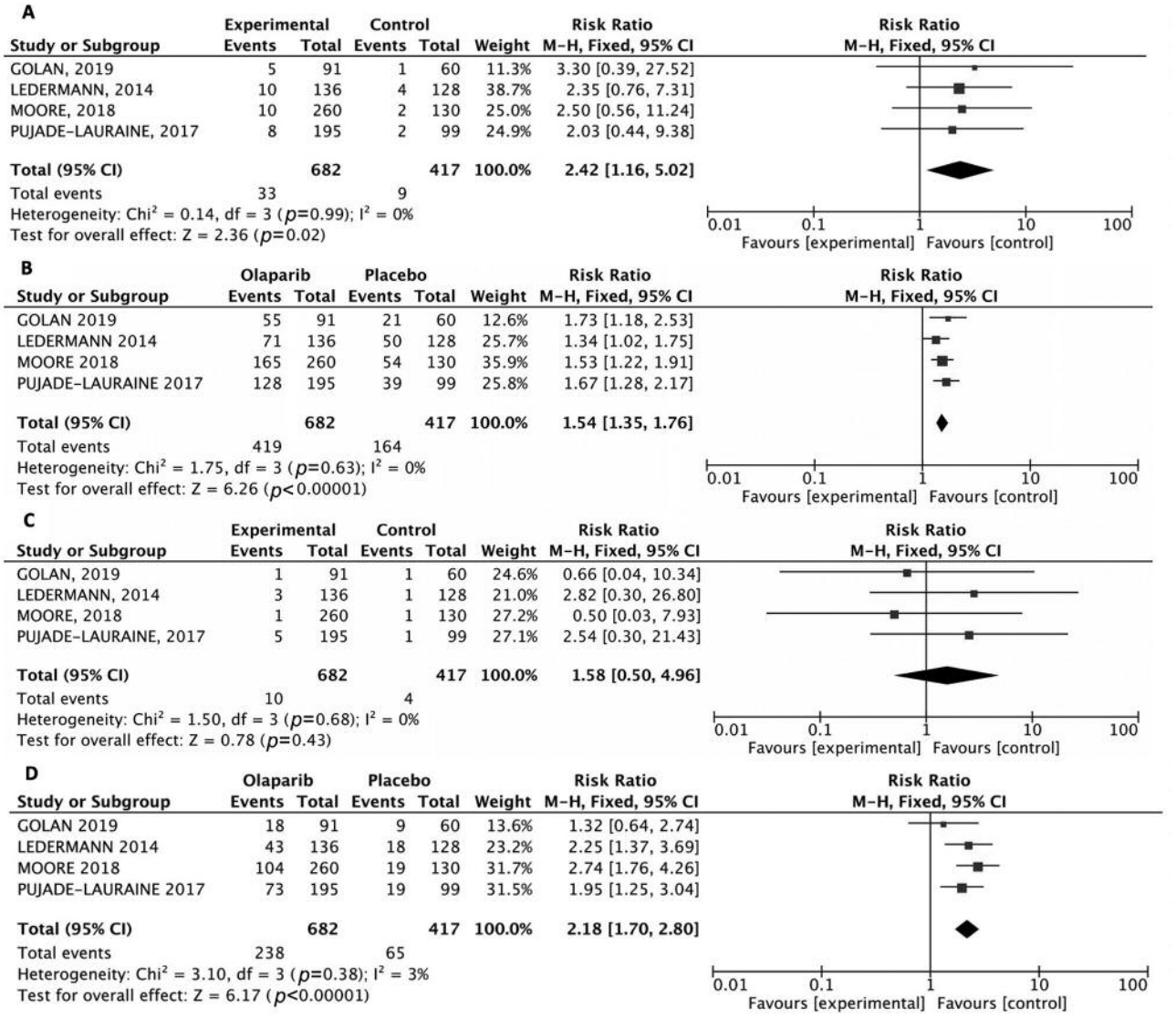

Figure 7. *Forest plot of comparison between olaparib maintenance treatment and placebo; the outcomes were risk ratio of fatigue (G3, G4: A; all-grade: B) and vomiting (G3, G4: C; all-grade: D). CI: Confidence interval.*

Regarding gastrointestinal toxicities, a meta-analysis by Liu *et al*. (22) has demonstrated a significant increase in the risk of ADEs correlated with PARP inhibitor treatment, especially high-grade nausea and vomiting. Nausea has also been reported to be the most prevalent side effect associated with olaparib administration (11). A proactive approach with antiemetic therapy (*e.g*. metoclopramide) might limit dose adjustments or discontinuations in patients who experience treatment-related nausea and vomiting (23). It has also been recommended to switch to full tablet dose in patients receiving lower dose capsules for gastrointestinal side effects, given the better benefit-risk ratio of tablet formulation with similar efficacy and lower pill burden (20).

We compared our results with previous similar meta-analysis. First, Zhou *et al*. in 2017 (24) investigated the overall incidence and RRs of severe hematologic toxicities among patients treated with PARP inhibitors, including olaparib. This meta-analysis showed that patients receiving olaparib had an increased risk of severe neutropenia, while the RR of high-grade anaemia failed to reach statistical significance (RR=1.50; 95%CI=0.77-2.95, p=0.236). Guo *et al*. in 2018 (25) showed an increase in risk of severe anaemia (RR=2.21, 95%CI=1.53-3.49 p<0.001) in RCTs evaluating olaparib monotherapy in advanced cancers, together with an increased risk of anorexia

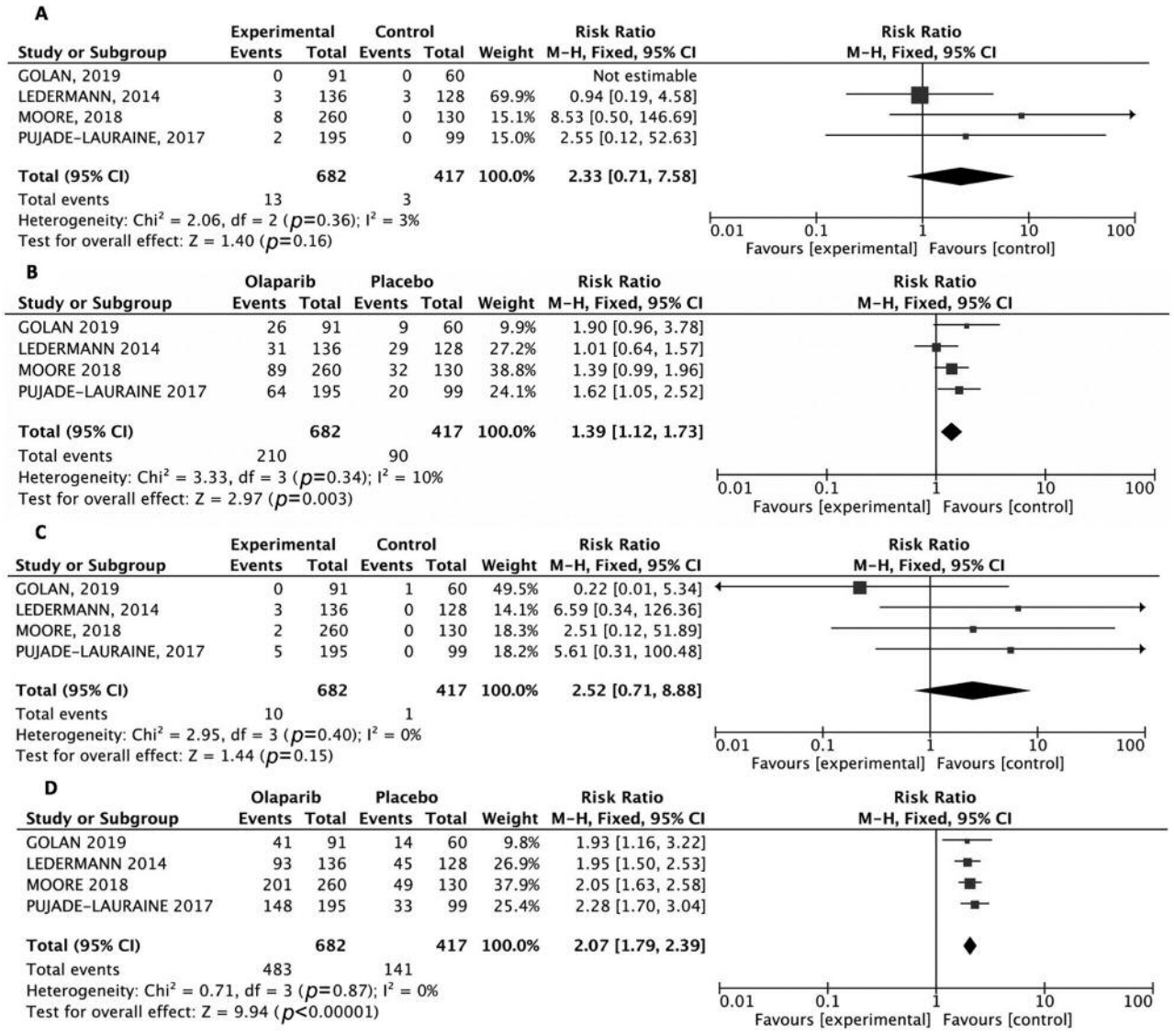

Figure 8. *Forest plot of comparison between olaparib maintenance treatment and placebo; the outcomes were risk ratio of diarrhea (G3, G4: A; all-grade: B) and nausea (G3, G4: C; all-grade: D). CI: Confidence interval.*

(RR=3.50, 95%CI=1.08-11.33.49, $p<0.037$), which was reported in only 2 of the 7 trials included. In 2019, a meta-analysis by Ruiz-Schutz *et al*. (26) showed that treatment with olaparib, in comparison with other interventions (placebo, chemotherapy), was associated with a significant increase in the risk of developing all-grade and high-grade fatigue and anaemia, in line with our findings. Yet, all these studies included RCTs evaluating Olaparib both as a monotherapy and in combination with chemotherapy agents, so it is conceivable that adverse events might be influenced by chemotherapy toxicities. Moreover, the first two meta-analyses considered the incidence and RR of only G3-G4 side effects.

Furthermore, our findings are in line with the most frequently reported ADEs from the latest retrospective real-world studies (6, 27, 28). Recently, real-world experiences with olaparib regarding Italian, Korean and Chinese patients affected by ovarian cancer have gathered robust evidence of the safety of maintenance olaparib. All-grade fatigue and nausea and G3-G4 anaemia were confirmed to be the most common toxicities recorded (6, 27, 28).

Our meta-analysis holds its own strengths and limitations. The strengths of our work regard the inclusions of only randomized placebo-controlled trials, the total number of patients and the high-quality statistical analysis. However, the results of this

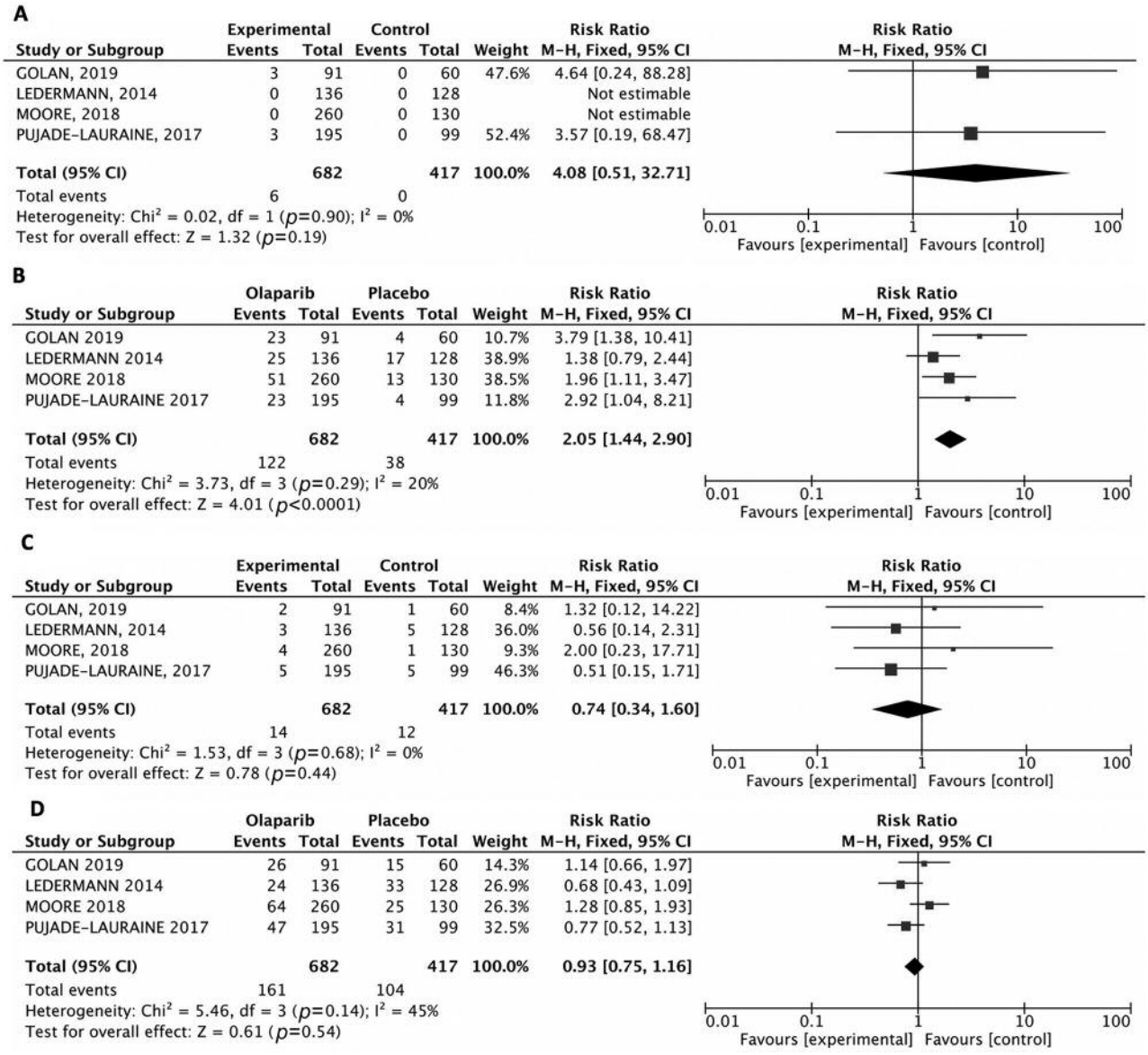

Figure 9. *Forest plot of comparison between olaparib maintenance treatment and placebo; the outcomes were risk ratio of decreased appetite (G3, G4: A; all-grade: B) and abdominal pain (G3, G4: C; all-grade: D). CI: Confidence interval.*

meta-analysis should be interpreted with caution because there are some limitations. First, the data were abstracted from published clinical trial results and were not gathered from individual patient records; and thus, the analysis of factors potentially contributing to development of haematological and non-haematological toxicities, such as concomitant treatments or additional comorbidities, was not possible. Second, the varying types of tumours, the under-representation of men compared to women, the impact of previous treatments in patients with relapsed disease and the different formulations of olaparib might be sources of heterogeneity. Third, the evaluation of long-term toxicities was limited by the relatively short follow-up of the last two RCTs (7, 8).

Conclusion

PARP inhibitors are a new class of small-molecule drugs that have profoundly modified the oncology landscape. In the era of tailor-made medicine, olaparib has demonstrated a clinical benefit as maintenance therapy in *BRCA1/2* mutation carriers affected by advanced platinum-sensitive ovarian and pancreatic cancers.

Although extended administration of olaparib may increase the risk of several haematological and non-haematological toxicities, our study suggests that olaparib is a relatively safe agent. However, special attention should be paid to olaparib-related ADEs, in order to improve drug compliance, to avoid therapy discontinuation and to optimize olaparib treatment. Furthermore, there is an urgent need for real-world data in order to better define safety profile and benefit-risk ratio, beyond the borders of traditional randomized clinical trials.

Conflicts of Interest

The Authors have stated that they have no conflicts of interest regarding this study.

Authors' Contributions

ADR, AR: Concept, design, statistical analysis and final review; MN: statistical analysis; ST, AP, NT, FA, VM, SDL: Data collection; DT, MCDM, GB: Final review and approval.

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