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Risk of fatigue and anemia in patients with advanced cancer treated with olaparib: A meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: : PARP inhibitors are a new class of drugs that are currently being studied in several malignancies. Olaparib is FDA-approved for advanced breast cancer and advanced ovarian cancer patients. Fatigue and anemia are among the most common cancer and treatment-related symptoms. Therefore, we conducted a meta-analysis of randomized controlled trials (RCT) to characterize the incidence and relative risks (RRs) of fatigue and anemia associated with olaparib.

Methods: : PubMed, Cohrane, Embase and abstracts presented at the annual meeting of the American Society of Clinical Oncology (ASCO) were searched for articles published from 2000 to June 2018. The eligible studies were phase II and III RCT of olaparib. Safety profile from each selected study was evaluated for all-grade and high-grade fatigue and anemia adverse events. Summary incidences and the RR, with 95% confidence intervals, of all-grade and high-grade events were calculated using random-effects or fixed-effects model based on the heterogeneity of selected studies.

Results: : A total of 9 trials were selected, and included 2074 patients with advanced ovarian, gastric, prostate, lung or breast cancer. 908 patients received placebo/control treatments and 1166 received olaparib alone or combination with other active cancer treatments. The RR of all-grade and high fatigue was 1.24 (95% CI, 1.10–1.39) and 1.71 (95% CI, 1.06–2.77), respectively. The RR of all-grade and high-grade anemia was 2.10 (95% CI, 1.48–2.98) and 3.15 (95% CI, 1.73–5.71), respectively.

Conclusion: : Our findings suggest that the olaparib treatment is associated with an increased risk of fatigue and anemia. Since fatigue and anemia are very common treatment related adverse events, and both can impair the quality of life of patients, it is important to identify them early and manage it accordingly in order to optimize the overall treatment.

1. Introduction

Olaparib (Lynparza; AstraZeneca, London, United Kingdom) was the first poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitor approved by U.S. Food and Drug Administration (FDA) for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy (Kim et al., 2015). Olaparib is also FDA approved as maintenance therapy in ovarian cancer patients after platinum-based chemotherapy, regardless of BRCA status, and in germline BRCA-mutated HER2-negative metastatic breast cancer previously treated with chemotherapy (Astra-Zeneca, 2019). In addition, olaparib is currently being investigated in several other malignancies with some promising activity, both as single or combined treatments, such as prostate cancer, non-small cell lung cancer and gastric cancer (Clarke et al., 2018; Garcia-Campelo et al., 2018; Bang et al., 2015, 2017; Drean et al., 2016).

Current clinical trials usually include a patient population without significant comorbidities and with good performance status. However, it is well known that after approval by regulatory agencies, a new drug

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is usually used in a broader patient population. Since olaparib is a new class of drug, it is important to better understand its adverse effects profile in order to optimize its use. Fatigue and anemia are among the most common reported adverse events on clinical trials with cancer drugs, and it is usually related to underlying malignancy and its treatment. Moreover, based on the expansion in use of PARP inhibitors to other cancers we anticipate that new indications and more patients receiving such treatment will increase significantly.

Therefore, we sought to investigate the incidence and risk of treatment related fatigue and anemia in an up-to-date meta-analysis of randomized clinical trials using olaparib.

2. Methods

2.1. Data source

A literature search was independently performed by two investigators using electronic databases including: Pubmed/Medline, Embase and Cochrane Library through January 2000 to June 2018, using the following search keywords: “Olaparib” and “Randomized” restricted to randomized controlled trials (RCT) published in English. We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (http://www.asco.org/ASCO) conferences held between January 2000 and June 2018. Additionally, we searched the clinical trial registration website (http://www.ClinicalTrials.gov) to obtain information on registration prospective trials. When more than one publication was identified from the same clinical trial, we used the most recent or complete report of that trial. The updated manufacture’s package insert from Olaparib was also accessed to identify relevant information (Astra-Zeneca, 2019).

2.2. Selection criteria

Studies had to meet the following criteria of eligibility: 1) articles published in English language, 2) prospective phase II or III randomized controlled trials (RCT) design in cancer patients; 3) participants assigned to treatment with Olaparib or control (placebo, chemotherapy, abiraterone or other therapies) and, 4) studies with available safety data reporting adverse events. We also considered conference abstracts if sufficient information on study design, characteristics of participants, interventions, outcomes and toxicity profile were available. Identified abstracts were then collected and coded by each investigator (FABS and VCR-S). The full text of potentially relevant studies were pulled, the methods and results sections were reviewed for trial design and reporting of fatigue and anemia. When data on adverse events could not be determined, efforts were made to contact the study authors. Single arm (phase I and II) and randomized clinical trials with olaparib in both arms were excluded due to lack of control groups.

2.3. Data extraction and quality assessment

Data extraction was conducted independently by two investigators according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) and any discrepancies between reviewers were resolved by consensus.

Different variables from each eligible study were extracted: first author’s name, publication year, register ID, trial phase, underlying malignancy, number of enrolled patients, dosing schedules used in olaparib and control arms, CTCAE (Common Terminology Criteria for Adverse Events) version, blinding, withdrawals, median progression free survival, median overall survival, median treatment duration, number of patients for analysis and number of the selected adverse events.

Data regarding the occurrence of adverse events were obtained from the safety profile or supplemental material of each study. All-grade and high-grade events of fatigue and anemia for each eligible study were collected. Adverse events grading was defined according to the CTCAE of the National Cancer Institute (NCI-CTC) (version 3 or 4; http://ctep.cancer.gov).

We assessed the methodological quality of the included trials using Cochrane Collaboration tool. Studies were graded as having a “low risk”, “high risk”, or “unclear risk” of bias across the 7 specified domains (Higgins et al., 2011). We also used the seven point Jadad ranking system that included randomization, double-blinding and withdrawals, a practice in agreement with other meta-analyses done in this context (Jadad et al., 1996).

2.4. Statistical analysis

For the calculation of incidence, the number of patients for each adverse event and the number of patients receiving Olaparib were extracted from the selected clinical trials. The proportion of patients with those adverse outcomes was derived from each trial. We also calculated relative risks (RRs) and 95% confidence intervals (95% CI) of each adverse event in patients assigned to Olaparib versus placebo/controls in the same trial. For studies reporting zero events in any arm, we applied a classic half-integer continuity correction to calculate the RR and variance (Rothman, 1998). In two trials (Robson et al., 2017; Kaye et al., 2012) olaparib was compared against active chemotherapy and in three trials (Bang et al., 2015, 2017; Oza et al., 2015) it was administered in doses that are not currently approved (less than 300 mg BID, or equivalent total daily dose). Therefore, in order to adjust for potential bias of increased incidence of chemotherapy related adverse events in control arm or decreased incidence of olaparib related adverse events, we conducted stratified analysis without those trials.

We examined heterogeneity in results across studies using the Cochrane's Q statistic, and inconsistency was quantified with the I^2 statistic [100% X (Q-df)/Q], which represents the percentage of total variation across studies that is attributable to heterogeneity rather than chance (Higgins et al., 2003). We considered a p-value of less than 0.10 as indicative of substantial heterogeneity. When substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported using inverse variance method. When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model was reported using the DerSimonian and Laird method that considers both within-study and between-study variations (DerSimonian and Laird, 1986).

Publication bias was evaluated through funnel plots (i.e., plots of study results against precision) and quantified by the Begg and Egger tests (Begg and Mazumdar, 1994; Egger et al., 1997). A two-tailed p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed by using package “meta” (ref. 1) in R Software (ref. 2) (Schwarzer, 2017). All statistical analyses were performed by using Stata/SE version 11.0 software (Stata Corporation, College Station, Texas).

3. Results

3.1. Search results

Our search strategy yielded a total of 225 publications potentially relevant on Olaparib. After the duplicates were removed, a total of 203 articles were identified. Screening of the titles and abstracts 158 manuscripts did not fulfill our inclusion criteria and were excluded, leaving 45 selected manuscripts. After subsequent screening, an additional 36 were excluded: 12 randomized phase 2 trials because olaparib was included in both arms, and 24 manuscripts were repeated in more than one bibliographic source. After the selection process, a total of 9 RCTs were considered eligible for meta-analysis (Clarke et al., 2018; Garcia-Campelo et al., 2018; Bang et al., 2015, 2017; Robson et al., 2017; Kaye et al., 2012; Oza et al., 2015; Ledermann et al., 2014; Pujade-Lauraine et al., 2017). The selection process is presented in

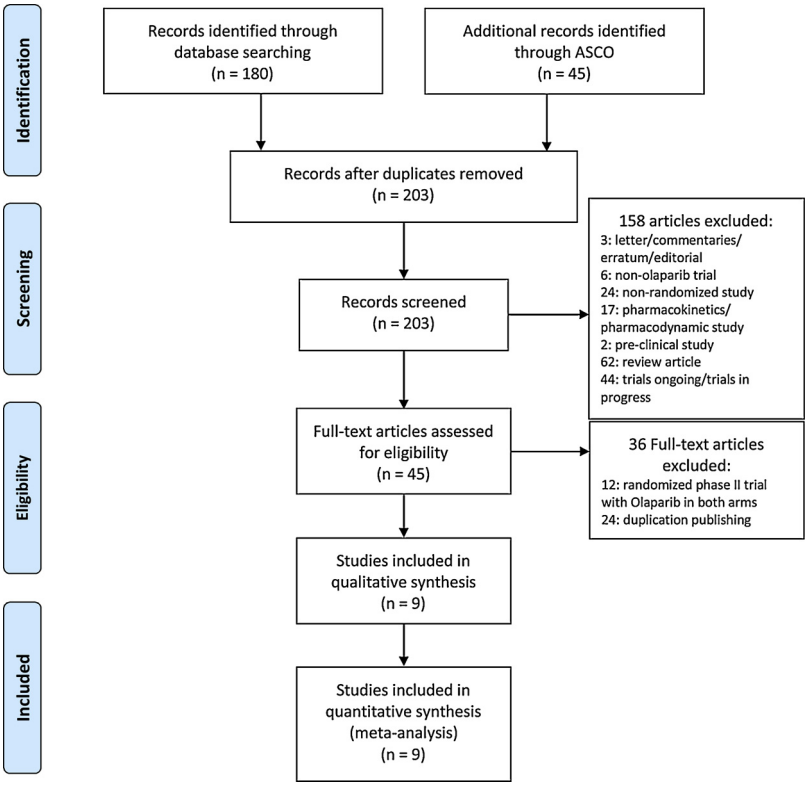

Fig. 1. PRISMA flowchart illustrating the selection of studies included in the present analysis. The illustration shows the number of records obtained from de database and final number of the studies included in the analysis.

Fig. 1.

3.2. Study quality

The included studies were published between 2012 and 2018. All included trials were randomized, with 6 phase 2 trials (Clarke et al., 2018; Garcia-Campelo et al., 2018; Bang et al., 2015; Kaye et al., 2012; Oza et al., 2015; Ledermann et al., 2014) and 3 phase 3 trials (Bang et al., 2017; Robson et al., 2017; Pujade-Lauraine et al., 2017). Eight trials (Clarke et al., 2018; Bang et al., 2015, 2017; Robson et al., 2017; Kaye et al., 2012; Oza et al., 2015; Ledermann et al., 2014; Pujade-Lauraine et al., 2017) were published in full manuscript and one trial (Garcia-Campelo et al., 2018) was presented at ASCO meeting. Using the Cochrane Collaboration tool for risk of bias classification, we found the quality of the included studies to be generally good and fair. Trials were also ranked for Jadad score (Table 1), with all trials categorized as being of good quality (achieving score of 3 or more). All 9 trials reported AEs according to the National Cancer Institute's CTCAE version 3 or 4 criteria.

3.3. Patients

The baseline characteristics of the enrolled studies are presented in Table 1. A total of 2074 patients were available for the meta-analysis (Olaparib: 1166; controls/placebo: 908). Patients included in those trials followed the eligibility criteria defined by each unique trial, which usually includes Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; adequate hematologic, cardiac and renal function. Underlying malignancies included gastric cancer, (Bang et al., 2015, 2017) prostate cancer, (Clarke et al., 2018) non-small cell lung cancer (NSCLC), (Garcia-Campelo et al., 2018) ovarian cancer (Kaye et al., 2012; Oza et al., 2015; Ledermann et al., 2014; Pujade-Lauraine et al., 2017) and breast cancer (Robson et al., 2017). All 9 included studies reported safety data on fatigue and anemia and were included in the analysis. In two trials, both in ovarian cancer, randomization was between placebo/control and olaparib (Ledermann et al., 2014; Pujade-Lauraine et al., 2017) or chemotherapy/control and olaparib. (Robson et al., 2017; Kaye et al., 2012) In three studies, olaparib was combined to cytotoxic chemotherapy, (Bang et al., 2015, 2017; Oza et al., 2015) in one trial olaparib was combined to new generation anti-androgen agent abiraterone (Clarke et al., 2018) and in 1 trial combined to EGFR tyrosine kinase inhibitor gefitinib. (Garcia-Campelo et al., 2018) The Olaparib dose used in the studies was 100 mg BID, (Bang et al., 2015, 2017) 200 mg BID, (Kaye et al., 2012; Oza et al., 2015) 200 mg TID, (Garcia-Campelo et al., 2018) 300 mg BID (Clarke et al., 2018; Robson et al., 2017; Pujade-Lauraine et al., 2017) or 400 mg BID. (Kaye et al., 2012; Ledermann et al., 2014) The capsule formulation was used in three trials (Kaye et al., 2012; Oza et al., 2015; Ledermann et al., 2014) and the tablet formulation was used in the other trials (Clarke et al., 2018; Bang et al., 2015; Robson et al., 2017; Pujade-Lauraine et al., 2017).

3.4. Incidence and relative-risk of fatigue

Using a random-effects model the summary incidence of all-grade and high-grade fatigue in olaparib-treated patients was 40% (heterogeneity: $I^2 = 0.91$, $p < 0.01$) and 3.7% (heterogeneity: $I^2 = 0.34$, $p = 0.14$), respectively, while in placebo-control was 32% (heterogeneity: $I^2 = 0.81$, $p < 0.01$) and 2.3% (heterogeneity: $I^2 = 0.0$, $p = 0.86$), respectively (Table 2). The relative-risk (RR) of all-grade and high-grade fatigue compared to placebo/control was 1.24 (95% CI, 1.10–1.39; $p = 0.0003$) and 1.71 (95% CI, 1.06–2.77; $p = 0.0292$), respectively (Fig. 2). When excluding the 2 trials that compared olaparib against active chemotherapy, (Robson et al., 2017; Kaye et al., 2012) the RR of all-grade and high-grade fatigue was 1.22 (95% CI, 1.01–1.47; $p = 0.0375$) (using random-effects model, heterogeneity test: $I^2 = 0.49$ and $p = 0.07$) and 1.89 (95% CI, 1.11–3.21; $p = 0.0181$), respectively (Fig. 3). After excluding the 3 trials (Bang

Table 1
Baseline characteristics of the included trials in final analysis.

Author, year	Phase	Histology	Patients enrolled	Treatment arms	Median age, years (range)	Median treatment duration, months (range)	Median OS, months (95% CI)	Median PFS, months (95% CI)	Patients for analysis	Jadad score
Bang et al. (2015)	2	Gastric cancer	266	Placebo + Paclitaxel[a]	60.5 (25-79)	2.12 (NR-NR)	8.3 (NR-NR)	3.55 (NR-NR)	62	5
				Olaparib 100 mg BID + Paclitaxel[a]	63 (31-77)	2.73 (NR-NR)	13.1 (NR-NR)	3.91 (NR-NR)	61	
Bang et al. (2017)	3	Gastric cancer	643	Placebo + Paclitaxel[a]	59 (IQR 50-65)	2.5 (IQR 1.5-4.2)	6.9 (6.3-7.9)	3.2 (2.2-3.5)	259	5
				Olaparib 100 mg BID + Paclitaxel[a]	58 (IQR 49-67)	3.7 (IQR 1.9-5.8)	8.8 (7.4-9.6)	3.7 (3.7-4.2)	262	
Clarke et al. (2018)	2	mCRPC	171	Placebo + Abiraterone 1000 mg QD	67 (IQR 62-74)	8.4 (IQR 3.8-14.0)	20.9 (17.6-26.3)	8.2 (5.5-9.7)	71	5
				Olaparib 300 mg BID + Abiraterone 1000 mg QD	70 (IQR 65-75)	10.3 (IQR 4.8-15.2)	22.7 (17.4-29.4)	13.8 (10.8-20.4)	71	
Garcia-Campelo et al. (2018)	2	NSCLC	182	Gefitinib 250 mg QD	68 (36-85)	NR	23.1 (19.1-28.5)	10.9 (9.3-13.3)	91	3
				Gefitinib 250 mg QD + Olaparib 200 mg TID	65 (39-85)	NR	23.3 (16.2-26.4)	12.8 (9.1-14.7)	91	
Kaye et al. (2012)	2	Ovarian cancer (BRCA1/2 positive)	97	PLD 50 mg/m2 q4w	53 (43-81)	NR	NR	7.1 (3.7-10.7)	32	3
				Olaparib 200 mg QD	58.5 (45-77)	NR	NR	6.5 (5.5-10.1)	32	
				Olaparib 400 mg QD	53.5 (35-76)	NR	NR	8.8 (5.4-9.2)	32	
Lederman et al. (2014)	2	Ovarian cancer	326	Placebo	59 (33-84)	4.7 (1.1-13.8)	27.8 (24.4-34.0)	4.8 (4.0-5.5)	128	5
				Olaparib 400 mg BID	58 (21-89)	6.9 (0.1-15.6)	29.8 (27.1-35.7)	8.4 (7.4-11.5)	136	
Oza et al. (2015)	2	Ovarian cancer	173	Carboplatin + Paclitaxel[b]	62 (31-79)	7.5 (IQR 4.3-9.8)	37.6 (27.8-44.6)	9.6 (9.1-9.7)	75	3
				Carboplatin + Paclitaxel + Olaparib[c]	59 (27-78)	9.8 (IQR 7.1-13.9)	33.8 (26.9-38.5)	12.2 (9.7-15.0)	81	
Pujade-Lauraine et al. (2017)	3	Ovarian cancer	295	Placebo	56 (IQR 49-63)	5.6 (NR-NR)	Not reached	5.5 (5.2-5.8)	99	5
				Olaparib 300 mg BID	56 (IQR 51-63)	19.4 (NR-NR)	Not reached	19.1 (16.3-25.7)	195	
Robson et al. (2017)	3	Breast cancer	302	Standard chemotherapy[d]	45 (24-68)	3.4 (0.7-23.0)	19.6 (NR-NR)	3.8 (NR-NR)	91	3
				Olaparib 300 mg BID	44 (22-76)	8.2 (0.5-28.7)	19.3 (NR-NR)	7.8 (NR-NR)	205	

mCRPC: Metastatic Castration Resistant Prostate Cancer. NSCLC: Non-small Cell Lung Cancer. PLD: Pegylated liposomal doxorubicin. NR: Not reported. OS: Overall Survival. PFS: Progression Free Survival, QD: once daily, IQR: interquartile range.

[a] Paclitaxel 80 mg/m2 i.v. day 1, 8 and 15, every 28 day-cycle.

[b] Carboplatin AUC6 + Paclitaxel 175 mg/m2, q3w.

[c] Carboplatin AUC4 + Paclitaxel 175 mg/m2, q3w. In the combination phase, Olaparib was administered with 200 mg BID on days 1–10, every 3 weeks. In the maintenance phase, Olaparib was administered with 400 mg BID, continuously.

[d] Included physicians choice of Capecitabine 2500 mg/m2 day 1–14, q3s; or, Eribulin 1.4 mg/m2 day 1 and 8, q3w; or, Vinorelbine 30 mg/m2 day 1 and 8, q3w.

Table 2
Treatment related fatigue adverse events in placebo/control and olaparib treated patients, and summary incidence meta-analysis.

			Treatment arms		Fatigue Adverse Events							
					Control/Placebo				Olaparib			
					All-grade		Grade ≥3		All-grade		Grade ≥3	
Author, year	Phase	Histology	Control/Placebo, n	Olaparib, n	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Bang et al. (2015)	2	Gastric cancer	62	61	20	32.3 (18.1-46.4)	2	3.2 (0.0-7.7)	15	24.6 (12.2-37.0)	1	1.6 (0.0-4.9)
Bang et al. (2017)	3	Gastric cancer	259	262	53	20.5 (15.0-26.0)	6	2.3 (0.5-4.2)	50	19.1 (13.8-24.4)	11	4.2 (1.7-6.7)
Clarke et al. (2018)	2	mCRPC	71	71	9	12.7 (4.4-21.0)	2	2.8 (0.0-6.7)	15	21.1 (10.4-31.8)	1	1.4 (0.0-4.2)
Garcia-Campelo et al. (2018)	2	NSCLC	91	91	29	31.9 (20.3-43.5)	2	2.2 (0.0-5.2)	36	39.6 (26.6-52.5)	8	8.8 (2.7-14.9)
Kaye et al. (2012)	2	Ovarian cancer (BRCA1/2 pos.)	32	64	15	46.9 (23.2-70.6)	3	9.4 (0.0-20.0)	34	53.1 (35.3-71.0)	4	6.3 (0.1-12.4)
Lederman et al. (2014)	2	Ovarian cancer	128	136	50	39.1 (28.2-49.9)	4	3.1 (0.1-6.2)	71	52.2 (40.1-64.4)	10	7.4 (2.8-11.9)
Oza et al. (2015)	2	Ovarian cancer	75	81	43	57.3 (40.2-74.5)	3	4.0 (0.0-8.5)	52	64.2 (46.8-81.7)	6	7.4 (1.5-13.3)
Pujade-Lauraine et al. (2017)	3	Ovarian cancer	99	195	39	39.4 (27.0-51.8)	2	2.0 (0.0-4.8)	128	65.6 (54.3-77.1)	8	4.1 (1.3-7.0)
Robson et al. (2017)	3	Breast cancer	91	205	21	23.1 (13.2-33.0)	1	1.1 (0.0-3.3)	59	28.8 (21.4-36.1)	6	2.9 (0.6-5.3)
		Summary incidence	**Fixed-effects model**			**26.1 (22.8-29.5)**		**2.3 (1.3-3.3)**		**31.5 (28.3-34.7)**		**3.7 (2.6-4.8)**
			Random-effects model			**31.8 (23.5-40.1)**		**2.3 (1.3-3.3)**		**40.1 (28.3-51.9)**		**3.9 (2.5-5.4)**
		Hetereogeneity			I^2 = 80.9%; Q = 41.81; p < 0.0001		I^2 = 0.0%; Q = 4.0; p = 0.8573		I^2 = 91.4%; Q = 92.90; p < 0.0001		I^2 = 34.4%; Q = 12.20; p = 0.1427	

mCRPC: Metastatic castration resistant prostate cancer.
NSCLC: Non-small cell lung cancer.

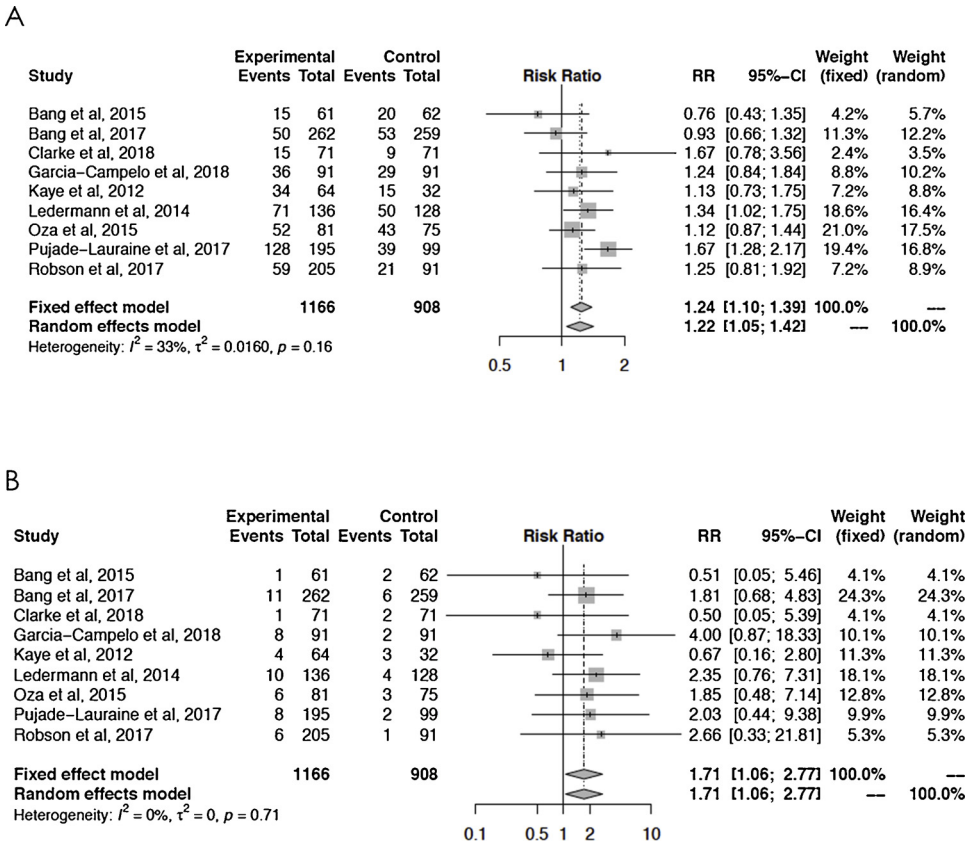

Fig. 2. Relative risk of all-grade (A) and high-grade (B) fatigue events associated with olaparib versus placebo/control.

et al., 2015, 2017; Oza et al., 2015) that used olaparib in doses lower than the ones FDA-approved, the RR for all-grade and high-grade fatigue was 1.42 (95% CI, 1.23–1.65; p < 0.0001) and 1.96 (95% CI, 1.04–3.71; p = 0.0378), respectively (Fig. 3). Finally, when evaluating only trials that compared single agent olaparib to placebo, the RR of all-grade and high-grade fatigue was 1.50 (95% CI, 1.24–1.81; p < 0.0001) and 2.23 (95% CI, 0.90–5.55; p = 0.084) (Fig. 3).

3.5. Incidence and relative-risk of anemia

Using a random-effects or fixed effects model the summary incidence of all-grade and high-grade anemia in olaparib-treated patients

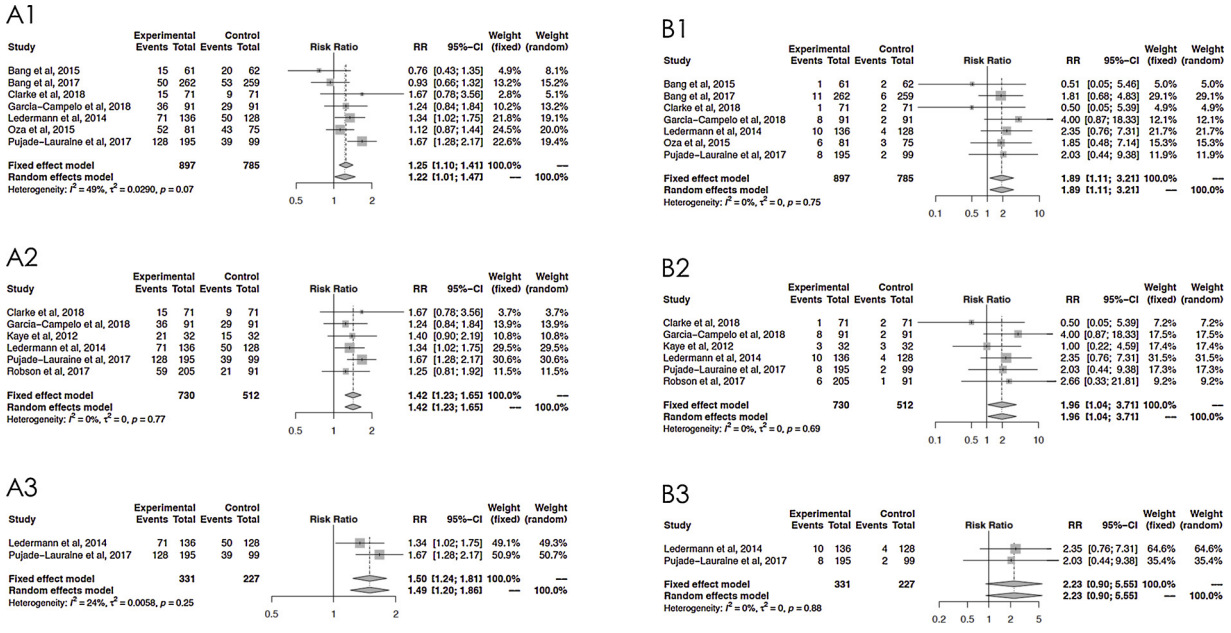

Fig. 3. Relative risk of all-grade (A) and high-grade (B) fatigue events associated with olaparib versus placebo/control in stratified analysis after excluding trials that had actvie chemotherapy in control arm only (A1 and B1), excluding trials with olaparib doses lower than 300 mg BID or equivalent total daily dose (A2 and B2) and including trials that compared single-agent olaparib to placebo (A3 and B3).

Table 3
Treatment related anemia adverse events in placebo/control and olaparib treated patients, and summary incidence meta-analysis.

			Treatment arms		Anemia Adverse Events							
					Control/Placebo				Olaparib			
					All-grade		Grade ≥3		All-grade		Grade ≥3	
Author, year	Phase	Histology	Control/Placebo, n	Olaparib, n	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Bang et al. (2015)	2	Gastric cancer	62	61	12	19.4 (8.4-30.3)	7	11.3 (2.9-19.7)	11	18.0 (7.4-28.7)	7	11.5 (3.0-20.0)
Bang et al. (2017)	3	Gastric cancer	259	262	62	23.9 (18.0-29.9)	19	7.3 (4.0-10.6)	101	38.6 (31.0-46.1)	38	14.5 (9.9-19.1)
Clarke et al. (2018)	2	mCRPC	71	71	1	1.4 (0.0-4.2)	0	0.7 (0.0-2.7)	22	31.0 (18.0-43.9)	15	21.1 (10.4-31.8)
Garcia-Campelo et al. (2018)	2	NSCLC	91	91	35	38.5 (25.7-51.2)	2	2.2 (0.0-5.2)	71	78.0 (59.9-96.2)	15	16.5 (8.1-24.8)
Kaye et al. (2012)	2	Ovarian cancer (BRCA1/2 pos.)	32	64	1	3.1 (0.0-9.3)	0	1.6 (0.0-5.9)	14	21.9 (10.4-33.3)	6	9.4 (1.9-16.9)
Lederman et al. (2014)	2	Ovarian cancer	128	136	7	5.5 (1.4-9.5)	1	0.8 (0.0-2.3)	29	21.3 (13.6-29.8)	7	5.2 (1.3-9.0)
Oza et al. (2015)	2	Ovarian cancer	75	81	16	21.3 (10.9-31.8)	5	6.7 (0.8-12.5)	21	25.9 (14.8-37.0)	7	8.6 (2.2-15.0)
Pujade-Lauraine et al. (2017)	3	Ovarian cancer	99	195	8	8.1 (2.5-13.7)	2	2.0 (0.0-4.8)	85	43.6 (34.3-52.9)	38	19.5 (13.3-25.7)
Robson et al. (2017)	3	Breast cancer	91	205	24	26.4 (15.8-36.9)	4	4.4 (0.1-8.7)	82	40.0 (31.3-48.7)	33	16.1 (10.6-21.6)
		Summary incidence	**Fixed-effects model**			**7.6 (5.8-9.4)**		**2.0 (1.1-3.0)**		**32.7 (29.4-36.0)**		**11.9 (10.0-13.9)**
			Random-effects model			**15.3 (8.2-22.3)**		**3.1 (1.3-4.9)**		**34.2 (25.5-43.1)**		**13.1 (9.3-17.0)**
		Hetereogeneity			I^2 = 91.8%; Q = 97.10; p < 0.0001		I^2 = 64.6%; Q = 22.61; p = 0.0039		I^2 = 85.4%; Q = 54.78; p < 0.0001		I^2 = 70.1%; Q = 26.74; p = 0.0008	

mCRPC: Metastatic castration resistant prostate cancer.
NSCLC: Non-small cell lung cancer.

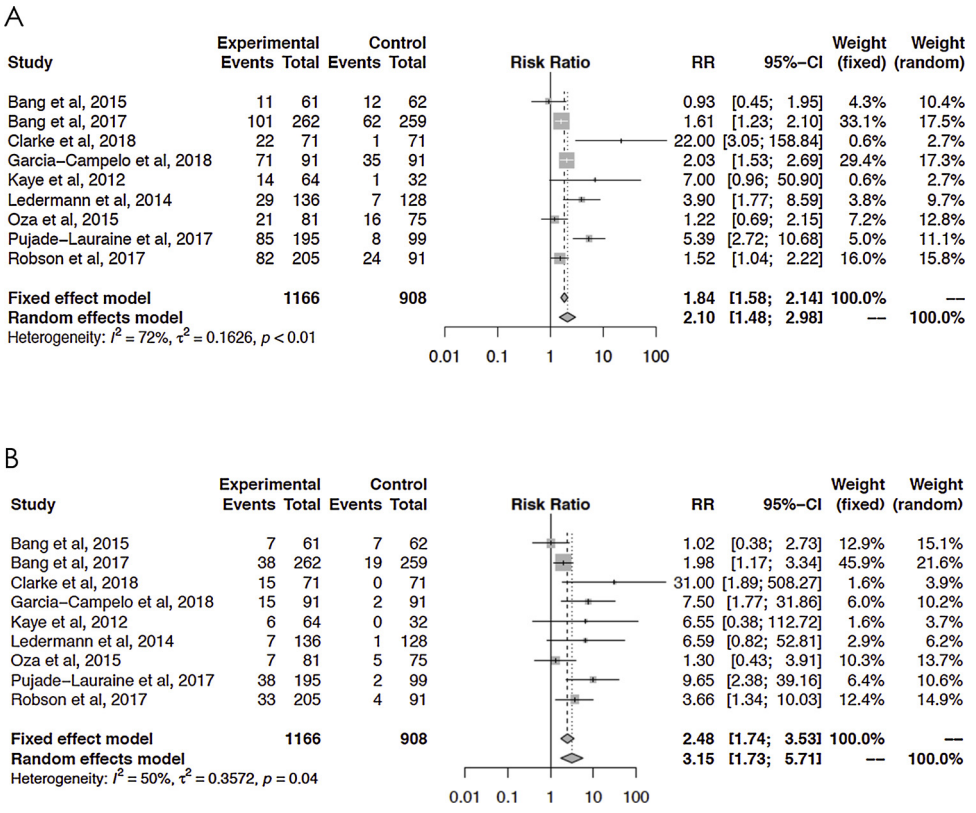

Fig. 4. Relative risk of all-grade (A) and high-grade (B) anemia events associated with olaparib versus placebo/control.

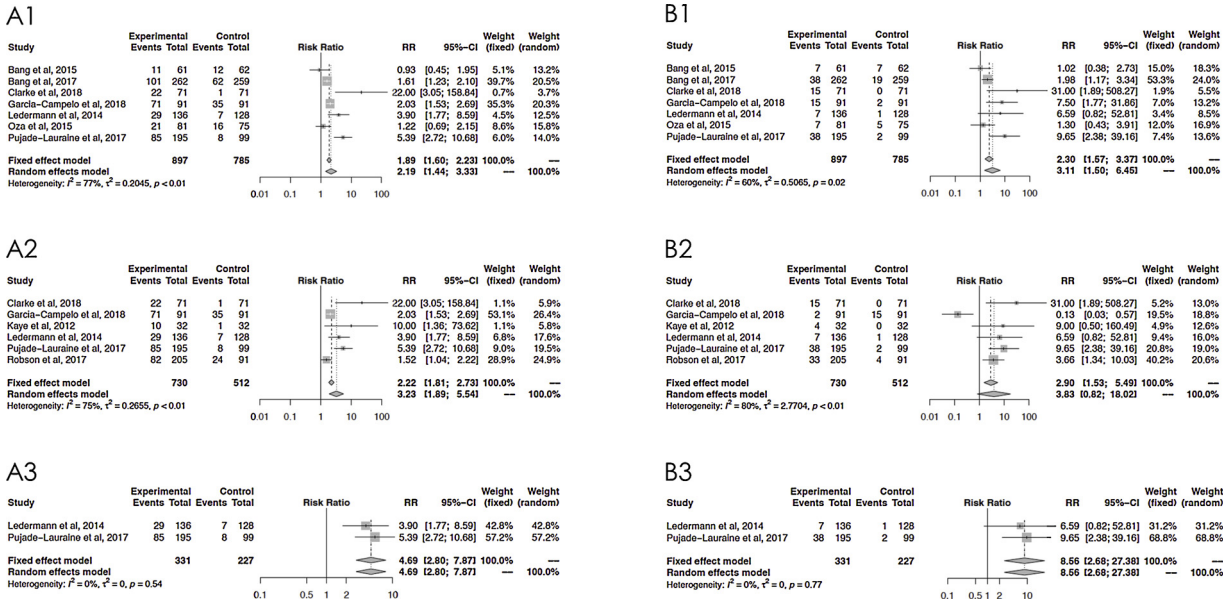

Fig. 5. Relative risk of all-grade (A) and high-grade (B) anemia events associated with olaparib versus placebo/control in stratified analysis after excluding trials that had actvie chemotherapy in control arm only (A1 and B1), excluding trials with olaparib doses lower than 300 mg BID or equivalent total daily dose (A2 and B2) and including trials that compared single-agent olaparib to placebo (A3 and B3).

was 34% (heterogeneity: $I^2 = 0.85$, $p < 0.01$) and 13% (heterogeneity: $I^2 = 0.70$, $p < 0.01$), respectively, while in placebo/control was 15% (heterogeneity: $I^2 = 0.92$, $p < 0.01$) and 3.1% (heterogeneity: $I^2 = 0.65$, $p < 0.01$), respectively (Table 3). Using a random-effects model, the RR of all-grade (heterogeneity: $I^2 = 0.72$; $p < 0.01$) and high-grade (heterogeneity: $I^2 = 0.50$; $p = 0.04$) anemia compared to placebo/control was 2.10 (95% CI, 1.48–2.98; $p < 0.0001$) and 3.15 (95% CI, 1.73–5.71; $p = 0.0002$), respectively (Fig. 4). When excluding the 2 trials that compared olaparib against active chemotherapy, (Robson et al., 2017; Kaye et al., 2012) the RR of all-grade and high-grade anemia was 2.19 (95% CI, 1.44–3.33; $p = 0.0002$) (using random-effects model, heterogeneity test: $I^2 = 0.77$ and $p < 0.01$) and 3.11 (95% CI, 1.50–6.45; $p = 0.0023$) (using random-effects model, heterogeneity test: $I^2 = 0.60$ and $p = 0.02$), respectively (Fig. 5). After excluding the 3 trials (Bang et al., 2015, 2017; Oza et al., 2015) that used olaparib in doses lower than the ones FDA-approved, the RR for

all-grade and high-grade anemia was 3.23 (95% CI, 1.89–5.54; $p < 0.0001$) (using random-effects model, heterogeneity test: $I^2 = 0.75$ and $p < 0.01$) and 3.83 (95% CI, 0.82–18.02; $p = 0.089$) (using random-effects model, heterogeneity test: $I^2 = 0.80$ and $p < 0.01$), respectively (Fig. 5). Finally, when evaluating only the trials that compared single agent olaparib to placebo, the RR of all-grade and high-grade anemia was 4.69 (95% CI, 2.80–7.87; $p < 0.0001$) and 8.56 (95% CI, 2.68–27.38; $p = 0.0003$) (Fig. 5).

3.6. Publication bias

No evidence of publication bias was detected for incidence or RR of fatigue or anemia by either the Begg's or the Egger's test (for RR of all-grade fatigue Begg's $P = 0.67$ and Egger's $P = 0.47$; for RR of high-grade fatigue Begg's $P = 0.40$ and Egger's $P = 0.27$; for RR of all-grade anemia Begg's $P = 0.40$ and Egger's $P = 0.16$; and for RR of high-grade anemia Begg's $P = 0.21$ and Egger's $P = 0.06$).

4. Discussion

To the best of our knowledge this is the first meta-analysis to demonstrate a significantly increased risk of fatigue and anemia associated with olaparib treatment in cancer patients. The summary incidence of all-grade and high-grade fatigue was 40% and 3.7% (Table 2), with a RR showing an increase of 24% and 71% in risk of olaparib-associated fatigue, respectively (Fig. 2). The increase in the risk of fatigue remained statistically significant after excluding trials that had active chemotherapy in the control arms, after excluding trials that administered olaparib in lower doses and after evaluating trials comparing single agent olaparib to placebo (Fig. 3). In addition, we also observed a significant increase in the order of 2.1 and 3.15 times higher the all-grade and high-grade risk of anemia, respectively (Fig. 4), and the risk of anemia also remained statistically significant after performing stratified analysis according to concomitant chemotherapy use and olaparib dose (Fig. 5).

Members of PARP family of enzymes are responsible for the repair mechanism of DNA single-strand breaks through the base excision repair pathway, and PARP keeps low-fidelity nonhomologous-end-joining DNA repair machinery in check (Patel et al., 2011). Inhibition of PARP and its DNA repair mechanisms can result in persistence of single-strand DNA breaks that eventually lead to formation of double-strand breaks. PARP inhibitors target tumors with deficiencies in double-strand DNA break repair, such as homologous recombination repair (HRR) deficiencies. HRR deficiency induces genomic instability and hyper dependence on alternative DNA repair mechanism, such as PARP. An additional mechanism of action of PARP inhibitors is the PARP trapping, in which PARP enzymes become trapped at DNA damage and prevent the recruitment of other DNA repair proteins. Therefore, it is associated with exquisite sensitivity to PARP inhibitors, which exhibit synthetic lethality to cells with defective HRR. Inhibition of base excision repair and trapping of PARP-DNA complexes at the replication fork are the most prevalent mechanisms of action of PARP inhibitors against HRR-deficient cells (Farmer et al., 2005; Pommier et al., 2016; Konstantinopoulos et al., 2015).

Fatigue is probably the most common cancer-related symptom. It is usually referred as a persistent lack of energy, exhaustion, depression, motivation loss and decreased mental work capacity that are not related to physical activity or exertion. This symptom can significantly affect patient's quality of life and also limit the administration of cancer treatment (Curt et al., 2000). It is also associated with varies types of cancer treatment, including chemotherapy, radiotherapy, hormone therapy and targeted therapy, (Santoni et al., 2015; Lasheen et al., 2017; Abrahams et al., 2016) and may also be associated with concomitant adverse events such as cachexia, anemia, hypothyroidism or adrenal dysfunction. (Ryan et al., 2007) Furthermore, some authors propose that cancer-related fatigue might be associated to the following processes: 1) central serotonin dysregulation; 2) disturbance of hypothalamic-pituitary-adrenal axis resulting in endocrine changes; 3) circadian rhythm disruption affecting endocrine rhythm, metabolic processes and immune system; and, 4) and altered muscle metabolism leading to decreased ATP concentration, creatine prosphate and protein synthesis, and to increased lactate production (Ryan et al., 2007). Considering that olaparib is not selective for tumor cells, inhibition of PARP in normal cells abrogates an important mechanism of DNA repair in these cells, which may be associated to biological deregulation that might contribute to cancer-related or treatment-related fatigue. Also, olaparib inhibits PARP 1 and 2, and PARP 2 has been associated in the regulation of red blood cell production, which may justify anemia related with olaparib (Zhao et al., 2015).

Additionally, olaparib treatment was associated with a significant increase in the incidence and risk of anemia. Furthermore, olaparib was even associated with rare cases of myelodisplastic syndrome (AstraZeneca, 2019). A recent meta-analysis evaluated the incidence and risk of severe (grade 3 and 4) hematologic toxicities in cancer patients treated with PARP inhibitors olaparib, veliparib and rucaparib in randomized clinical trials. The incidence of high-grade anemia in olaparib treated patients was 8.2% compared to 4.7% in control/placebo. However, the RR of olaparib associated high-grade anemia failed to reach statistical significance (RR of 1.5, 95% CI 0.77–2.95) (Zhou et al., 2017). In our meta-analysis, we did observe a significant increase in the all-grade (34.2% versus 15.3% [RR of 2.10; 95% CI 1.48–2.98]) and high-grade (13.1% versus 3.1% [RR of 3.15; 95% CI 1.73–5.71]) risk of anemia (using random-effects model) (Table 3 and Fig. 4). The reason for these discordant results is probably related to the fact that we included more trials in our analysis, and we also evaluated all-grade anemia, while the previous work evaluated only high-grade anemia. The increased risk of anemia could have had an indirect impact on olaparib-associated fatigue. However, since we did not have access to individual patient data we could not adjust the risk of fatigue according to anemia.

We also performed stratified sub-group analysis according to some potential confounders (Figs. 3 and 5), such as: 1) excluding trials with active chemotherapy in the control arm only and not in the olaparib arm; 2) excluding trials with olaparib doses lower than the one approved by the FDA; and, 3) including only trials that compared single-agent olaparib against placebo. The RR of all-grade and high-grade anemia and fatigue remained statistically significant in all sub-group analysis. Of note, when evaluating the sub-group of trials using only FDA-approved doses of olaparib (300 mg, for tablets, or 400 mg, for capsules, BID) we observed a 42% and 96% increase in the risk of all-grade and high-grade fatigue (Fig. 3), respectively, compared to 24% and 71% when considered all trials (Fig. 2), including those with olaparib in lower doses. The same effect was observed for all-grade and high-grade anemia, with RRs of 3.2 and 3.8 times higher (Fig. 5), respectively, for trials using olaparib in full dose, compared to 2.1 and 3.1 (Fig. 4), respectively.

An important aspect of PARP inhibitor toxicities is that they may change over cycles, specially hematological toxicity (Berek et al., 2018). Further analyses of common adverse events with olaparib revealed that the majority occurred within the first two months of treatment, were generally transient, and managed without dose reductions (Matulonis et al., 2015; Friedlander et al., 2016). Furthermore, a recent publication of quality of life with olaparib maintenance in patients with ovarian cancer showed no significant deleterious effect on quality of life despite the toxicity associated with the drug (Friedlander et al., 2018).

Our work has some limitations. First, this is a trial-level meta-analysis, and we did not have access to individual patient data, therefore we could not adjust for individual confounders (i.e. anemia or hypothyroidism). However, it is important to point out that this is inherent to meta-analyses of literature-based studies. Nevertheless, meta-analyses from individual patient data can also carry significant bias, as

data is only available to limited numbers of research groups and for only a few types of studies that have high public health priority; consequently, few opportunities exist for pooled analyses. Second, fatigue is very subjective and patients may perceive it as physical tiredness or exhaustion, a need for reduced activity, reduced motivation and/or mental fatigue, (Ahlberg et al., 2003) and in this regard ideally would have been to evaluate patient reported outcomes. We used adverse events data reported according to NCI CTCAE grading system that also includes the subjectivity of the investigators when grading the event, although randomization and blinding process avoid this type of bias. Third, different concomitant treatments, olaparib doses and malignancies in included trials might account for some heterogeneity shown in our meta-analysis. Fourth, we did not include other PARP inhibitors in our analysis, therefore we cannot extrapolate these findings. However, there is a previous meta-analysis of PARP inhibitors in epithelial ovarian cancer that suggested that there were not major differences in adverse events profiles comparing different agents (Staropoli et al., 2018). In addition, we did not find any evidence of publication bias in our meta-analysis.

In conclusion, this meta-analysis shows that olaparib is associated with a significant increase in the risk of all-grade and high-grade fatigue and anemia adverse events. Nevertheless, it is important to remember that despite the current findings, olaparib showed a significant increase in patients' outcomes in several clinical trials and should continue to be offered to these patients. However, as this class of drugs gains greater clinical use, practitioners must be aware of the risks associated with their use in order to provide rigorous monitoring and continue to improve patient outcomes.

Declaration of Competing Interest

FABS: Research funding (Astra Zeneca, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen); Speaker's bureau (Astra Zeneca, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen, Astellas, Bayer); Advisory or Consultant role (Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Janssen, Astellas, Bayer); Travel grant (Merck Sharp & Dohme, Janssen, Astellas). FRK: Speaker's bureau (Astra Zeneca, Roche, Janssen, Astellas, Bayer); Advisory or Consultant role (Merck Sharp & Dohme, Janssen); Travel grant (Janssen, Sanofi). FCM: Research funding (Janssen); Speaker's bureau (Janssen, Astellas, Bayer, Sanofi); Advisory or Consultant role (Janssen, Astellas, Bayer, Sanofi); Travel grant (Janssen, Astellas, Bayer, Sanofi). JMP: Speaker's bureau (Astra Zeneca); Advisory or Consultant role (Astra Zeneca); Travel grant (Astra Zeneca). RY: Research funding (AstraZeneca, BMS, Janssen, MSD, Roche); Travel grant (Bayer, Janssen, Pfizer, Sanofi, Zodiac, Roche). VCRS, DVPA, CZO, LMG, NFC, GDZM, RCM: none.

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