The Breast 60 (2021) 26–34

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Efficacy and safety of PARP inhibitors in patients with BRCA-mutated advanced breast cancer: A meta-analysis and systematic review

Ximu Sun [b], Xin Wang [a], Jie Zhang [a], Zhixia Zhao [a], Xin Feng [b, *, 1], Lihong Liu [c, **, 1], Zhuo Ma [a, ***, 1]

[a] Department of Pharmacy, Beijing Chao-Yang Hospital, Capital Medical University, 8 Gongren Tiyuchang Nanlu, Chaoyang District, Beijing, 100020, China
[b] Department of Pharmacy, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, No.17, Qi He Lou Street, Dongcheng District, Beijing, 100026, China
[c] Department of Pharmacy, China-Japan Friendship Hospital, No.2 Yinghuayuan Dongjie, Chaoyang District, Beijing, 100029, China

ARTICLE INFO

Article history:
Received 12 April 2021
Received in revised form
29 July 2021
Accepted 16 August 2021
Available online 21 August 2021

Keywords:
Poly(ADP-ribose) polymerase inhibitors
Breast cancer
Triple-negative breast cancer
BRCA mutation

ABSTRACT

Objective: This meta-analysis aimed to investigate the efficacy and safety of poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors in **BRCA**-mutated advanced breast cancer patients comprehensively.

Methods: We conducted a systematic literature research through PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, China National Knowledge Infrastructure (CNKI), wanfang, China Biology Medicine disc (CBMdisc), and ClinicalTrials.gov from inception to January 2021. Randomized controlled trials (RCTs) with available data comparing PARP inhibitors versus control therapy in **BRCA**-mutated advanced breast cancer were eligible for analysis. Statistical analyses were performed with Review Manager (RevMan) version 5.4 and R version 4.0.3.

Results: 1706 studies were retrieved in total, and 4 RCTs with 1540 patients were eligible for meta-analysis finally. The results showed that progression-free survival (PFS) and overall survival (OS) were significantly improved in germline **BRCA**-mutated breast cancer patients with PARP inhibitors (HR 0.64, 95% CI [0.56–0.74]; HR 0.86, 95% CI [0.74–0.99], respectively) with no significant heterogeneity across studies ($I^2 = 22\%$, χ^2 p = 0.28; $I^2 = 0\%$, χ^2 p = 0.70, respectively). There was no significant difference in the overall adverse events (AEs), grade≥3 AEs and AEs leading to treatment discontinuation between PARP inhibitor arms and control arms (RR 1.01, 95% CI [0.99–1.02]; RR 0.95, 95% CI [0.83–1.09]; RR 1.17, 95% CI [0.87–1.57], respectively). Based on the available data, PARP inhibitors provided comparable or better results than control arms in improving the quality of life in **BRCA**-mutated advanced breast cancer patients.

Conclusions: PARP inhibitors prolonged PFS and OS among patients with **BRCA**-mutated advanced breast cancer with tolerable safety and improved quality of life.

© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Contents

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: fengxin1115@ccmu.edu.cn (X. Feng), liulihong@bjcyh.com (L. Liu), mazhuo2013@163.com (Z. Ma).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.breast.2021.08.009
0960-9776/© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Introduction

According to the latest data from International Agency for Research on Cancer (IARC), breast cancer, the most frequent gynecologic malignancy has surpassed lung cancer for the first time, becoming the most commonly diagnosed cancer in the world [1]. About 5–10% of breast cancer patients carry germline breast cancer susceptibility genes (breast related cancer antigen, **BRCA**) mutation. Patients with a **BRCA**1 mutation are predisposed to hereditary and triple-negative breast cancer (TNBC) [2]. Females with **BRCA** mutation have a cumulative risk of breast cancer at age 70 years of 45–65% [3]. The lifetime risks in males of breast cancer are 1.2% and 6.8% carried **BRCA** 1 or 2 mutation, respectively [4]. To date, it is virtually not possible to cure advanced breast cancer. But we can alleviate the clinical symptoms, improve the quality of life and prolong the survival time of patients by optimizing the treatment, so as to achieve the purpose of long-term survival [5].

Poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitors can recognize DNA lesions and inhibit PARP activity while trapping PARP1 on DNA in repairing single-string breaks (SSBs). This mechanism shows a potential therapeutic significance for germline **BRCA**-mutated (g**BRCA**m) breast cancer and has been confirmed by clinical trials [6]. To date, two PARP inhibitors have been approved by FDA for g**BRCA**m and human epidermal growth factor receptor-2 (HER2) negative breast cancer. Olaparib is used for the treatment of adult patients with deleterious or suspected deleterious g**BRCA**m, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting and patients with hormone receptor (HR)-positive breast cancer who have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy [7]. Talazoparib is indicated for the treatment of adult patients with deleterious or suspected deleterious g**BRCA**m and HER2-negative locally advanced or metastatic breast cancer [8]. However, the efficacy and safety of PARP inhibitors in breast cancer until now was still under-evaluated. Previous meta-analyses only include 2 studies investigating single-agent PARP inhibitors versus monochemotherapy [9,10]. Therefore, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to comprehensively assess the benefit and risk of PARP inhibitor (PARPi) monotherapy or combination therapy versus chemotherapy or placebo in **BRCA**-mutated advanced breast cancer.

2. Material and methods

Our meta-analysis was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Report Items for Systematic Reviews and Meta-analyses (PRISMA) statement [11,12].

2.1. Search strategies

We conducted a systematic literature search of PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, China National Knowledge Infrastructure (CNKI), wanfang, China Biology Medicine disc (CBMdisc) from inception to January 2021. The website of ClinicalTrials.gov also was examined to retrieve unpublished eligible trials with presented outcomes of interest. The search terms were “breast cancer”, “mammary cancer”, “poly (ADP-ribose) polymerase inhibitors”, “PARP inhibitors”, “olaparib”, “niraparib”, “rucaparib”, “talazoparib”, “veliparib”, and “RCT” combined with the Boolean operators (AND, OR and NOT). We also searched the references list of relevant reviews, meta-analyses, and the oncological meeting abstracts from ESMO (the European Society for Medical Oncology), ASCO (the American Society of Clinical Oncology), CSCO (the Chinese Society of Clinical Oncology) to identify additional studies.

2.2. Eligibility criteria

Inclusion criteria: 1) Phase II or III RCTs with published available data. 2) Eligible patients were locally advanced, metastatic or recurrent breast cancer with **BRCA** mutation. 3) Patients were treated with PARP inhibitors (alone or in combination) in the experimental arm and chemotherapy plus placebo or other treatment of physician's choice (TPC) in the control arm. 4) Available information on interested outcomes.

Exclusion criteria: 1) Case report or series, letter, editorials, commentaries, review, meta-analysis, cohort studies or case-control studies. 2) Studies without available data on interested outcomes. 3) Studies only have single arm. 4) Patients in the treatment and control arms were both treated with PARP inhibitors. 5) Non-randomized controlled trials. 6) In vitro or basic studies. 7) PARP inhibitors were used for neoadjuvant or adjuvant treatment.

2.3. Outcomes

The primary outcome was progression-free survival (PFS), the time from randomization to disease progression or death from any cause. The secondary outcomes included overall survival (OS, the time from randomization to death due to any cause), the safety outcomes (common adverse events [AEs], grade≥3 AEs and AEs leading to discontinuation), and quality of life (QoL) using standard tools.

2.4. Data extraction

Two investigators independently assessed the eligibility of retrieved studies and extracted the following data: study characteristics (NCT number, clinical trial acronym, phase), patients enrolled, breast cancer stage, HER2 status, treatment arm, control arm, duration of treatment and follow-up, hazard ratios (HR) and 95% confidence intervals (CIs) of PFS and OS (adjusted HR and 95%CI were preferred), numbers of AEs, grade≥3 AEs, AEs leading to discontinuation, and any data about QoL. We contacted corresponding authors or sponsors for missing data. Discrepancies were resolved by the third investigator.

2.5. Risk of bias assessment

Two investigators assessed the quality of included studies independently referring to the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials [13]. The risk of bias included selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. Disagreements were resolved by consulting a third reviewer for arbitration.

2.6. Statistical analysis

For PFS and OS, pooled HR with 95% CI was calculated by the generic inverse of variance method with the fixed-effect model. Risk ratio (RR) and 95% CIs were calculated for categorical outcomes. Two-sided $p < 0.05$ were considered statistically significant. Statistical heterogeneity was quantified using Higgins inconsistency index (I^2) test and Chi-squared (χ^2) test with p value. Significant statistical heterogeneity was defined by a $\chi^2 p < 0.10$ or $I^2 > 50\%$. Exploratory subgroup analyses of PFS were conducted according to the type of treatment (PARPi plus chemotherapy vs PARPi monotherapy), type of **BRCA** mutation (**BRCA**1-mutated vs **BRCA**2-mutated), hormone-receptor status (TNBC vs non-TNBC), prior exposure to platinum-based chemotherapy (prior platinum cohort vs no prior platinum cohort), prior exposure to cytotoxic chemotherapy (prior cytotoxic chemotherapy cohort vs no prior cytotoxic chemotherapy cohort), and history of central nervous system (CNS) metastases (CNS metastases vs no CNS metastases). Exploratory subgroup analyses of AEs investigated if toxicity differed according to the type of control drug (placebo vs TPC). Sensitivity analysis was conducted to assess the stability of our meta-analysis by gradually eliminating each study one by one and re-running the analyses. Finally, publication bias was evaluated by funnel plots, Begg's rank correlation test [14] and Egger's linear regression test [15]. Statistical analysis was performed with Review Manager (RevMan) version 5.4 and R version 4.0.3.

3. Results

3.1. Study selection and characteristics

The search flow of the studies was shown in Fig. 1. The systematic literature search retrieved 1706 studies in total. After duplicates removal, 1411 studies were screened title and abstracts by two reviewers. 19 studies were accessed the potential eligibility by screening full-text. Finally, 4 studies [2,16–18] with 1540 patients were eligible for quantitative synthesis, and the characteristics of included studies were shown in Table 1. Among 1540 patients, less than 2% of patients were males and the median age of patients ranged from 44 to 47 years. Most of the patients included were HER2 negative, and only one study enrolled 5% HER2 positive patients only if they were ineligible for or progressed on prior HER2-directed therapy [17]. Of the 4 eligible studies, 2 were on veliparib [16,17], and 1 each was on talazoparib [18] and olaparib [2]. In 2 studies, PARP inhibitors were investigated as monotherapy against TPC, including capecitabine, eribulin, gemcitabine, and vinorelbine. In 2 studies, PARP inhibitors were investigated in combination with carboplatin-paclitaxel and compared with placebo. The risk of bias of included studies was presented in Suppl Fig 1-2. Among the 4 studies, 2 studies were open-label. Although 1 study claimed that it was a randomized trial, the information of random sequence generation and allocation concealment was incomplete. Publication bias was not detected by the funnel plot with visible symmetry (Suppl Fig 3) in meta-analyses (Begg's $p = 1.000$ and Egger's $p = 0.973$).

3.2. Progression-free survival

The results of PFS showed a significant advantage in PARP inhibitors (HR 0.64, 95% CI [0.56–0.74]) compared with control whether in combination or alone (HR 0.73, 95% CI [0.60–0.88]; HR 0.56, 95% CI [0.46–0.68], respectively) with no significant heterogeneity across studies ($I^2 = 22\%$, χ^2 $p = 0.28$, Fig. 2A). The median PFS of patients treated with PARP inhibitors monotherapy were 7.0 and 8.6 months, while the median PFS of patients treated with TPC were 4.2 and 5.6 months [2,18]. Median PFS was 14.5 months and 14.1 months in the PARP inhibitors combined with carboplatin-paclitaxel group versus 12.6 months and 12.3 months in the carboplatin-paclitaxel group [16,17].

Table 2 showed the subgroup analysis results and the forest plots of subgroup analysis were presented in supplementary material in detail (Suppl Fig. 4 A-E). In the subgroup analysis according to the type of **BRCA** mutation, hormone-receptor status, prior exposure to platinum-based chemotherapy, prior exposure to cytotoxic chemotherapy, and CNS metastases history, PARP inhibitors were associated with improved PFS reaching statistical significance in either subgroup. Notably, we pleasantly found that PARP inhibitors were also effective for TNBC (HR 0.61, 95% CI [0.51–0.75], Suppl Fig 4B), which is the toughest breast cancer type nowadays. However, in the subgroup analysis according to the history of CNS metastases, the improvement in PFS with PARPi reached the statistical significance only in the no CNS metastases cohort (HR 0.63, 95% CI [0.53–0.75], Suppl Fig 4E), suggesting PARP had a limited effect on patients with CNS metastases.

The results of sensitivity analysis were presented in Suppl Tab 1. The pooled HR and 95% CI didn't change when we excluded each study in turn.

3.3. Overall survival

There was no significant heterogeneity across studies ($I^2 = 0\%$, χ^2 $p = 0.70$) with 2 combination chemotherapy studies and 2 monotherapy studies. The pooled HR with 95% CI (0.86 [0.74–0.99], $p = 0.03$, Fig. 2B) indicated that OS was improved with PARP inhibitors. The median OS of patients in EMBRACA trial treated with PARPi monotherapy was 19.3 months, while the median OS of patients treated with TPC was 19.5 months [19]. In OlympiAD trial, median OS was 19.3 months with olaparib versus 17.1 months with

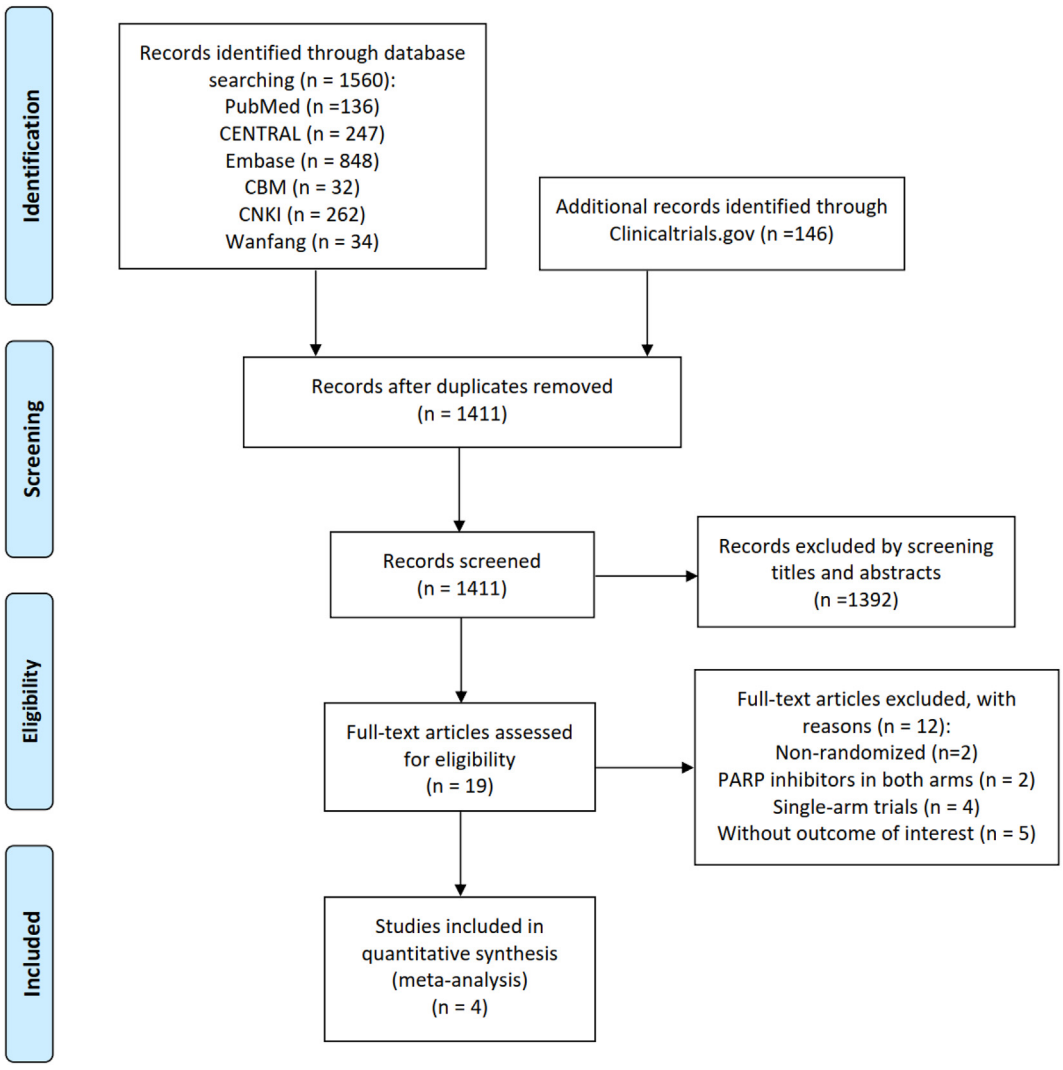
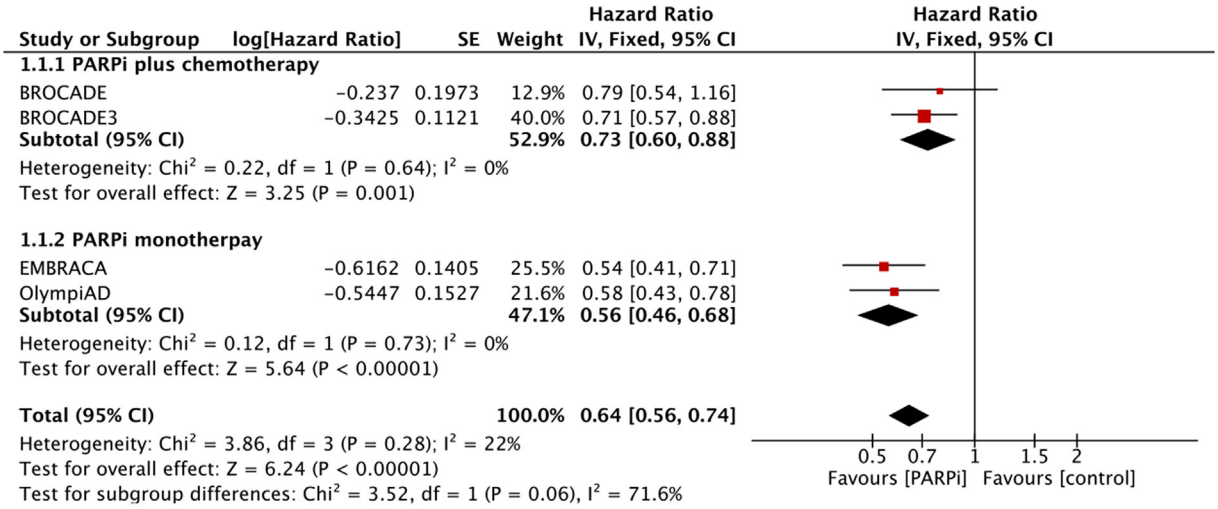


Fig. 1. Flowchart of studies selection. CENTRAL: the Cochrane Central Register of Controlled Trials; CNKI: China National Knowledge Infrastructure; CBMdisc: China Biology Medicine disc.

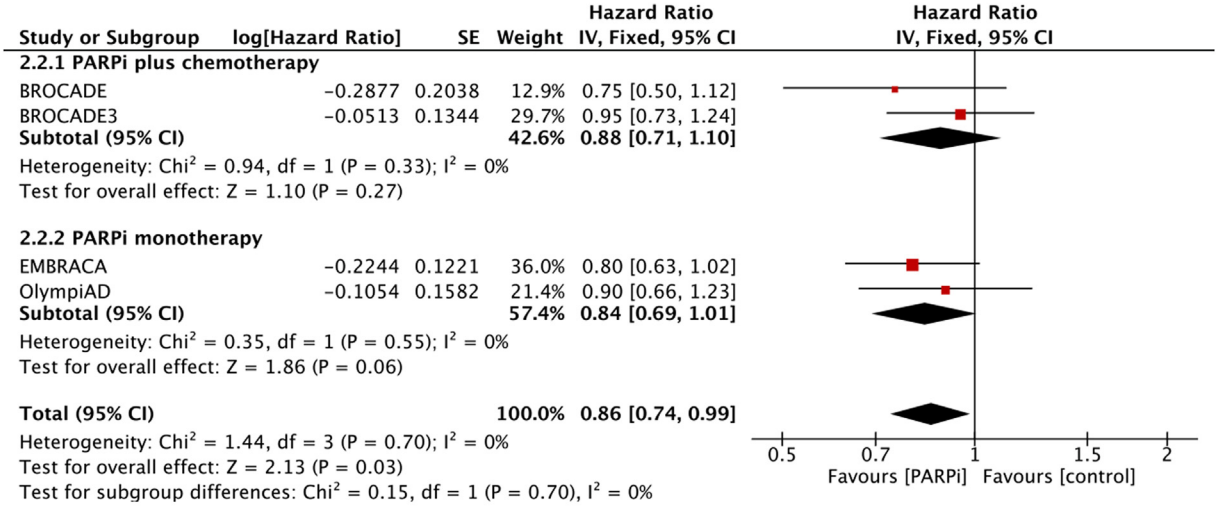
Table 1
Characteristics of included studies.

NCT number& acronym	Phase	Patients enrolled	Experimental arm & n	Control arm & n	Eligible patients	HER2 status	Median follow-up (months)	Median treatment
02163694 [16] BROCADE3	3	513	veliparib (120 mg, bid) plus carboplatin-paclitaxel, 337	placebo plus carboplatin-paclitaxel, 172	locally advanced or metastatic	negative	T[a]: 35.7 (24.9–43.6) C[a]: 35.5 (23.1–45.9)	T: 350 ± 318 days C: 252 ± 263 days
02000622 [2] OlympiAD	3	302	olaparib tablets (300 mg, bid), 205	capecitabine, eribulin, or vinorelbine, 97	metastatic	negative	T: 25.3 C: 26.3	T[c]: 8.2 months (0.5–28.7) C[c]: 3.4 months (0.7–23.0)
01506609 [17] BROCADE	2	294	veliparib (120 mg, bid) plus carboplatin-paclitaxel, 97	placebo plus carboplatin-paclitaxel, 99	locally recurrent or metastatic	negative& positive[d]	NA	T: 12 (1–48) cycles C: 10 (1–33) cycles
01945775 [18] EMBRACA	3	431	talazoparib (1 mg, qd), 287	capecitabine, eribulin, gemcitabine, or vinorelbine, 144	locally advanced or metastatic	negative	T[b]: 44.9 (37.9–47.0) C[b]: 36.8 (34.3–43.0)	T[c]: 6.9 months (0.03–61.4) C[c]: 3.9 months (0.2–36.3)

T: treatment arm; C: control arm; qd: once daily; bid: twice daily.
[a] Interquartile range.
[b] 95% confidence intervals (CIs).
[c] Range;
[d] HER2 positive: ineligible for or progressed on prior HER2-directed therapy.



A



B

Fig. 2. A: Forest plots of PFS stratified by PARPi plus chemotherapy and PARPi monotherapy. B: Forest plots of OS stratified by PARPi plus chemotherapy and PARPi monotherapy. PFS: progression-free survival; OS: overall survival; PARPi: poly (adenosine diphosphate–ribose) polymerase inhibitors; TPC: treatment of physician's choice.

Table 2
Subgroup analysis of PFS.

Subgroup		No. of studies	Heterogeneity (I^2, χ^2p)	Test for subgroup differences (p)	HR [95%CI]
BRCA mutation	**BRCA**1	4	0%, 0.68	0.77	0.64 [0.53, 0.78]
	BRCA2	4			0.62 [0.51, 0.75]
TNBC	non-TNBC	4	27%, 0.21	0.65	0.65 [0.54, 0.79]
	TNBC	4			0.61 [0.51, 0.75]
Previous platinum therapy	yes	3	0%, 0.66	0.52	0.70 [0.50, 0.99]
	no	3			0.62 [0.53, 0.73]
Previous cytotoxic therapy	yes	3	0%, 0.75	1.00	0.69 [0.55, 0.86]
	no	3			0.69 [0.56, 0.85]
History of CNS metastases	yes	2	68%, 0.03	0.81	0.79 [0.13, 4.97]
	no	2			0.63 [0.53, 0.75]

PFS: progression-free survival; **BRCA**: breast related cancer antigen; TNBC: triple-negative breast cancer; CNS: central nervous system; HR: hazard ratio; CI: confidence interval.

TPC [20]. In BROCADE trial, the interim median OS was 28.3 months in the PARPi combined with carboplatin-paclitaxel group versus 25.9 months in the placebo plus carboplatin-paclitaxel group [17]. In BROCADE3 preplanned interim analysis of overall survival,

median OS of PARPi plus chemotherapy group and placebo plus chemotherapy group was 33.5 months and 28.2 months, respectively [16].

3.4. Adverse events

AEs were reported in all 4 studies and assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 or 4.03.

3.4.1. Adverse events of any grade

The incidences of overall AEs in PARPi arms and control arms were 98.8% (909/920) and 98.1% (475/484), respectively. As shown in Table 3, PARP inhibitors didn't increase the risk of AEs of any grade compared with the control groups (RR 1.01, 95% CI [0.99–1.02]), either placebo plus chemotherapy group (RR 1.00, 95% CI [0.99–1.02]) or TPC group (RR 1.01, 95% CI [0.99–1.04]). With respect to specific adverse events, thrombocytopenia, anaemia, nausea, cough, and upper respiratory tract infection were more common in PARP inhibitors treatment groups compared with control arms. However, the use of PARP inhibitors decreased the risk of palmar-plantar erythrodysesthesia syndrome (RR 0.04, 95% CI [0.01–0.09]).

3.4.2. Adverse events of high grade

PARP inhibitors didn't increase the risk of grade≥3 AEs compared with the control groups (RR 0.95, 95% CI [0.83–1.09]), either placebo plus chemotherapy group (RR 1.00, 95% CI [0.93–1.07]) or TPC group (RR 0.88, 95% CI [0.65–1.20]). Most frequent (>10%) grade≥3 AEs in PARP inhibitors groups were blood system toxicities, such as neutropenia (38.61%), anaemia (29.03%), thrombocytopenia (24.15%), and leukopenia (13.19%). The quantitative analysis results of grade≥3 AEs were showed in Suppl Tab 2.

3.4.3. Adverse events leading to treatment discontinuation

There was no significant difference in AEs rate leading to treatment discontinuation between PARPi groups and TPC control groups (RR 0.74, 95% CI [0.43–1.28]). However, compared with placebo plus chemotherapy groups, PARPi groups significantly increased this risk (RR 1.43, 95% CI [1.00–2.04]).

Table 3
AEs.

AEs	Intervention	No. of studies	Effect model	RR [95% CI]	Heterogeneity		Subgroup	Total	
					I^2	χ^2 p	differences (p)	p	Total RR [95% CI]
Any AEs	placebo	2	fixed	1.00 [0.99–1.02]	39%	0.18	0.46	0.27	1.01 [0.99–1.02]
	TPC	2		1.01 [0.99–1.04]					
Neutropenia	placebo	2	random	0.98 [0.93–1.04]	83%	<0.0001	0.09	0.16	0.85 [0.68–1.07]
	TPC	2		**0.69 [0.52–0.92]**					
Thrombocytopenia	placebo	2	random	1.10 [1.00–1.21]	93%	<0.00001	<0.0001	**0.02**	**1.84 [1.11–3.06]**
	TPC	2		**4.52 [2.38–8.55]**					
Anaemia	placebo	2	random	**1.15 [1.04–1.27]**	90%	<0.00001	0.007	**0.05**	**1.51 [1.01–2.25]**
	TPC	2		**2.09 [1.11–3.95]**					
Leukopenia	placebo	2	fixed	1.06 [0.86–1.30]	0%	0.76	0.34	0.22	1.12 [0.93–1.35]
	TPC	2		1.32 [0.88–2.00]					
Alopecia	placebo	2	random	1.10 [0.96–1.26]	72%	0.001	0.29	0.76	0.96 [0.72–1.27]
	TPC	2		0.54 [0.15–1.99]					
Fatigue	placebo	2	fixed	0.95 [0.82–1.10]	35%	0.20	0.06	0.44	1.05 [0.93–1.19]
	TPC	2		1.21 [0.98–1.48]					
Asthenia	placebo	2	fixed	1.10 [0.83–1.45]	29%	0.24	0.23	0.84	1.03 [0.79–1.33]
	TPC	1		0.70 [0.36–1.39]					
Decreased appetite	placebo	2	fixed	0.94 [0.72–1.23]	0%	0.55	0.47	0.98	1.00 [0.81–1.24]
	TPC	2		1.10 [0.79–1.53]					
Pyrexia	placebo	2	fixed	0.89 [0.66–1.21]	0%	0.90	0.84	0.33	0.88 [0.67–1.14]
	TPC	1		0.83 [0.48–1.45]					
Nausea	placebo	2	random	**1.16 [1.04–1.30]**	54%	0.09	0.64	**0.02**	**1.20 [1.04–1.40]**
	TPC	2		1.30 [0.82–2.04]					
Diarrhoea	placebo	2	fixed	**1.28 [1.05–1.56]**	31%	0.22	0.04	0.17	1.12 [0.95–1.32]
	TPC	2		0.89 [0.67–1.18]					
Vomiting	placebo	2	random	1.03 [0.83–1.29]	53%	0.09	0.28	0.18	1.22 [0.92–1.61]
	TPC	2		1.49 [0.80–2.76]					
Constipation	placebo	2	fixed	1.13 [0.91–1.41]	0%	0.77	0.64	0.34	1.09 [0.91–1.31]
	TPC	2		1.03 [0.74–1.43]					
Headache	placebo	2	fixed	1.04 [0.84–1.29]	4%	0.37	0.09	0.07	1.18 [0.09–1.40]
	TPC	2		**1.43 [1.06–1.93]**					
Cough	placebo	2	fixed	1.28 [0.92–1.79]	0%	0.49	0.29	**0.004**	**1.45 [1.12–1.88]**
	TPC	2		**1.70 [1.14–2.53]**					
Dyspnoea	placebo	2	fixed	0.91 [0.67–1.24]	35%	0.22	0.30	0.99	1.00 [0.77–1.29]
	TPC	1		1.23 [0.76–1.99]					
Upper respiratory tract infection	placebo	1	fixed	**2.06 [1.02–4.17]**	0%	0.39	0.39	**0.05**	**1.65 [1.01–2.72]**
	TPC	1		1.33 [0.65–2.72]					
Back pain	placebo	2	fixed	0.97 [0.73–1.28]	49%	0.12	0.06	0.20	1.16 [0.92–1.46]
	TPC	2		**1.53 [1.04–2.25]**					
Arthralgia	placebo	2	fixed	0.93 [0.71–1.21]	0%	0.41	0.61	0.72	0.96 [0.75–1.23]
	TPC	1		1.13 [0.55–2.35]					
PPES	placebo	0		NA					
	TPC	2	fixed	**0.04 [0.01–0.09]**	0%	0.39	NA	**<0.00001**	**0.04 [0.01–0.09]**
AEs leading to Discontinuation	placebo	2	fixed	1.43 [1.00–2.04]	26%	0.26	0.05	0.30	1.17 [0.87–1.57]
	TPC	2		0.74 [0.43–1.28]					

AE: adverse event; TPC: treatment of physician's choice; RR: risk ratio; CI: confidence interval; NA: not available; PPES: Palmar-plantar erythrodysesthesia syndrome.

3.5. Quality of life

In BROCADE3 study, no significant difference between PARPi treatment and placebo treatment was observed in EORTC QLQ-C30 questionnaire (European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire), breast cancer-specific QLQ-BR23 questionnaire, EQ-5D-5L (EuroQol 5 Dimension 5 Level) and Brief Pain Inventory questionnaires [16]. In OlympiAD study, an improvement of the adjusted mean (±SE) score on the QLQ-C30 change from baseline across all time points was observed in the olaparib group (3.9 ± 1.2) while a deterioration was observed in the TPC group (−3.6 ± 2.2), with an estimated difference of 7.5 points (95% CI [2.5–12.4]; P = 0.004). The median time to a significant decrease (≥10 points) in QLQ-C30 score was 15.3 months in the TPC group while it not reached in the olaparib group (HR 0.44, 95% CI [0.25–0.77]; P = 0.004) [2]. In EMBRACA study, there was a clinically meaningful improvement in GHS/QoL scores (QLQ-C30) in the talazoparib group (2.1, 95% CI [0.1–4.1]) while a significant deterioration in the TPC group (−5.7, 95% CI [−10.0 to −1.4]; P = 0.001). A significant improvement of change from baseline in the breast symptoms (QLQ-BR23) in the talazoparib group (−4.9, 95% CI [−6.5 to −3.2]) was observed, with a non-significant change in the TPC group (0.1,95% CI [-3.2 to 3.5]). In addition to the improvement of questionnaire scores and symptoms, the time to deterioration in both the GHS/QoL and QLQ-BR23 was delayed in the talazoparib group compared with the TPC groups [19].

4. Discussion

To our knowledge, this is the largest meta-analysis to comprehensively assess the efficacy and safety of PARP inhibitors in **BRCA** mutation breast cancer. The overall results indicated that PARPi whether in combination with carboplatin-paclitaxel or as monotherapy, is a compelling treatment option for **BRCA**-mutated breast cancer patients with improved survival (PFS and OS) and acceptable toxicity.

At present, the guidelines [5,21] and labels [7,8] recommended PARP inhibitors for the treatment of HER2 negative advanced or metastatic breast cancer patients with g**BRCA**m. As a common inherited gene mutation associated with breast cancer, **BRCA** mutation seems to be a potential therapeutic target. **BRCA**1/2 are the main functional genes of homologous recombination. Once the **BRCA** gene mutated, PARP inhibitors can prevent non-homologous end joining by blocking PARP leading to synthetic death, which supports the application of PARP inhibitors in **BRCA**-mutated breast cancer [22–24]. The **BRCA** mutation can be divided into somatic and germline mutation. To date, the significance of somatic **BRCA** mutation in the treatment of breast cancer needs to be further studied. Only germline **BRCA** mutation breast cancer was approved for clinical indications and all eligible patients in the presented meta-analysis were g**BRCA**m [5,21,25,26]. Previous basic studies demonstrated that **BRCA**2-mutated cells were more sensitive to PARP inhibitors than **BRCA**1-mutated cells [24,27,28]. However, the presented meta-analysis didn't show significant heterogeneity in efficacy between **BRCA**1 and 2 mutations to PARP inhibitors.

Notably, the outcomes of PFS in the subgroup analysis confirmed the possibility of the efficacy of PARP inhibitors in TNBC (HR 0.61, 95% CI [0.51–0.75]) [3]. TNBC accounts about for 10–15% of all breast cancer with younger onset age, higher histological grade, more visceral metastasis, faster progression, poorer prognosis and shorter survival. Traditional endocrine therapy and HER2 targeted therapy have no effect on it. Pathogenic variants in **BRCA** are associated with a high risk of breast cancer and a higher risk of TNBC [29]. Meanwhile, **BRCA** mutational status is a biomarker for personalized and targeted therapy in TNBC with clinically validation [30].

Previous meta-analyses have shown that PARPi had single-agent activity in **BRCA**-mutated HER2-negative metastatic breast cancer [9,10], which was consistent with our stratified results of PARPi monotherapy (PFS: HR 0.56, 95% CI [0.46–0.68]). Meanwhile, our meta-analysis also assessed the efficacy of PARP inhibitors combined with carboplatin-paclitaxel (PFS: HR 0.73, 95% CI [0.60–0.88]), which confirmed that PARP inhibitors can enhance the cancer cells' sensitivity to platinum-based chemotherapy. Platinum chemotherapy is the preferred option in patients with g**BRCA**m-associated advanced breast cancer [21]. In TNT trial, carboplatin had double the objective response rate of docetaxel in subjects with patients with g**BRCA**m-associated breast cancer (68% versus 33%) [31]. In our subgroup analysis, the efficacy was observed in both patients without prior platinum exposure and patients with prior platinum exposure who had a disease-free interval of at least 6 or 12 months after the last platinum dose. However, the studies included didn't take into account the assessment of PARP inhibitors in platinum-resistant disease. In general, the best treatments and sequencing of treatments for patients with **BRCA** mutation HER2-negative breast cancer are still unclear and require further research.

PARP inhibitors have been common accompanied by a specific pattern of toxicities including general symptoms (like fatigue), gastrointestinal toxicities (such as nausea, constipation, vomiting, and diarrhoea) and hematologic toxicities (such as anemia, thrombocytopenia, and neutropenia) [32–34]. In addition to these common adverse events, renal, neurological, respiratory, musculoskeletal, cardiovascular toxicities and secondary malignancies have also been reported in clinical trials [35–37]. In our meta-analysis, PARP inhibitors were well tolerated with manageable toxicity. The most frequent AEs were nausea (62.07%), anaemia (61.09%), thrombocytopenia (58.46%), neutropenia (57.39%), and fatigue (46.09%), which were consistent with previous studies. Compared with TPC, single-agent PARPi significantly increased the risk of thrombocytopenia, anaemia, cough, dyspnoea, headache, and back pain but reduced the risk of neutropenia and palmar-plantar erythrodysesthesia syndrome. When PARP inhibitors were added to carboplatin-paclitaxel, they increased the risk of anaemia, nausea, diarrhoea and upper respiratory tract infection. The incidence of AEs leading to discontinuation from PARPi groups and control groups showed no significant difference. Although PARPi-related hematologic toxicities were common, they were generally grade 1–2 without inducing dose discontinuation or leading to death. Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) was a kind of secondary hematologic malignancy that can be induced by PARP inhibitors. In studies included in our meta-analysis, only one patient occurred PARPi-AML at 2 years after randomization (41 days after receiving the lase dose of talazoparib) and died 18 days after diagnosis. Although PARPi-MDS/AML had a high mortality rate (45%), the incidence of PARPi-MDS/AML was very low (0.73%, 95% CI [0.50–1.07]) based on a meta-analysis including 18 placebo-controlled RCTs [38].

The efficacy and tolerable safety provided stable evidence of PARP inhibitors application in clinical, but it still needs to be balanced with QoL. The PARP monotherapy showed an improvement of QoL comparing with the baseline. Compared with TPC, PARPi not only statistically significantly improved the QoL, but also delayed the time to deterioration. When PARPi was added into chemotherapy, it did not reduce the QoL while increasing the efficacy. But the data were insufficient for quantitative analysis and more studies were needed to support it. The maintenance or improvement of QoL and patient-reported outcomes should be part of comprehensive consideration in future.

However, some limitations of our meta-analysis should be acknowledged. First, the presented meta-analysis only included five studies with a small sample and insufficient individual patient data. Second, some of the eligible studies were not powered for OS with limited follow-up. Third, our meta-analysis couldn't address the relative benefits of PARP inhibitors and platinum-based chemotherapy in **BRCA**-mutated HER2 negative breast cancer patients, as the platinum was not included as TPC in the control group. Despite the above limitations, we believe that all the analyses performed may aid in presenting a brief assessment of the role of PARP inhibitors in the management of patients with **BRCA**-mutated HER2-negative advanced breast cancer. A strength of the present analysis was the stratification of advanced breast cancer patients according to **BRCA** mutation and hormone receptor status, giving supportive data of the applications in TNBC patients.

Contributors

Zhuo Ma, Lihong Liu, and Xin Feng were responsible for the conception and design of the study. Ximu Sun and Zhuo Ma drafted the original writing of the manuscript. Ximu Sun did the data extraction and statistical analysis. Xin Wang, Jie Zhang, and Zhixia Zhao contributed to the methodological support. All authors contributed to the critical review and editing of the manuscript and approved the final version of the manuscript.

Funding

Not applicable.

Declaration of competing interest

All authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.08.009.

References

[1] Last accessed at 2021.2.28, https://www.iarc.who.int/faq/latest-global-cancer-data-2020-qa/.
[2] Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 2017 Aug 10;377(6):523–33. https://doi.org/10.1056/NEJMoa1706450.
[3] Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. Nat Rev Dis Primers 2019 Sep 23;5(1):66. https://doi.org/10.1038/s41572-019-0111-2.
[4] Nielsen FC, van Overeem Hansen T, Sørensen CS. Hereditary breast and ovarian cancer: new genes in confined pathways. Nat Rev Canc 2016 Sep;16(9):599–612. https://doi.org/10.1038/nrc.2016.72.
[5] Breast Cancer Expert Committee of National Cancer Quality Control Center. Breast cancer expert committee of China anti-cancer association; cancer drug clinical research committee of China anti-cancer association. [Guidelines for clinical diagnosis and treatment of advanced breast cancer in China (2020 edition)]. Zhonghua Zhong Liu Za Zhi 2020 Oct 23;42(10):781–97. https://doi.org/10.3760/cma.j.cn112152-20200817-00747. Chinese.
[6] Tutt A, Robson M, Garber JE, et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. Lancet 2010 Jul 24;376(9737):235–44. https://doi.org/10.1016/S0140-6736(10)60892-6.
[7] Last accessed at 2021.1.7, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s016lbl.pdf.
[8] Last accessed at 2021.1.7, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/211651s006lbl.pdf.
[9] Poggio F, Bruzzone M, Ceppi M, et al. Single-agent PARP inhibitors for the treatment of patients with BRCA-mutated HER2-negative metastatic breast cancer: a systematic review and meta-analysis. ESMO Open 2018 Jun 20;3(4):e000361. https://doi.org/10.1136/esmoopen-2018-000361.
[10] Wang J, Zhang Y, Yuan L, et al. Comparative efficacy, safety, and acceptability of single-agent poly (ADP-ribose) polymerase (PARP) inhibitors in BRCA-mutated HER2-negative metastatic or advanced breast cancer: a network meta-analysis. Aging (Albany NY) 2020 Nov 30;13(1):450–9. https://doi.org/10.18632/aging.202152.
[11] Last accessed at 2021.1.4, https://training.cochrane.org/handbook/current.
[12] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009 Jul 21;339:b2535. https://doi.org/11.1136/bmj.b2535.
[13] Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011 Oct 18;343:d5928. https://doi.org/10.1136/bmj.d5928.
[14] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
[15] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[16] Diéras V, Han HS, Kaufman B, et al. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2020 Oct;21(10):1269–82. https://doi.org/10.1016/S1470-2045(20)30447-2.
[17] Han HS, Diéras V, Robson M, et al. Veliparib with temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in patients with BRCA1/2 locally recurrent/metastatic breast cancer: randomized phase II study. Ann Oncol 2018 Jan 1;29(1):154–61. https://doi.org/10.1093/annonc/mdx505.
[18] Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. N Engl J Med 2018 Aug 23;379(8):753–63. https://doi.org/10.1056/NEJMoa1802905.
[19] Litton JK, Hurvitz SA, Mina LA, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol 2020 Nov;31(11):1526–35. https://doi.org/10.1016/j.annonc.2020.08.2098.
[20] Robson ME, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. Ann Oncol 2019 Apr 1;30(4):558–66. https://doi.org/10.1093/annonc/mdz012.
[21] Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020 Dec;31(12):1623–49. https://doi.org/10.1016/j.annonc.2020.09.010.
[22] Gourley C, Balmaña J, Ledermann JA, et al. Moving from poly (ADP-Ribose) polymerase inhibition to targeting DNA repair and DNA damage response in cancer therapy. J Clin Oncol 2019 Sep 1;37(25):2257–69. https://doi.org/10.1200/JCO.18.02050.
[23] Kaelin Jr WG. The concept of synthetic lethality in the context of anticancer therapy. Nat Rev Canc 2005 Sep;5(9):689–98. https://doi.org/10.1038/nrc1691.
[24] Hollis RL, Churchman M, Gourley C. Distinct implications of different BRCA mutations: efficacy of cytotoxic chemotherapy, PARP inhibition and clinical outcome in ovarian cancer. OncoTargets Ther 2017 May 11;10:2539–51. https://doi.org/10.2147/OTT.S102569.
[25] Gradishar WJ, Anderson BO, Abraham J, et al. Breast cancer, version 3.2020, NCCN clinical practice guidelines in Oncology. J Natl Compr Canc Netw 2020 Apr;18(4):452–78. https://doi.org/10.6004/jnccn.2020.0016.
[26] Ditsch N, Untch M, Kolberg-Liedtke C, et al. AGO recommendations for the diagnosis and treatment of patients with locally advanced and metastatic breast cancer: update 2020. Breast Care 2020 Jun;15(3):294–309. https://doi.org/10.1159/000508736.
[27] Bolton KL, Chenevix-Trench G, Goh C, et al. Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. JAMA 2012 Jan 25;307(4):382–90. https://doi.org/10.1001/jama.2012.20.
[28] Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005 Apr 14;434(7035):917–21. https://doi.org/10.1038/nature03445.
[29] Hu C, Hart SN, Gnanaolivu R, et al. A population-based study of genes previously implicated in breast cancer. N Engl J Med 2021 Feb 4;384(5):440–51. https://doi.org/10.1056/NEJMoa2005936.
[30] Sporikova Z, Koudelakova V, Trojanec R, Hajduch M. Genetic markers in triple-negative breast cancer. Clin Breast Canc 2018 Oct;18(5):e841–50. https://doi.org/10.1016/j.clbc.2018.07.023.
[31] Tutt A, Tovey H, Cheang MCU, et al. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. Nat Med 2018 May;24(5):628–37. https://doi.org/10.1038/s41591-018-0009-7.
[32] Zhou JX, Feng LJ, Zhang X. Risk of severe hematologic toxicities in cancer patients treated with PARP inhibitors: a meta-analysis of randomized controlled trials. Drug Des Dev Ther 2017 Oct 13;11:3009–17. https://doi.org/10.2147/DDDT.S147726.
[33] Liu Y, Meng J, Wang G. Risk of selected gastrointestinal toxicities associated with poly (ADP-ribose) polymerase (PARP) inhibitors in the treatment of ovarian cancer: a meta-analysis of published trials. Drug Des Dev Ther 2018 Sep 17;12:3013–9. https://doi.org/10.2147/DDDT.S164553.
[34] LaFargue CJ, Dal Molin GZ, Sood AK, et al. Exploring and comparing adverse events between PARP inhibitors. Lancet Oncol 2019 Jan;20(1):e15–28. https://doi.org/10.1016/S1470-2045(18)30786-1.
[35] Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017 Oct

28;390:1949–61. https://doi.org/10.1016/S0140-6736(17)32440-6. 10106.
[36] Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016 Dec 1;375(22):2154–64. https://doi.org/10.1056/NEJMoa1611310.
[37] Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017 Sep;18(9):1274–84. https://doi.org/10.1016/S1470-2045(17)30469-2.
[38] Morice PM, Leary A, Dolladille C, et al. Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database. Lancet Haematol 2021 Feb;8(2):e122–34. https://doi.org/10.1016/S2352-3026(20)30360-4.