Efficacy and safety of PARP inhibitors in the treatment of BRCA-mutated breast cancer: An updated systematic review and meta-analysis of randomized controlled trials

Xiaoyu Sun
China Medical University
Suying Xu
China Medical University
Yiming Li
Chinese Academy of Medical Sciences
Xuemei Lv
China Medical University
Minjie Wei
China Medical University
Miao He (hemiao_cmu@126.com)
China Medical University

Research Article

Keywords: PARP inhibitors, breast cancer, efficacy, safety, meta-analysis

Posted Date: May 25th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1668303/v1

Abstract

Background: Poly-ADP-ribose polymerase inhibitors have emerged as a new class of therapeutic agents for breast cancer patients with BRCA mutations; however, the efficacy and toxicity of PARP inhibitors have not been clearly established.

Methods: This study comprehensively evaluated the efficacy and safety of PARP inhibitors in BRCA mutated breast cancer patients. Online databases were systematically searched, and six clinical trials were included in the meta-analysis. The primary endpoint of efficacy was PFS, secondary endpoints are OS and ORR. In addition, we also assessed safety.

Results: The results of the meta-analysis showed that PARP inhibitors can effectively improve the PFS, and OS of patients compared with the control group. The pooled HR (PARP inhibitor vs control group) was 0.63 (95 % CI, 0.55– 0.73) in PFS and 0.83 (95% CI, 0.73 -0.95) in OS among all patients. In terms of safety, PARP inhibitors show controllable adverse reactions. There were no significant differences in overall AEs or grade≥3 AEs between the PARP inhibitor arms and the control arms.

Conclusions: In general, this study demonstrates PARP inhibitors perform well in both monotherapy and combination therapy, not only can provide substantial survival benefit, but also do not increase the additional toxicity burden, and the clinical application is promising.

Background:

Breast cancer is one of the deadliest female malignancies and has surpassed lung cancer as the most common diagnosed cancer worldwide(1). According to the latest statistics, there are estimated to be 287,850 new cases of breast cancer and 43,250 deaths in the United States in 2022(2). In the latest statistics for breast cancer in China, breast cancer in women is estimated to account for 16.72% (306,000) of all new cancers in 2016 (3). In recent years, in addition to early screening, the main treatment measures for breast cancer include breast-conserving surgery, radiotherapy, and mastectomy(4–6). According to breast cancer susceptibility gene studies, breast cancer susceptibility gene (BRCA) is the most common oncogene, and patients with BRCA mutations have a higher risk of breast cancer(7).

BRCA1/2 is a gene associated with breast and ovarian cancers and plays an important role in homologous recombinant DNA repair, known as a tumor suppressor gene(8). BRCA1/2 plays a role in homologous repair (HR) by participating in the synthesis of multiprotein complexes that recognize and repair certain damaged broken DNA duplexes on the one hand, and on the other hand, BRCA1/2 plays a role in the protection of stalled replication forks(9, 10). When BRCA1/2 is mutated, it causes homologous recombination repair defects (HRD), impairs DNA repair, and leads to irregular DNA synthesis, which may increase genomic instability, lead to cell cycle arrest and apoptosis, and increase the risk of malignant tumor development(10–13).

PolyADP - ribose polymerase (PARP) is a class of multifunctional enzymes that play an important role in the DNA repair pathway by participating in DNA base excision repair and DNA single-strand break repair(14–16).While, PARP inhibitors (PARPis) are highly tumor-specific and are only very sensitive to breast cancers with BRCA mutations(17, 18). Through the synthetic lethality, whereby PARPis treat breast cancer by inhibiting DNA single-strand break repair in tumor cells defective in homologous recombination, producing double-strand breaks that lead to selective death of BRCA mutant cells(18, 19) (Fig. 1).

Currently, PARPis have been found to play an important role in the treatment of BRCA1/2-mutated breast cancer in studies targeting the molecular targets of breast cancer. Several PARPis have been approved by the Food and Drug Administration (FDA) as clinical treatments for BRCA1/2 mutated breast cancer(20). In recent years, a large number of clinical trials have shown that PARPis olaparib, veliparib, and talazoparib exert better efficacy and safety in the treatment of BRCA-mutated breast cancer and have great prospects for development. This review will provide an up-to-date and comprehensive evaluation of the efficacy and safety of PARPis in BRCA-mutated breast cancer treatment, to provide objective basis for the clinical treatment of breast cancer, and meta-analysis will be conducted on the relevant literatures published so far.

Materials And Methods

Search Strategy

RCTs of PARPis in BRCA-mutated breast cancer were searched from PubMed, Embase, Cochrane Library, Web of Science, and CNKI. In addition, we also searched the minutes of the meeting, including: The American Society of Clinical Oncology (ASCO) and the ESMO and the Clinical Trials-Registration website (http://www. ClinicalTrials.gov) to ensure that our search is comprehensive and comprehensive. The following combination of MeSH-terms and keywords strategy was used: “Breast Neoplasms”“Poly(ADP-ribose) Polymerases inhibitors”“PARPis” “talazoparib”“olaparib”“niraparib”“rucaparib”“veliparib”“BRCA mutation”“BRCA-mutated”. Qualified clinical studies were screened according to the inclusion criteria. Two researchers, Sun and Xu independently screened the titles and abstracts of all the citations through literature search. Any disagreements between the reviewers were resolved by consensus through discussion. For duplicated clinical trials, only the most complete or up-to-date publications were included. This systematic review and meta-analysis were carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement recommendations (http://www.prisma-statement.org/).

Inclusion and Exclusion Criteria

Included trials were required to meet the following criteria: (1) Phase II or III RCTs in which PARPis alone or in combination with other drugs were used as intervention and conventional chemotherapy or placebo were used as controls. (2) Women 18 years or older with BRCA mutations in breast cancer. (3) sufficient data to assess efficacy outcomes (PFS, OS, and ORR) and safety outcomes.

Exclusion criteria were mainly as follows: (1) reviews, meta-analysis, commentaries, or conference abstracts. (2) Phase I clinical trials or single-arm trials. (3) trials with incomplete data. (4) the study evaluating the efficacy of PARPis during adjuvant therapy.

Data Extraction

Data extraction and recording were performed independently by two investigators according to inclusion criteria. The following information was acquired from each included study: the trial name, first author, publication time, phase, number in each arm, type of PARPis, type of control groups, HR or RR with 95% CI for OS and PFS analysis, ORR and occurrence of AEs. If the PFS is represented only by the Kaplan-Meier curve, the data is digitized and extracted using Engauge digitizer 4.1 software. In case of trials that did not include all survival analysis, we also reviewed each clinical trial's supplement.

Risk of bias assessment

Two reviewers used the Cochrane Risk of Bias tool to conduct a quality assessment of the risk of bias. Seven items were evaluated according to "yes" (low bias), "no" (high bias) and "unclear" (unclear bias), including sequence generation (selection bias); allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective outcome reporting (reporting bias), and other potential sources of bias. The total result was presented as percentages in a figure.

Statistical Analyses

For dichotomous variables (ORR), the relative risk (RR) and 95% CI were calculated for each study. Analysis of event occurrence time variables using HR and 95% CI (PFS and OS). All data were expressed as the combination of HR or RR and 95%CI, and $p<0.05$ was statistically significant. We assessed the between-study heterogeneity by using the inconsistency index (I^2 statistic), which estimates the percentage of total variability across all studies(21). I^2 regarded an estimated value applied three fixed knots at 25%, 50% and 75% as an indicator of mild, moderate, and high heterogeneity. If the test showed $I^2>50\%$ or $p<0.10$, the data were calculated through a random-effects (RE) model(22). Otherwise, a fixed-effects (FE) model was used to pool effect size(22). To deeply explore the heterogeneity and its potential influence, subgroup analysis was performed. Meta-regression analysis was employed to examine which characteristics might be the possible source of heterogeneity. In addition to, publication bias was also estimated by Egger's test and Begg's test(23, 24). Sensitivity analysis, which examined the robustness of included trials to different aspects from methodological bias. All p-values were two-sided, and all statistical analyses were performed using Review Manager 5.3 and Stata 12.0 software.

Results

Literature selection and study characteristics

First, we determined our search formula, and through this search strategy identified 1153 studies, of which 6 were conference abstracts. According to inclusion and exclusion criteria, 6 studies from the randomized controlled trials (RCTs) were eventually included in this meta-analysis. The specific search and study selection process is shown in Fig. 2. Among them, there are two EMBRACA tests, and one of them has updated the OS(25, 26). It is noteworthy that, iniparib was not included as a PARP inhibitor in search formula. There is evidence that it is not a real PARP inhibitor, and it does not rely on PARPis to function(27, 28).

These included RCTs were published in 2016-2021. A total of 1477 BRCA-mutated patients, which from phase II and III clinical trials, were eventually included in this meta-analysis. The characteristics of the included studies and enrolled patients are listed in Table 1. Three of them studied the PARPis in combination with chemotherapy, and three evaluated the efficacy of PARPis alone. BROCADE is a randomized, partially blind phase II clinical trial (NCT01506609), assessed the safety and efficacy of intermittent veliparib with carboplatin/paclitaxel (VCP) or temozolomide (VT)(29). BROCADE3 is a randomized, double-blind, placebo-controlled phase III clinical trial. That is, veliparib or placebo in combination with carboplatin and paclitaxel to evaluate the efficacy of platinum in combination with PARPis(30). Shivaani Kummar et al. conducted a randomized phase II trial of veliparib in combination with cyclophosphamide or cyclophosphamide alone(31). Three other studies respectively assessed the efficacy of veliparib or olaparib as monotherapy. Notably, we included a recently published Phase III randomized trial: the OlympiA trial(32). It was a large international randomized trial that evaluated one year of adjuvant olaparib vs placebo after chemotherapy and local treatment in germline BRCA mutation (gBRCAm) carriers with human epidermal growth factor receptor 2 (HER2)-negative breast cancer. In March 2022, the European Society of Medical Oncology (ESMO) virtual plenary was updated with a significant overall survival benefit (hazard ratio (HR) 0.68, $p = 0.009$)(33). The risk of bias for each study was assessed according to the Cochrane Manual 5.1.0 assessment criteria (Fig. 3). Randomization was unclear in four studies, and two studies had other unclear risk of bias. Overall, the risk of bias is low.

Table 1

Main study characteristics of the included trials.

Trials (first author)	Year	Phase	Identifier	Treatment arms	Target	BRCA	Disease phenotype	Patients	RR Control arm	RR Experiment arm	OS HR 95%CI	PF HR 95
Mark Robson	2017		NCT02000622	Olaparib vs Cape/eribulin/ VRB	PARP1 PARP2	Mut	HER2-	302	97	205	0.90 (0.63-1.29)	0.5 (0. 0.8
Jennifer K Litton	2018		NCT01945775	Talazoparib vs Cape/eribulin/ GEM /VRB	PARP1 PARP2	Mut	HER2-	431	144	287	0.848 (0.670-1.073)	0.5 (0. 0.7
Véronique Diéras	2020		NCT02163694	Vel +CP-PTX vs PBO+CP-PTX	PARP1 PARP2	Mut	HER2-	509	172	337	0.95 (0.73-1.23)	0.7 (0. 0.8
H.S. Han	2017		NCT01506609	Vel +CP /PTX vs PBO+CP/PTX	PARP1 PARP2	Mut	All	196	99	97	0.750 (0.503–1.117)	0.7 (0. 1.1
Shivaani Kummar	2016		NCT01306032	Vel +CTX vs CTX	PARP1 PARP2	Mixed	TNBC	39	18	21	NR	0.3 (0. 0.8
A.N.J. Tutt	2021		NCT02032823	Olaparib vs PBO	PARP1 PARP2	Mut	HER2-	1836	921	915	0.68 (0.51-0.91)	NR

Cape= Capecitabine; VRB= vinorelbine; GEM=gemcitabine; CP= carboplatin; PTX= paclitaxel; CTX= cyclophosphamide; PBO= placebo; Vel= Veliparib

Efficacy

Primary endpoint: PFS

Progression-free survival (PFS) is the primary endpoint of most studies but cannot be obtained in one study (OlympiA)(32). Since disease-free survival (DFS) was the primary endpoint of this study, we excluded this study and pooled the results of five other studies. Due to the moderate heterogeneity (I^2 = 29%, p = 0.23), we chose the fixed-effects model. From the forest map, we found that PARPis were closely related to the improvement of PFS, with HR 0.63 ([95% CI, 0.55-0.73], p < 0.00001; Fig. 4a). Additionally, PARPis, either single-agent or in combination, significantly prolonged PFS in patients compared with control groups (HR 0.56 [95%CI, 0.46 to 0.68], p < 0.00001; HR 0.71 [95%CI, 0.59 to 0.85], p = 0.00002, respectively) and it was noteworthy that there was no significant difference in the benefit of PFS between monotherapy and combination therapy (p = 0.09; Fig. 4b). In addition, we compared the median PFS data provided in the included study (Table 2). Median survival was significantly longer in the PARPis arms than in the placebo or chemotherapy arms.

In breast cancer, two PARPis, olaparib and talazoparib, have been approved for treatment of gBRCAm carriers with metastatic HER2-negative breast cancer, respectively(25, 34). On March 11, 2022, the FDA approved olaparib for the adjunctive treatment of HER2-negative in adults with gBRCAm who are at high risk for early breast cancer and who have previously received neoadjuvant or adjuvant chemotherapy(35). Veliparib, while not approved by the FDA, has shown promising results in several clinical trials in gBRCAm carriers with metastatic HER2-negative breast cancer patients(36, 37). Therefore, we focused on the PFS benefits of HER2-negative breast cancer in the subgroup analysis. In a subgroup analysis based on hormone receptor status, we found an exciting correlation between PARPis and improved PFS in both triple negative breast cancer (TNBC) and HER2-negative hormone receptor (HR)-positive breast cancer patients (HR 0.59 [95%CI, 0.49 to 0.72], p < 0.00001; HR 0.66 [95%CI, 0.54 to 0.80], p < 0.00001，respectively; Fig. 4c) . Furthermore, there is no significant heterogeneity (I^2 = 41%, p = 0.15; I^2 = 48%, p = 0.14).

Breast cancer patients with BRCA1/2 mutations are more sensitive to platinum drugs such as cisplatin and carboplatin than the wild type(38, 39). The effect of prior use of platinum therapy was also analyzed. However, PARPis significantly improved PFS in patients not receiving platinum-based therapy with HR 0.64 ([95% CI, 0.55 to 0.75] p < 0.00001; Fig. 4d). For platinum-treated patients, the risk of disease progression was also statistically significant in the PARP inhibitor group (HR 0.70 [95%CI, 0.53 to 0.91]). As for BRCA mutation status, PARP inhibitors benefit uniformly in BRCA mutation 1 or 2 (Supplementary Figure1a).

Secondary endpoint: OS and ORR

We included three single-agent studies and two combination chemotherapy studies to analyze overall survival (OS) without significant heterogeneity (I^2 = 0%, p = 0.51). The pooled HR with 0.83 ([95% CI, 0.73 to 0.95], p = 0.005; Fig. 5a) indicated significant improvement in OS with PARPis. Interestingly, in the

Table 2

Median progression-free survival of the included trials.

Trials (first author)	Year	Median progression-free survival (months)		Hazard ratio (95% CI)	P	NCT
		PARP inhibitors therapy	Placebo or chemotherapy			
H.S. Han	2017	14.1	12.3	0.79(0.55-1.16)	0.227	01506609
Jennifer K Litton	2018	8.6	5.6	0.54(0.41-0.71)	< 0.001	01945775
Mark Robson	2017	7.0	4.2	0.58(0.43-0.80)	< 0.001	02000622
Véronique Diéras	2020	14.5	12.6	0.70(0.57-0.87)	0.0016	02163694

subgroup analysis, the significant improvement in OS with PARPis compared to the control groups was statistically significant only in the monotherapy subgroup (HR 0.80 [95%CI, 0.68 to 0.94], $p = 0.008$; Fig. 5b). There was no statistical significance in combined chemotherapy subgroup (HR 0.88 [95%CI, 0.71 to 1.10], $p = 0.027$).

Overall, five studies provided data for objective response rate (ORR) analysis. The pooled results showed a significant correlation between ORR and the experimental arms (RR 1.55 [95% CI, 1.02 to 2.34], $p = 0.04$, $I^2 = 90\%$;), with high heterogeneity (Fig. 5c). Subgroup analysis observed that monotherapy had a higher ORR rate than combination therapy (RR 2.21 [95% CI, 1.73 to 2.84] and RR 1.11 [95% CI, 0.93 to 1.33], respectively; Fig. 5d).

Safety

In addition to efficacy, we also paid attention to the possible adverse reactions of PARPis, that is, safety analysis. The comparative safety profile in terms of the (adverse events) AEs of interest is shown in Table 3 and Supplementary Figure1. Overall, Forest plot results showed there is no difference in the probability of AEs between the PARPis arms and the placebo or chemotherapy arms, regardless of whether it was AEs of any grade with RR 1.03 ([95% CI, 0.96 to 1.11], $p = 0.40$) or AEs grade≥3 with RR 1.09 ([95% CI, 0.74 to 1.61], $p = 0.65$; Fig. 6a and Fig. 6b). RE model was used due to high heterogeneity ($I^2 = 97\%$, respectively). Notably, in subgroup analyses of AEs of any grade, the incidence of AEs with monotherapy and combination therapy was similar and there was no difference between each and their control groups (RR 1.04 [95% CI, 0.96 to 1.12], $p = 0.34$ and RR 1.02 [95% CI, 0.92 to 1.14], $p = 0.68$; Fig. 6c). The results of the subgroup with AE grade≥3 were the same as above(Fig. 6d).

Table 3

RRs of grade 3 or higher AEs comparing PARPis groups with the control groups

Adverse event type	PARP inhibitors	Placebo/ Chemotherapy	RR (95% CI)	I^2(%)	P
Anemia	385/1852	99/1406	2.92(0.86-9.84)	94	0.08
Neutropenia	452/1852	271/1406	0.97(0.64-1.47)	88	0.89
Leukopenia	169/1852	81/1406	1.21(0.96-1.53)	75	0.10
Lymphopenia	15/307	3/144	2.94(0.84-10.36)	0	0.09
Fatigue	58/1831	24/1388	1.61(1.00-2.57)	43	0.05
Nausea	29/1831	12/1388	1.38(0.74-2.57)	46	0.31
Vomiting	27/1852	8/1406	1.78(0.87-3.66)	21	0.12
Diarrhea	26/1831	22/1388	0.69(0.27-1.74)	49	0.43
Headache	14/1831	7/1388	1.09(0.46-2.58)	0	0.84

In addition, we also assessed the safety of different PARPis shown in Table 4. Olaparib has a higher risk than the other two drugs for any type of AEs of grade≥3 (RR 1.78 [95% CI, 1.49 to 2.13], $p = 0.02$). Similarly, for hematologic AEs, olaparib also showed a statistically significant higher risk of anemia compared to talazoparib and veliparib (RR 14.27 [95% CI, 6.68 to 30.47], $p < 0.00001$), while vilipalib had the lowest risk of anemia of the three (RR 1.02 [95% CI, 0.97 to 1.06], $p < 0.00001$). Talazoparib had better decreased white cell counts (RR 0.84 [95% CI, 0.42 to 1.96], $p = 0.01$). Interestingly, the above results were not reported in previous META analyses. Other safety results suggest that PARPis may increase the risk of fatigue, nausea, and headaches.

Table 4.

RRs of grade 3 or higher AEs according to drug type.

Sensitivity analyses and publication bias

Sensitivity analysis was used to assess the impact of individual studies on the overall results. The results showed that except for NCT02163694 for ORR and NCT02032823 for AEs, a single study did not significantly change the overall results of HRs (for PFS and OS) and RRs (for ORR and AEs), which demonstrated the robustness of the analysis (Supplementary Figure 2). We evaluated the publication bias of the included literatures by Begg's Funnel Plot and Egger's Test, and the results showed that there was no publication bias in PFS,OS,ORR and AEs (Begg's funnel plot $p = 0.806$ for PFS, $p = 0.806$ for OS, $p = 0.806$ for ORR, $p = 0.452$ for AEs; Egger's test $p = 0.410$ for PFS, $p = 0.665$ for OS, $p = 0.186$ for ORR, $p = 0.12$ for AEs; Supplementary Figure 3).

Discussion

Adverse events	RR (95% CI)			P
	Olaparib (t=2, n=2111)	Talazoparib (t=1, n=412)	Veliparib (t=3, n=735)	
Any type	1.78(1.49-2.13)	1.05(0.75-1.48)	1.02(0.97-1.06)	0.02
Anemia	14.27(6.68-30.47)	8.44(3.82-18.67)	1.16(0.94-1.45)	<0.00001
Neutropenia	1.81(1.19-2.76)	0.64(0.46-0.88)	1.05(0.95-1.16)	0.34
Leukopenia	2.53(1.32-4.85)	0.84(0.42-1.69)	1.24(0.94-1.65)	0.01
Fatigue	3.92(1.49-10.32)	0.77(0.23-2.59)	1.22(0.67-2.24)	0.04
Nausea	6.24(0.77-50.64)	0.22(0.02-2.41)	1.48(0.69-3.18)	0.16
Vomiting	5.35(0.65-44.36)	1.03(0.27-3.91)	2.22(0.74-6.67)	0.06
Diarrhea	1.19(0.27-5.30)	0.13(0.03-0.60)	1.06(0.52-2.13)	0.29
Headache	1.19(0.27-5.30)	2.20(0.26-18.66)	1.06(0.25-4.38)	0.58

In conclusion, this is the most recent and comprehensive meta-analysis known to evaluate the efficacy and safety of PARPis in BRCA-mutated breast cancer. The overall results suggest that PARPis, whether monotherapy or combination therapy, demonstrates the strong and excellent therapeutic effect, significantly improves survival, and is well tolerated by patients with possible toxicity.

Since olaparib entered clinical trials for the first time in 2009, PARPAis have gradually become emerging targets for cancer treatment in the past decade(40). In 2018, olaparib and talazoparib were approved for the treatment of with HER2-negative advanced or metastatic breast cancer patients with gBRCAm. As research continues, PARPis are also being evaluated in combination with other drugs. In the Phase III BROCADE3 trial, the addition of veliparib to carboplatin and paclitaxel significantly improved median PFS compared to placebo added to carboplatin and paclitaxel, with encouraging results. In two previously reported meta-analyses, monotherapy with PARPis improved PFS but not OS(41, 42). In contrast, our meta-analysis showed significant improvement in both OS and PFS in monotherapy with PARPis. The results are certainly encouraging. In addition, our meta-analysis also evaluated the efficacy of PARPis in combination with chemotherapeutic agents. Although OS and ORR did not improve, PFS had significant benefits (HR 0.71 [95%CI, 0.59 to 0.85], $p = 0.00002$), which is consistent with the stratified results of our PARPis combination therapy(43). Meanwhile, our analysis also noted that there was no significant difference in benefit between monotherapy and combination therapy, which may provide strong evidence for future clinical drug combination.

Our meta-analysis also aimed to provide perspectives on potential patients who may benefit more from PARPis. Despite the results of previous meta-analyses, only TNBC patients achieved statistically significant improvement in PFS based on a subgroup analysis of hormone receptor status(41). However, our results suggest that patients with hormone-receptor-positive tumors also benefit from better PFS (HR 0.66 [95%CI, 0.54 to 0.80], $p < 0.00001$). According to the guidelines, platinum-based chemotherapy is the preferred option for patients with advanced breast cancer associated with gBRCAm(44). It is important to note that PFS results were significantly improved compared to PARPis and chemotherapy in patients with or without prior platinum-based therapy, which also differs from what has been reported in previous meta-analyses(41, 42).

As PARPis are gradually approved for clinical use, their safety and tolerability in patients are of great value and indispensable significance. In general, PARPis appear to be safe and well tolerated in breast cancer patients despite the hematologic gastrointestinal adverse effects, such as anemia, leukopenia, nausea, and vomiting, consistent with previously reported results. Specifically, we evaluated the safety of three different PARPis. Results showed that olaparib had the most severe adverse reactions, while talazoparib and veliparib had less severe adverse reactions. This may be because the control group for olaparib in the latest trial we included was placebo, so there was an increased risk of adverse effects. It may also be related to different doses of PARPis. The current approved dose of Olaparib is 300 mg twice daily, while talazoparib, the strongest PARP trapper, has the lowest recommended dose(45).

This meta-analysis is considered to have several limitations. First, as with other reported meta-analyses, the data obtained are based on research-level evidence rather than individual patient data results, lacking some raw data. Second, it cannot be denied that ORR and AEs have high data heterogeneity, which may introduce selection bias into the results. Finally, single-arm and Phase I trials were excluded from this meta-analysis, so there are some limitations in the assessment of safety.

Looking further ahead, there have been many clinical trials exploring the efficacy of different PARPis in breast cancer. These included phase III trials of niraparib in HER2-negative and gBRCAm breast cancer patients (BRAVO)(46). The role of PARP inhibitors in neoadjuvant therapy for breast cancer patients has also been evaluated, for example: BrighTNess and GeparOLA studies(47, 48). It is believed that as clinical trials continue to end, PARPis in the treatment of breast cancer will be more outstanding performance.

Conclusions

Our results confirm and strengthen the efficacy and safety of PARPis in BRCA mutated breast cancer patients, and more specifically clarify the efficacy of PARPis alone or in combination with other chemotherapy drugs. However, beyond the approved indications, the therapeutic value of PARPis for patients with other types of breast cancer still needs to be further evaluated in future studies.

Abbreviations

BRCA breast cancer susceptibility gene

HR homologous repair

HRD homologous recombination repair defects

PARP PolyADP - ribose polymerase

PARPis PARP inhibitors

FDA Food and Drug Administration

RCTs randomized controlled trials

VCP veliparib with carboplatin/paclitaxel

VT veliparib with temozolomide

gBRCAm germline BRCA mutation

ESMO European Society of Medical Oncology

HR hazard ratio

PFS progression-free survival

DFS disease-free survival

TNBC triple negative breast cancer

OS overall survival

ORR objective response rate

AEs adverse events

ASCO American Society of Clinical Oncology

Declarations

Data availability

The data underlying this article are available in the article and in its supplementary material.

Acknowledgements

Not applicable

Authors' Contributions

XYS and SYX conceived the study. A systematic review of the literature was performed by XYS, YML, XYS and XML and XYS were statistically analyzed. All authors contributed to the interpretation of the data. XYS, SYX, MH, and MJW wrote the first draft, and all authors contributed to writing, correcting, and approving the final version of the manuscript.

Conflicts of interest statement

The authors declare that they have no competing interests.

Funding

This work was supported by National Natural Science Foundation of China and Liaoning joint fund key program (No.U21A20422), National Natural Science Foundation of China (NSFC, No. 81972794), and Shenyang S&T Projects (20-204-4-22).

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Web links and urls

ClinicalTrials.gov.https://clinicaltrials.gov/

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021;71(3):209-49.
2. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA: a cancer journal for clinicians. 2022;72(1):7-33.
3. Zheng R, Zhang S, Zeng H, Wang S, Sun K, Chen R, et al. Cancer incidence and mortality in China, 2016. Journal of the National Cancer Center. 2022.
4. Kummerow KL, Du L, Penson DF, Shyr Y, Hooks MA. Nationwide trends in mastectomy for early-stage breast cancer. JAMA surgery. 2015;150(1):9-16.
5. Harbeck N, Gnant M. Breast cancer. Lancet (London, England). 2017;389(10074):1134-50.
6. McGuire KP, Santillan AA, Kaur P, Meade T, Parbhoo J, Mathias M, et al. Are mastectomies on the rise? A 13-year trend analysis of the selection of mastectomy versus breast conservation therapy in 5865 patients. Annals of surgical oncology. 2009;16(10):2682-90.
7. Zhang J, Sun J, Chen J, Yao L, Ouyang T, Li J, et al. Comprehensive analysis of BRCA1 and BRCA2 germline mutations in a large cohort of 5931 Chinese women with breast cancer. Breast cancer research and treatment. 2016;158(3):455-62.
8. Tutt A, Ashworth A. The relationship between the roles of BRCA genes in DNA repair and cancer predisposition. Trends Mol Med. 2002;8(12):571-6.
9. D'Andrea AD. Mechanisms of PARP inhibitor sensitivity and resistance. DNA repair. 2018;71:172-6.
10. Varol U, Kucukzeybek Y, Alacacioglu A, Somali I, Altun Z, Aktas S, et al. BRCA genes: BRCA 1 and BRCA 2. Journal of BUON : official journal of the Balkan Union of Oncology. 2018;23(4):862-6.
11. Carvalho JF, Kanaar R. Targeting homologous recombination-mediated DNA repair in cancer. Expert opinion on therapeutic targets. 2014;18(4):427-58.
12. Korhonen L, Brännvall K, Skoglösa Y, Lindholm D. Tumor suppressor gene BRCA-1 is expressed by embryonic and adult neural stem cells and involved in cell proliferation. Journal of neuroscience research. 2003;71(6):769-76.
13. Jasin M. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. Oncogene. 2002;21(58):8981-93.
14. Dantzer F, de La Rubia G, Ménissier-De Murcia J, Hostomsky Z, de Murcia G, Schreiber V. Base excision repair is impaired in mammalian cells lacking Poly(ADP-ribose) polymerase-1. Biochemistry. 2000;39(25):7559-69.
15. Brown JS, O'Carrigan B, Jackson SP, Yap TA. Targeting DNA Repair in Cancer: Beyond PARP Inhibitors. Cancer discovery. 2017;7(1):20-37.
16. Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. The New England journal of medicine. 2009;361(2):123-34.
17. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(7035):917-21.
18. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005;434(7035):913-7.
19. Helleday T. Homologous recombination in cancer development, treatment and development of drug resistance. Carcinogenesis. 2010;31(6):955-60.
20. Li H, Liu ZY, Wu N, Chen YC, Cheng Q, Wang J. PARP inhibitor resistance: the underlying mechanisms and clinical implications. Molecular cancer. 2020;19(1):107.
21. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
22. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods. 2010;1(2):97-111.
23. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ (Clinical research ed). 2011;343:d4002.
24. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. Journal of clinical epidemiology. 2001;54(10):1046-55.
25. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. The New England journal of medicine. 2018;379(8):753-63.
26. Litton JK, Hurvitz SA, Mina LA, Rugo HS, Lee KH, Gonçalves A, 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. Annals of oncology : official journal of the European Society for Medical Oncology. 2020;31(11):1526-35.
27. Chuang HC, Kapuriya N, Kulp SK, Chen CS, Shapiro CL. Differential anti-proliferative activities of poly(ADP-ribose) polymerase (PARP) inhibitors in triple-negative breast cancer cells. Breast cancer research and treatment. 2012;134(2):649-59.
28. Patel AG, De Lorenzo SB, Flatten KS, Poirier GG, Kaufmann SH. Failure of iniparib to inhibit poly(ADP-Ribose) polymerase in vitro. Clinical cancer research : an official journal of the American Association for Cancer Research. 2012;18(6):1655-62.
29. Han HS, Diéras V, Robson M, Palácová M, Marcom PK, Jager A, 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. Annals of oncology : official journal of the European Society for Medical Oncology. 2018;29(1):154-61.
30. Diéras V, Han HS, Kaufman B, Wildiers H, Friedlander M, Ayoub JP, et al. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology. 2020;21(10):1269-82.
31. Kummar S, Wade JL, Oza AM, Sullivan D, Chen AP, Gandara DR, et al. Randomized phase II trial of cyclophosphamide and the oral poly (ADP-ribose) polymerase inhibitor veliparib in patients with recurrent, advanced triple-negative breast cancer. Investigational new drugs. 2016;34(3):355-63.
32. Tutt ANJ, Garber JE, Kaufman B, Viale G, Fumagalli D, Rastogi P, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. The New England journal of medicine. 2021;384(25):2394-405.
33. Tung N, Garber JE. PARP inhibition in breast cancer: progress made and future hopes. NPJ Breast Cancer. 2022;8(1):47.

34. Robson M, Goessl C, Domchek S. Olaparib for Metastatic Germline BRCA-Mutated Breast Cancer. The New England journal of medicine. 2017;377(18):1792-3.
35. A.N.J.Tutt., J.Garber., R.D.Gelber., al. e. Pre-specified event driven analysisof Overall Survival (OS) in the OlympiA phase lll trial of adjuvant olaparib(OL) ingermline BRCA1/2 mutation (gBRCAm) associated breast cancer. ESMO VirtualPlenary2022.
36. Arun BK, Han HS, Kaufman B, Wildiers H, Friedlander M, Ayoub JP, et al. Efficacy and safety of first-line veliparib and carboplatin-paclitaxel in patients with HER2- advanced germline BRCA+ breast cancer: Subgroup analysis of a randomised clinical trial. European journal of cancer (Oxford, England : 1990). 2021;154:35-45.
37. Puhalla SL, Diéras V, Arun BK, Kaufman B, Wildiers H, Han HS, et al. Relevance of Platinum-free Interval and BRCA Reversion Mutations for Veliparib Monotherapy after Progression on Carboplatin/Paclitaxel for gBRCA Advanced Breast Cancer (BROCADE3 Crossover). Clinical cancer research : an official journal of the American Association for Cancer Research. 2021;27(18):4983-93.
38. Tassone P, Tagliaferri P, Perricelli A, Blotta S, Quaresima B, Martelli ML, et al. BRCA1 expression modulates chemosensitivity of BRCA1-defective HCC1937 human breast cancer cells. British journal of cancer. 2003;88(8):1285-91.
39. Birkbak NJ, Wang ZC, Kim JY, Eklund AC, Li Q, Tian R, et al. Telomeric allelic imbalance indicates defective DNA repair and sensitivity to DNA-damaging agents. Cancer discovery. 2012;2(4):366-75.
40. Mateo J, Lord CJ, Serra V, Tutt A, Balmaña J, Castroviejo-Bermejo M, et al. A decade of clinical development of PARP inhibitors in perspective. Annals of oncology : official journal of the European Society for Medical Oncology. 2019;30(9):1437-47.
41. Poggio F, Bruzzone M, Ceppi M, Conte B, Martel S, Maurer C, 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;3(4):e000361.
42. Chang XF, Ren XL, Yang JQ, Shi JJ, Bai JH, Cui MS, et al. Evaluation of efficacy and safety of PARP inhibitors in breast cancer: A systematic review and meta-analysis. Breast (Edinburgh, Scotland). 2021;59:44-50.
43. Sun X, Wang X, Zhang J, Zhao Z, Feng X, Liu L, et al. Efficacy and safety of PARP inhibitors in patients with BRCA-mutated advanced breast cancer: A meta-analysis and systematic review. Breast (Edinburgh, Scotland). 2021;60:26-34.
44. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Annals of oncology : official journal of the European Society for Medical Oncology. 2020;31(12):1623-49.
45. Slade D. PARP and PARG inhibitors in cancer treatment. Genes Dev. 2020;34(5-6):360-94.
46. Cortesi L, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. Target Oncol. 2021;16(3):255-82.
47. Loibl S, O'Shaughnessy J, Untch M, Sikov WM, Rugo HS, McKee MD, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. The Lancet Oncology. 2018;19(4):497-509.
48. Fasching PA, Link T, Hauke J, Seither F, Jackisch C, Klare P, et al. Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency (GeparOLA study). Annals of oncology : official journal of the European Society for Medical Oncology. 2021;32(1):49-57.

Figures

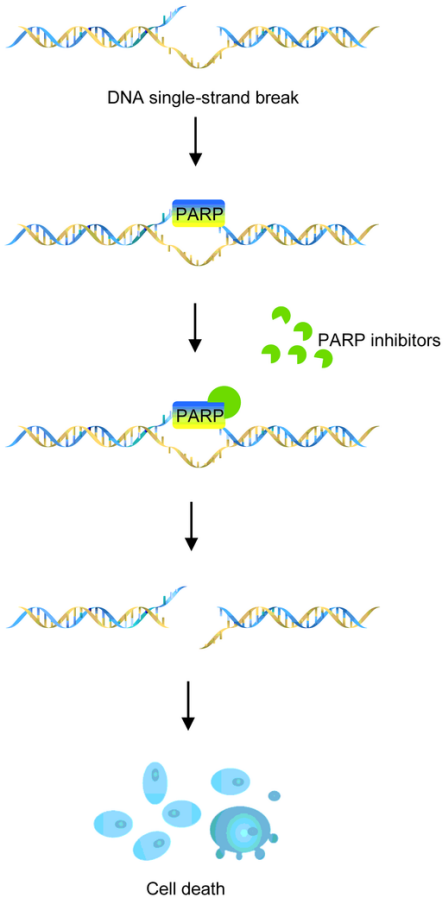


Figure 1

Mechanism of action of PARPis.

PARPis can kill BRCA-mutated tumor cells by the synthetic lethality.

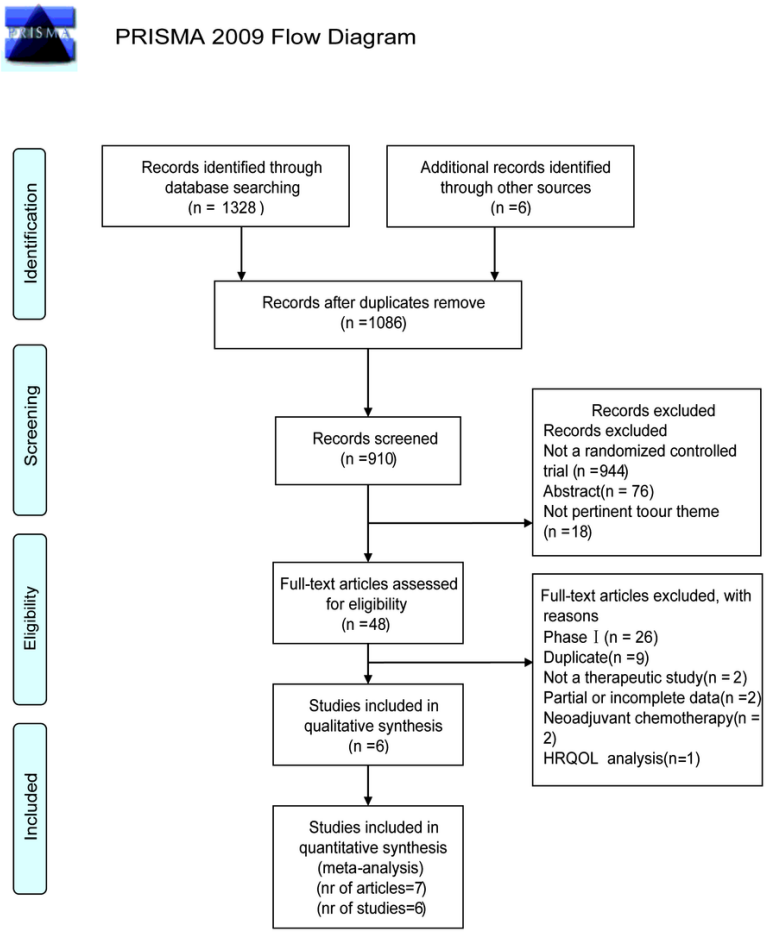
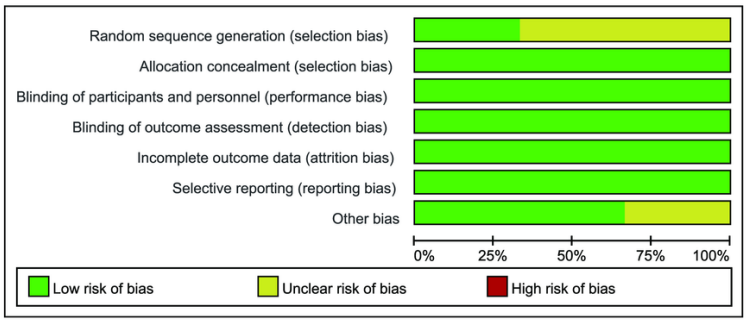


Figure 2

The PRISMA flow diagram.

This diagram illustrates the inclusion and exclusion of studies.

a



b

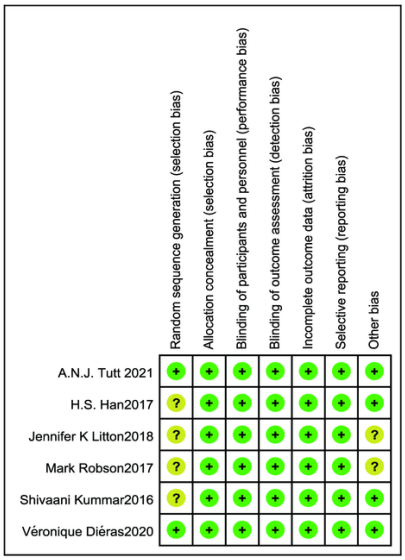


Figure 3

Risk of bias analysis.

(a) Risk of bias graph. (b) risk of bias summary.

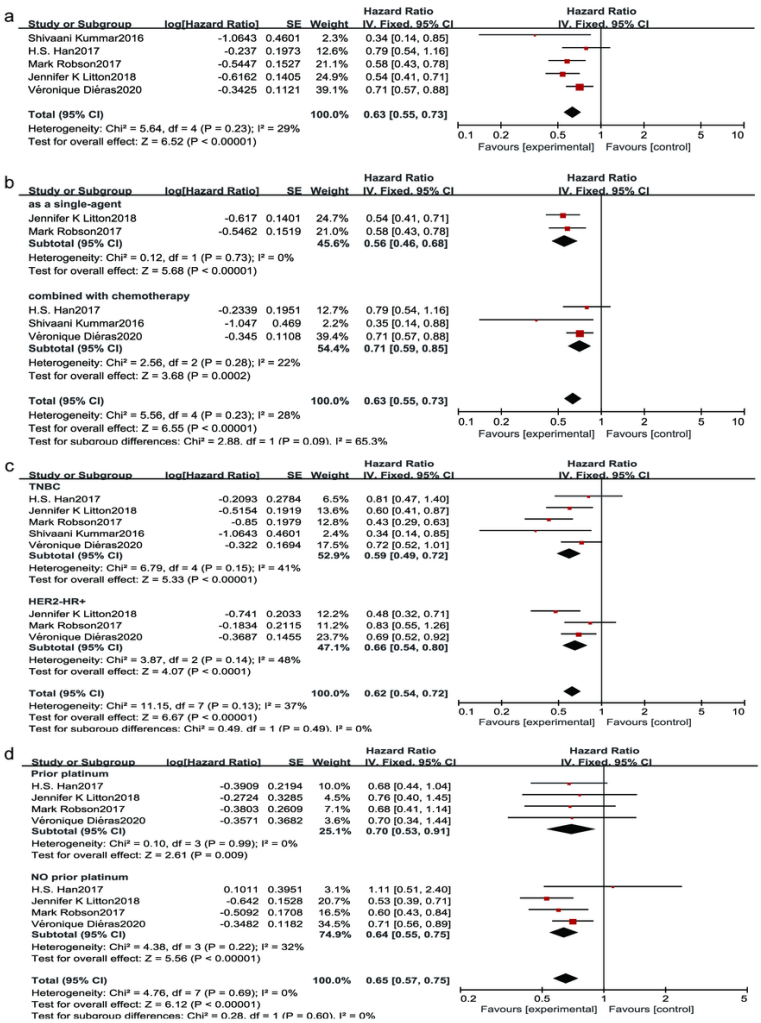


Figure 4

forest Plots for PFS and its subgroups comparing PARPis to control.

(a) PFS. (b) comparing PFS in single-agent and combination with chemotherapy. (c) comparing PFS in TNBC and $HER2^{-}HR^{+}$. (d) comparing PFS in prior platinum and no prior platinum.

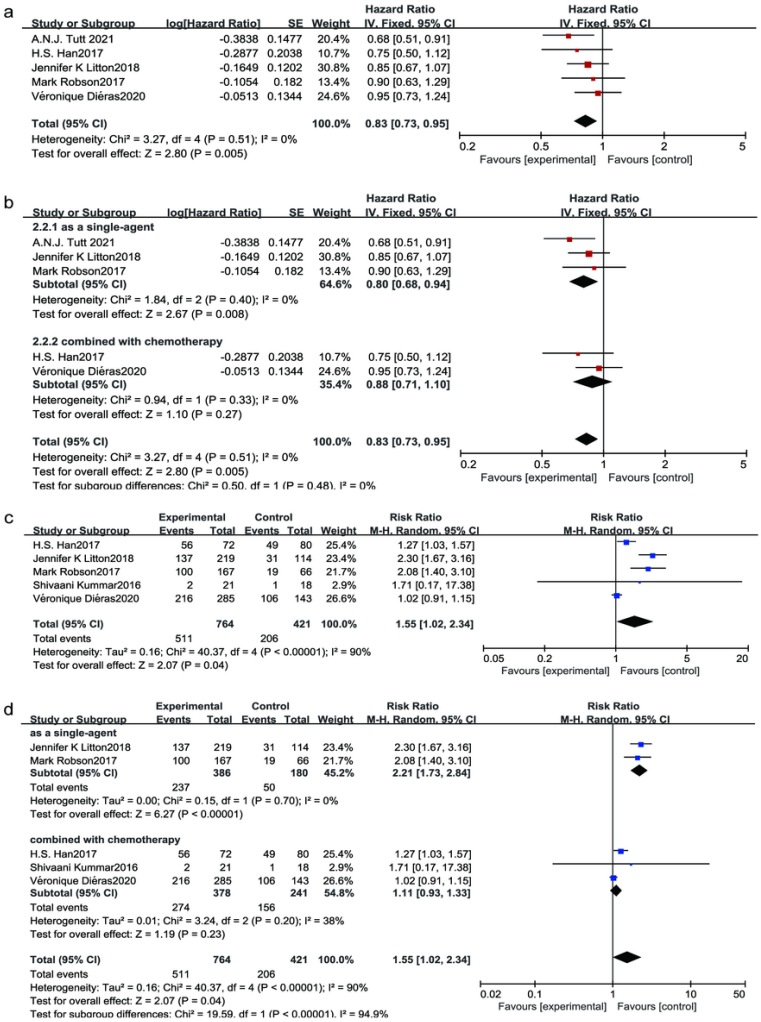


Figure 5

Forest Plots for OS and ORR comparing PARPis to control.

(a) OS. (b) comparing OS in single-agent and combination with chemotherapy. (c) ORR. (d) comparing ORR in single-agent and combination with chemotherapy.

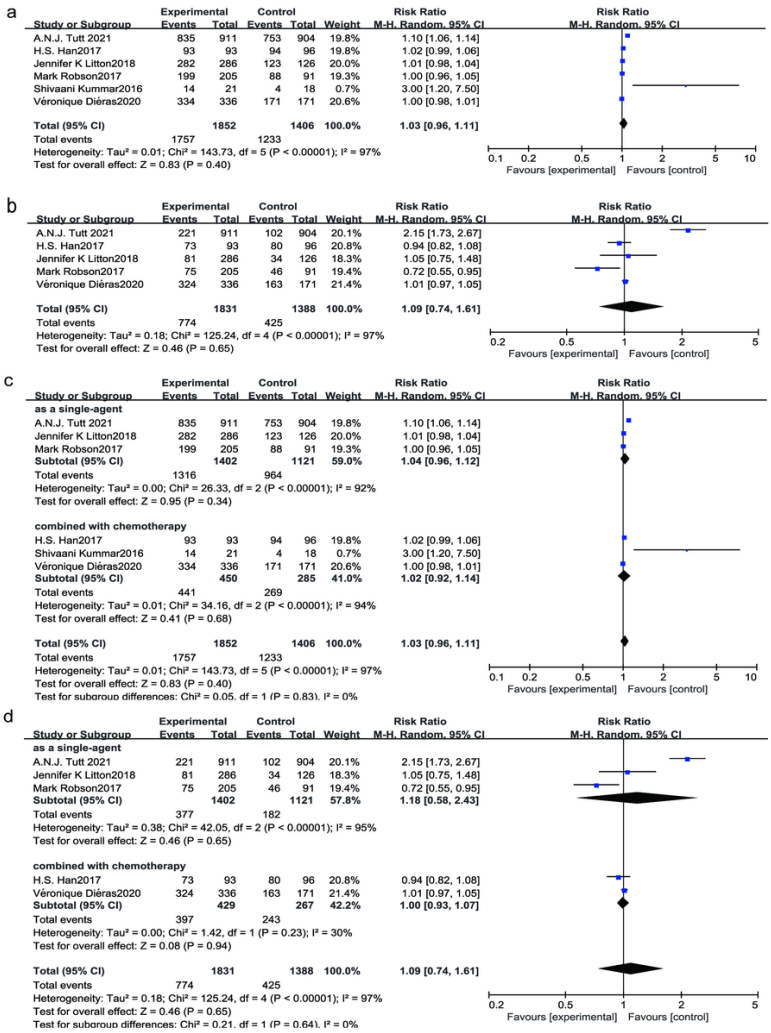


Figure 6

Forest Plots for AEs and AEs of grade ≥3 comparing PARPis to control.

(a) AEs. (b) AEs of grade ≥3. (c) comparing AEs in single-agent and combination with chemotherapy. (d) comparing AEs of grade ≥3 in single-agent and combination with chemotherapy.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SUPPLEMENTARYMATERIAL.doc