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Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer (Review)

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[Intervention Review]

Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer

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ABSTRACT

Background

Ovarian cancer is the sixth most common cancer in women world-wide. Epithelial ovarian cancer (EOC) is the most common; three-quarters of women present when disease has spread outside the pelvis (stage III or IV). Treatment consists of a combination of surgery and platinum-based chemotherapy. Although initial responses to chemotherapy are good, most women with advanced disease will relapse.

PARP (poly (ADP-ribose) polymerase) inhibitors (PARPi), are a type of anticancer treatment that works by preventing cancer cells from repairing DNA damage, especially in those with breast cancer susceptibility gene (*BRCA*) variants. PARPi offer a different mechanism of anticancer treatment from conventional chemotherapy.

Objectives

To determine the benefits and risks of poly (ADP-ribose) polymerase) inhibitors (PARPi) for the treatment of epithelial ovarian cancer (EOC).

Search methods

We identified randomised controlled trials (RCTs) by searching the Cochrane Central Register of Controlled Trials (Central 2020, Issue 10), Cochrane Gynaecological Cancer Group Trial Register, MEDLINE (1990 to October 2020), Embase (1990 to October 2020), ongoing trials on www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials, the National Research Register (NRR), FDA database and pharmaceutical industry biomedical literature.

Selection criteria

We included trials that randomised women with EOC to PARPi with no treatment, or PARPi versus conventional chemotherapy, or PARPi together with conventional chemotherapy versus conventional chemotherapy alone.

Data collection and analysis

We used standard Cochrane methodology. Two review authors independently assessed whether studies met the inclusion criteria. We contacted investigators for additional data. Outcomes included overall survival (OS), objective response rate (ORR), quality of life (QoL) and rate of adverse events.

Main results

We included 15 studies (6109 participants); four (3070 participants) with newly-diagnosed, advanced EOC and 11 (3039 participants) with recurrent EOC. The studies varied in types of comparisons and evaluated PARPi. Eight studies were judged as at low risk of bias in most of the domains. Quality of life data were generally poorly reported. Below we present six key comparisons. The majority of participants had *BRCA* mutations, either in their tumour (s*BRCA*mut) and/or germline (g*BRCA*mut), or homologous recombination deficiencies (HRD) in their tumours.

Newly diagnosed EOC

Overall, four studies evaluated the effect of PARPi in newly-diagnosed, advanced EOC. Two compared PARPi with chemotherapy and chemotherapy alone. OS data were not reported. The combination of PARPi with chemotherapy may have little to no difference in progression-free survival (PFS) (two studies, 1564 participants; hazard ratio (HR) 0.82, 95% confidence interval (CI 0).49 to 1.38; *very low-certainty evidence)*(no evidence of disease progression at 12 months' 63% with PARPi versus 69% for placebo).

PARPi with chemotherapy likely increases any severe adverse event (SevAE) (grade 3 or higher) slightly (45%) compared with chemotherapy alone (51%) (two studies, 1549 participants, risk ratio (RR) 1.13, 95% CI 1.07 to 1.20; *high-certainty evidence*). PARPi combined with chemotherapy compared with chemotherapy alone likely results in little to no difference in the QoL (one study; 744 participants, MD 1.56 95% CI -0.42 to 3.54*; moderate-certainty evidence).*

Two studies compared PARPi monotherapy with placebo as maintenance after first-line chemotherapy in newly diagnosed EOC. PARPi probably results in little to no difference in OS (two studies, 1124 participants; HR 0.81, 95%CI 0.59 to 1.13; *moderate-certainty evidence*) (alive at 12 months 68% with PARPi versus 62% for placebo). However, PARPi may increase PFS (two studies, 1124 participants; HR 0.42, 95% CI 0.19 to 0.92; *low-certainty evidence*) (no evidence of disease progression at 12 months' 55% with PARPi versus 24% for placebo). There may be an increase in the risk of experiencing any SevAE (grade 3 or higher) with PARPi (54%) compared with placebo (19%)(two studies, 1118 participants, RR 2.87, 95% CI 1.65 to 4.99; *very low-certainty evidence*), but the evidence is very uncertain. There is probably a slight reduction in QoL with PARPi, although this may not be clinically significant (one study, 362 participants; MD -3.00, 95%CI -4.48 to -1.52; *moderate-certainty evidence).*

Recurrent, platinum-sensitive EOC

Overall, 10 studies evaluated the effect of PARPi in recurrent platinum-sensitive EOC. Three studies compared PARPi monotherapy with chemotherapy alone. PARPi may result in little to no difference in OS (two studies, 331 participants; HR 0.95, 95%CI 0.62 to 1.47; *low-certainty evidence*) (percentage alive at 36 months 18% with PARPi versus 17% for placebo). Evidence is very uncertain about the effect of PARPi on PFS (three studies, 739 participants; HR 0.88, 95%CI 0.56 to 1.38; *very low-certainty evidence*)(no evidence of disease progression at 12 months 26% with PARPi versus 22% for placebo). There may be little to no difference in rates of any SevAE (grade 3 or higher) with PARPi (50%) than chemotherapy alone (47%) (one study, 254 participants; RR 1.06, 95%CI 0.80 to 1.39; *low-certainty evidence*).

Four studies compared PARPi monotherapy as maintenance with placebo. PARPi may result in little to no difference in OS (two studies, 560 participants; HR 0.88, 95%CI 0.65 to 1.20; *moderate-certainty evidence*)(percentage alive at 36 months 21% with PARPi versus 17% for placebo). However, evidence suggests that PARPi as maintenance therapy results in a large PFS (four studies, 1677 participants; HR 0.34, 95% CI 0.28 to 0.42; *high-certainty evidence*)(no evidence of disease progression at 12 months 37% with PARPi versus 5.5% for placebo). PARPi maintenance therapy may result in a large increase in any SevAE (51%) (grade 3 or higher) than placebo (19%)(four studies, 1665 participants, RR 2.62, 95%CI 1.85 to 3.72; *low-certainty evidence*). PARPi compared with chemotherapy may result in little or no change in QoL (one study, 229 participants, MD 1.20, 95%CI -1.75 to 4.16; *low-certainty evidence).*

Recurrent, platinum-resistant EOC

Two studies compared PARPi with chemotherapy. The certainty of evidence in both studies was graded as very low. Overall, there was minimal information on the QoL and adverse events.

Authors' conclusions

PARPi maintenance treatment after chemotherapy may improve PFS in women with newly-diagnosed and recurrent platinum-sensitive EOC; there may be little to no effect on OS, although OS data are immature. Overall, this is likely at the expense of an increase in SevAE. It is disappointing that data on quality of life outcomes are relatively sparse. More research is needed to determine whether PARPi have a role to play in platinum-resistant disease.

PLAIN LANGUAGE SUMMARY

Do PARP inhibitors improve survival in women with ovarian cancer, and what are the side effects?

Key messages

Compared to an inactive 'dummy' medication (placebo), PARP (poly (ADP-ribose) polymerase) inhibitors (PARPi) given as daily tablet treatment after chemotherapy (maintenance treatment):

- may have little to no effect on the amount of time someone with advanced epithelial ovarian cancer (EOC) will live overall (although this outcome may change as more data become available);

- probably delay disease progression in women with newly-diagnosed EOC;

- probably delay disease progression in women with recurrent platinum-sensitive EOC;

- probably cause an increase in the risk of severe side effects.

We are very uncertain about whether a delay in disease progression has a beneficial effect on quality of life, as data are inconsistently reported, but the limited data suggest that PARPi may improve symptoms by delaying disease progression.

What is epithelial ovarian cancer?

EOC is a cancer that arises from the lining (epithelium) of the ovaries, fallopian tube and the abdominal cavity (peritoneum). Because cells have immediate access to the abdominal cavity, EOC often presents at a late stage. Initial treatment is with a combination of surgery, ideally to remove all visible disease, and chemotherapy. Disease will recur in most people and further treatment is required. Scientists have therefore been looking at new ways to stop cancer cells growing.

What are PARP inhibitors?

Being able to repair DNA is vital to cell survival. Normal cells have more than one DNA repair pathway. However, cancer cells often have defects in DNA repair pathways. The *BRCA* gene is involved in DNA repair and is commonly damaged (mutated) in people with EOC. Blocking another DNA repair pathway with a PARPi stops cancer cells from repairing DNA, causing cells to die. PARPi therefore differ from conventional chemotherapy, and are likely to work better in *BRCA*-mutated cells.

What did we want to find out?
We wanted to find out if PARPi treatment, given either with chemotherapy or afterwards as a maintenance treatment:

- delays death;

- delays disease progression;

- improves quality of life;

- has any unwanted side effects.

What did we do?
We searched for randomised control trials (clinical studies where the treatment or care people receive is chosen at random) from 1990 to Oct 2020. We searched for studies using PARPi in women with newly-diagnosed EOC and those whose cancer had returned, either more than six months after stopping platinum-based chemotherapy (platinum-sensitive relapse) or within six months of platinum-based chemotherapy (platinum-resistant relapse). We collected data, summarised results, and rated our confidence in the evidence, based on factors, such as whether women and their doctors knew what treatment they were having, how studies were conducted, and how many women were included in studies.

What did we find?

We found 15 randomised trials of PARP inhibitors (6109 participants) (four studies including 3070 women with newly-diagnosed EOC (first-line treatment) and 11 studies including 3039 women with recurrent cancer). We found 17 ongoing studies.

First-line treatment

PARPi, in addition to chemotherapy, given**during** chemotherapy:

— made little to no difference in how long ovarian cancer took to return (progress/recur);

— probably slightly increased serious side effects experience by women during chemotherapy.

However, continuing PARPi after chemotherapy, compared to placebo as a maintenance treatment, often over many months, probably delayed the cancer recurring/progressing.

PARPi maintenance treatment **after** chemotherapy:

— probably delayed recurrence of ovarian cancer (no disease progression at 12 months: 55% with PARPi versus 24% for placebo);

— probably little to no difference in how long women survived overall, despite delay in recurrence, although more information may change this outcome over time;

— may be at the expense of an increase in the risk of severe side effects with PARPi, although evidence for this is very uncertain.

Treatment of platinum-sensitive recurrent EOC

Compared to conventional chemotherapy treatment, PARPi:

— may have little to no difference in terms of overall survival, delay in progression of disease, quality of life and risk of serious side effects.

All of these studies only included patients with *BRCA* mutations, so it is not clear whether these results would be similar in non-*BRCA* patients.

PARPi as maintenance treatment, after chemotherapy for platinum-sensitive ovarian cancer:

— had a large effect on delaying recurrence of disease (no disease progression at 12 months 37% with PARPi versus 5.5% for placebo);

— had little to no difference in the overall survival time after treatment;

— may be at the expense of a large increase in the risk of severe side effects.

Treatment of platinum-resistant recurrent EOC

PARPi compared with chemotherapy:

— we are very uncertain about the outcomes, as the quality of the evidence was very low.

What limited our confidence in the evidence?

Although half of the studies were at low risk of bias, some studies used methods that risk introducing bias and some studies were small. Reporting of quality of life data overall was poor or different methods were used, limiting our ability to combine data on these outcomes.

How up to date is this review?

The evidence in this review is current to October 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table - Newly-diagnosed EOC: PARPi with chemotherapy compared with chemotherapy alone

Newly-diagnosed EOC: PARPi with chemotherapy compared with chemotherapy alone

Patient or population: newly-diagnosed EOC
Setting: specialist hospital
Intervention: PARPi with chemotherapy
Comparison: Chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Chemotherapy alone	Risk with PARPi with chemotherapy				
Overall survival - not reported	-	-	-	-	-	
Progression-free survival (PFS) assessed with: alive without evidence of disease progression follow-up: 26 months	Moderate 630 per 1000[a]	**685 per 1000** (529 to 797)	**HR 0.82** (0.49 to 1.38) [survival without evidence of disease progression]	1564 (2 RCTs)	⊕⊝⊝⊝ Very low[b,c,d,e]	PARPi with chemotherapy probably results in little to no difference in progression-free survival.
Quality of life (QoL) assessed with: European Organization for Research and Treatment of Cancer Questionnaire Scale from: 0 to 100	The mean quality of life was **-2.89**	**1.56 higher** (0.42 lower to 3.55 higher)	-	744 (1 RCT)	⊕⊕⊕⊝ Moderate[c,d]	PARPi with chemotherapy likely results in little to no difference in the quality of life.
Any severe adverse event (grade 3 or higher) (G3+ SevAE) assessed with: NCI-CTCAE	447 per 1000	**505 per 1000** (478 to 536)	**RR 1.13** (1.07 to 1.20)	1549 (2 RCTs)	⊕⊕⊕⊕ High[c]	PARPi with chemotherapy likely increases any severe adverse event (grade 3 or higher) slightly.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **EOC:** epithelial ovarian cancer; **HR:** hazard Ratio; **PARPi:** poly (ADP-ribose) polymerase) inhibitors; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_426407798344781835.

[a] The control risk of being alive without evidence of disease progression at 12 months (63%) was taken from the control arm of the VELIA study.
[b] Downgraded by two levels for inconsistency (I2>90%)
[c] Note: Indirectness one of the trials (PAOLA-1) included bevacizumab in its chemotherapy regimen.
[d] Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing a line of no effect)
[e] Note: A single study contributed data for this outcome

Summary of findings 2. Summary of findings table - Newly-diagnosed EOC: PARPi monotherapy compared with placebo (maintenance therapy)

Newly diagnosed EOC: PARPi monotherapy compared with placebo (maintenance therapy)

Patient or population: newly-diagnosed EOC
Setting: specialist hospital
Intervention: PARPi monotherapy (maintenance)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PARPi monotherapy (maintenance)				

Overall survival (OS) assessed with: number alive follow-up: range 14 months to 41 months	Moderate 620 per 1000[a]	**679 per 1000** (583 to 754)	**HR 0.81** (0.59 to 1.13) [survival]	1124 (2 RCTs)	⊕⊕⊕⊖ Moderate[b,c]	PARPi monotherapy likely results in little to no difference in overall survival, although this is based on immature data and more mature data may alter this result.
Progression-free survival (PFS) assessed with: alive without evidence of disease progression follow-up: range 14 months to 41 months	Low 240 per 1000[d]	**549 per 1000** (269 to 763)	**HR 0.42** (0.19 to 0.92) [survival without evidence of disease progression]	1124 (2 RCTs)	⊕⊕⊖⊖ Low[e,f]	PARPi monotherapy may increase progression-free survival.
Quality of Life (QoL) assessed with: The Trial Outcome Index (TOI) score on the Functional Assessment of Cancer Therapy–Ovarian Cancer questionnaire	The mean quality of Life was **3.30**	MD **3 lower** (4.48 lower to 1.52 lower)[g]	-	362 (1 RCT)	⊕⊕⊕⊖ Moderate[h,i,j]	PARPi monotherapy probably results in a slight reduction in Quality of Life, although this may not be clinically meaningful.
Any severe adverse event (grade 3 or higher) (G3+ SevAE) assessed with: NCI-CTCAE	187 per 1000	**537 per 1000** (309 to 934)	**RR 2.87** (1.65 to 4.99)	1118 (2 RCTs)	⊕⊖⊖⊖ Very low[i,k]	PARPi monotherapy may increase/have little to no effect on any severe adverse event (grade 3 or higher) but the evidence is very uncertain.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **EOC:** epithelial ovarian cancer;**HR:** hazard ratio; **MD:** mean difference;**PARPi:** poly (ADP-ribose) polymerase) inhibitors; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_426409458601301064.

[a] The control risk of being alive at 36 months (62%) was taken from the control arm of the ICON7 study.
[b] Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing a line of no effect)
[c] Note: Analysis based on immature data
[d] The control risk of being alive without evidence of disease progression at 12 months (24%) was taken from the control arm of the PRIMA study.
[e] Downgraded by two levels due to inconsistency (indicator of statistical heterogeneity I2 >90%), which was probably caused by the population recruited in both studies (SOLO1 included only women with BRCA mutation)
[f] Note: The evidence was not downgraded for imprecision despite wide confidence intervals around the effect estimate as the pooled effect still indicates the benefit of PARPi use over placebo.
[g] adjusted mean change from baseline to 2 years
[h] Note: data limited to a population of patients with BRCA mutation
[i] Downgraded by one level due to imprecision (wide confidence interval around the effect estimate)
[j] Note: A single study contributed data for this outcome
[k] Downgraded by two levels due to inconsistency (indicator of statistical heterogeneity I2 >80%)

Summary of findings 3. Summary of findings table - Platinum-sensitive recurrent EOC: PARPi monotherapy compared with chemotherapy

Platinum-sensitive recurrent EOC: PARPi monotherapy compared with chemotherapy

Patient or population: platinum-sensitive recurrent EOC
Setting: specialist hospital
Intervention: PARPi monotherapy
Comparison: Chemotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Chemotherapy	Risk with PARPi monotherapy				
Overall survival (OS) assessed with: number alive at 36 months follow-up: range 4 months to 14 months	Low 166 per 1000[a]	**182 per 1000** (71 to 328)	**HR 0.95** (0.62 to 1.47) [survival]	331 (2 RCTs)	⊕⊕⊖⊖ Low[b,c,d]	PARPimonotherapy may result in little to no difference in overall survival.
Progression-free survival (PFS) assessed with: alive without evidence of disease progression at 12 months	Low		**HR 0.88** (0.56 to 1.38)	739 (3 RCTs)	⊕⊖⊖⊖ Very low[c,d,f,g]	The evidence is very uncertain about the effect of PARPi-

follow-up: range 4 months to 29 months	220 per 1000[e]	**264 per 1000** (124 to 428)	[survival without evidence of disease progression]			monotherapy on progression free survival.
Quality of Life (QoL) assessed with: The Trial Outcome Index (TOI) score on the Functional Assessment of Cancer Therapy–Ovarian Cancer questionnaire	The mean quality of Life was **-3.6** points	MD **1.2 points higher** (1.76 lower to 4.16 higher)	-	229 (1 RCT)	⊕⊕⊖⊖ Low[f,h,i]	The evidence suggests that PARPi monotherapy results in little to no difference in QoL.
Any severe adverse event (grade 3 or higher) (G3+ SevAE) assessed with: NCI-CTCAE	474 per 1000	**502 per 1000** (379 to 658)	**RR 1.06** (0.80 to 1.39)	254 (1 RCT)	⊕⊕⊖⊖ Low[d,f]	The evidence suggests that PARPi monotherapy results in little to no difference in any SevAE (grade 3 or higher).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard Ratio; **MD:** mean difference; **PARPi:** poly (ADP-ribose) polymerase) inhibitors; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_426414839953371161.

[a] The control risk of being alive at 36 months (16.6%) was taken from the control arm (conventional treatment) of the ICON4 study.
[b] Note: both studies were judged at high risk of bias due to study design (open-label); however, the evidence was not downgraded as OS is a hard, objective outcome.
[c] Downgraded by one level due to indirectness (50% of participants in the ICEBERG3 trial were platinum-resistant).
[d] Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing a line of no effect)
[e] The control risk of being alive without evidence of disease progression at 12 months (22%) was taken from the control arm (chemotherapy) of Oza 2015 study.
[f] Downgraded by one level due to risk of bias (open-label studies)
[g] Downgraded by two levels due to inconsistency (indicator of statistical heterogeneity I2 > 70%)
[h] Note: The evidence is limited only to participants with BRCA mutation
[i] Downgraded by one level due to imprecision (wide confidence interval around the effect estimate)

Summary of findings 4. Summary of findings table - Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy)

Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy)

Patient or population: platinum-sensitive recurrent EOC
Setting: specialist hospital
Intervention: PARPi monotherapy (maintenance therapy)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with PARPi monotherapy (maintenance therapy)				
Overall survival (OS) assessed with: number alive at 36 months follow-up: NR months	Low 166 per 1000[a]	**206 per 1000** (116 to 311)	**HR 0.88** (0.65 to 1.20) [alive]	560 (2 RCTs)	⊕⊕⊕⊖ Moderate[b,d,e]	PARPi monotherapy (maintenance therapy) probably results in little to no difference in OS.
Progression-free survival (PFS) assessed with: number alive without evidence of disease progression at 12 months follow-up follow-up: median 17 months	Low 55 per 1000[c]	**373 per 1000** (296 to 444)	**HR 0.34** (0.28 to 0.42) [survival without evidence of disease progression]	1677 (4 RCTs)	⊕⊕⊕⊕ High[b]	PARPi monotherapy (maintenance therapy) results in a large increase in PFS.
Quality of Life - European Quality of Life 5-dimensionsquestionnaire - Participants with BRCA mutation (QoL) assessed with: European Quality of Life–5 Dimensions questionnaires Health Utility Index	The mean quality of Life - European Quality of Life 5-dimensionsquestionnaire - Participants with BR-	**MD 0.02 points higher** (0.01 lower to 0.05 higher)	-	339 (1 RCT)	⊕⊕⊕⊖ Moderate[f]	PARPi monotherapy (maintenance therapy) probably results in little to no difference in QoL.

	CA mutation was **0.783** points					
Any severe adverse event (grade 3 or higher) (G3+ SevAE) assessed with: NCI-CTCAE	193 per 1000	**506 per 1000** (358 to 719)	**RR 2.62** (1.85 to 3.72)	1665 (4 RCTs)	⊕⊕⊖⊖ Low[d,g]	The evidence suggests that PARPi monotherapy (maintenance therapy) results in a large increase in any SevAE (grade 3 or higher).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard Ratio; **MD:** mean difference; **PARPi:** poly (ADP-ribose) polymerase) inhibitors;**RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
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See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_426425278373060041.

[a] The control risk of being alive at 36 months (16.6%) was taken from the control arm (conventional treatment) of the ICON4 study.
[b] Note: One study contributing data to the analysis for this outcome included only participants with BRCA mutation.
[c] The control risk of being alive without evidence of disease progression at 12 months (5.5%, an average) was taken from the control arms of ARIEL3 and Study 19 (Ledermann 2012) studies.
[d] Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing a line of no effect)
[e] Note: Analysis based on immature data
[f] Downgraded by one level due to imprecision (only a subset of participants from a single study contributed data to the analysis for this outcome).
[g] Downgraded by two levels due to inconsistency (indicator of statistical heterogeneity I2 >70%)

Summary of findings 5. Summary of findings table - Platinum-sensitive recurrent EOC: PARPi with chemotherapy compared with chemotherapy alone

Platinum-sensitive recurrent EOC: PARPi with chemotherapy compared with chemotherapy alone

Patient or population: platinum-sensitive recurrent EOC
Setting: specialist hospital
Intervention: PARPi with chemotherapy

Comparison: Chemotherapy alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Chemotherapy alone	Risk with PARPi with chemotherapy				
Overall survival (OS) assessed with: not reported	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	(1 RCT)	-	
Progression-free survival (PFS) assessed with: e of disease progression at 12 months follow-up follow-up: median 33 months	Moderate 220 per 1000	**224 per 1000** (158 to 313)	**HR 1.02** (0.69 to 1.51)	75 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c,d,e]	The evidence is very uncertain about the effect of PARPi with chemotherapy on progression-free survival.
Quality of Life - not reported	-	-	-	-	-	
Any severe adverse event (grade 3 or higher) (G3+ SevAE) assessed with: not reported	573 per 1000	**654 per 1000** (510 to 843)	**RR 1.14** (0.89 to 1.47)	156 (1 RCT)	⊕⊕⊖⊖ Low[b,d]	PARPi with chemotherapy may result in little to no difference in any severe adverse event (grade 3 or higher).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard Ratio; **PARPi:** poly (ADP-ribose) polymerase) inhibitors; **RCT:** randomised controlled trial;**RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_426427989803404645.

[a] The control risk of being alive without evidence of disease progression at 12 months (22%) was taken from the control arm (chemotherapy) of Oza 2015 study.
[b] Downgraded by one level due to risk of bias (study design: open-label)
[c] Downgraded by one level due to risk of bias (concern over early closure of Kummar 2015)
[d] Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing a line of no effect)
[e] Note: a single, small (<100 participants) study contributed data to the analysis for this outcome

Summary of findings 6. Summary of findings table - Platinum-resistant recurrent EOC: PARPi monotherapy compared with chemotherapy

Platinum-resistant recurrent EOC: PARPi monotherapy compared with chemotherapy

Patient or population: platinum-resistant recurrent EOC
Setting: specialist hospital
Intervention: PARPi monotherapy
Comparison: Chemotherapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Chemotherapy	Risk with PARPi monotherapy				
Overall survival - not reported	-	-	-	-	-	
Progression-free survival - not reported	-	-	-	-	-	
Any severe adverse events (grade 3 or higher) (G3+ SevAE) assessed with: unclear	515 per 1000	**598 per 1000** (407 to 876)	**RR 1.16** (0.79 to 1.70)	100 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c]	The evidence suggests that PARPi monotherapy results in little to no difference in any SevAE (grade 3 or higher).
Quality of Life - not reported	-	-	-	-	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **PARPi:** poly (ADP-ribose) polymerase) inhibitors; **RCT:** randomised controlled trial;**RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_426368977301116995.

[a] Downgraded by one level due to risk of bias (study design: open-label)
[b] Downgraded by one level due to imprecision (wide confidence interval around the effect estimate crossing a line of no effect)
[c] Downgraded by one level due to publication bias (data available only as a conference abstract).

BACKGROUND

This is an updated version of a review first published in 2010 in the *Cochrane Database of Systematic Reviews* (Issue 6).

Description of the condition

In 2018, worldwide, around 300,000 women were diagnosed with epithelial ovarian cancer (EOC), and 184,799 died from the disease, corresponding to an annual incidence of 6.6 cases per 100,000 women, an annual mortality rate of 4.3 deaths per 100,000, and a cumulative lifetime risk of 0.5% (GLOBOCAN 2018). In terms of incidence, it is the sixth most common cancer, and it is the seventh most common cause of cancer death in women. EOC poses a diagnostic challenge: the onset is often insidious; the symptoms are vague; and may mimic other, non-malignant, conditions. This may lead to a delay in diagnosis and currently three-quarters of women with EOC are diagnosed when the disease has spread throughout the abdomen (stage III or IV) (Lheureux 2019), when the five-year survival is 20% to 30% (Jemal 2008). EOC accounts for 90% of all ovarian cancers and typically presents in post-menopausal women, with a peak incidence in women in their early sixties, although it does occur in younger women, often associated with genetic predispositions (Quinn 2001).

More recent data suggest that the origin of EOC may often be the lining of the fallopian tubes. Intra-epithelial precursor lesions (so-called serous tubal intra-epithelial carcinoma or STIC) are commonly found in the fimbrial ends of fallopian tubes removed from women at high risk of developing EOC due to breast cancer susceptibility gene (*BRCA)* variants (*BRCA*-mut) (Erickson 2013). These STIC lesions are microscopic and may explain why EOC is difficult to identify at an early stage, since it has immediate access to the abdominal cavity and often does not typically arise from an ovarian cyst, which could be seen on an ultrasound scan. Sadly, this has prohibited an effective population level screening test for EOC (Menon 2021).

The development of rapid sequencing technology has enabled scientists and clinicians an opportunity to better understand the biology of EOC. It is now clear that different histological subtypes of EOC have characteristic somatic landscapes. Endometrioid EOC commonly associates with pathogenic variants in *PTEN (p*hosphatase and tensin homolog), clear cell EOC often harbours pathogenic variants in *ARID1A* and the majority of high-grade serous EOC demonstrate a pathogenic variant in *TP53* (Ledermann 2016). The Cancer Genome Atlas was a groundbreaking collaborative study in which numerous cancer types underwent comprehensive molecular characterisation; the first results published were from EOC (TCGA 2016). These data demonstrated an overrepresentation of *BRCA1/2* pathogenic variants and the importance of homologous recombination dysfunction (HRD) in the oncogenesis of EOC. Such insights into EOC biology have enabled the development of novel and targeted therapies, which have shown promise in clinical trials. Herein we will explore the utility of one such molecular targeted therapy: poly (ADP-ribose) polymerase (PARP) (inhibition.

Description of the intervention

Management of advanced EOC consists of a combination of debulking surgery and platinum-based chemotherapy, with or without the addition of a taxane (Stewart 1999). A recently updated Cochrane Review found that there was no difference in survival in women with The International Federation of Gynecology and Obstetrics (FIGO) stage IIC-IV disease, if surgery were performed before or after the first few cycles of chemotherapy (Coleridge 2021). However, despite good initial responses to platinum agents and taxanes, most women have disease relapse, require further treatment with chemotherapy, and eventually develop resistance to conventional chemotherapeutic agents; only around 30% of women are cured using the current treatment modalities (Lheureux 2019). Response to platinum-based chemotherapy is not uniform across all patients. At diagnosis, EOC that responds to platinum-based therapy is considered platinum-sensitive. Platinum-resistant EOC was originally defined as disease recurrence/progression within six months of completion of first-line platinum-based chemotherapy. The term now also applies to include patients progressing within six months after multiple lines of chemotherapy, or to those who do not respond to platinum-based chemotherapy in a relapsed setting. These classifications are important when assessing new treatments, as they speak to the biology of the cancer and also enable an evaluation in the context of current therapies. It is these conventional therapies against which new interventions are often measured, acting as a control.

Conventional chemotherapeutic agents have activity on all rapidly dividing cells, hence the common side effects such as bone marrow suppression and mucositis (inflammation and ulceration of the mucous membranes lining the digestive tract). Increasing knowledge of the genetic basis for cancer has led to the development of novel 'targeted' agents, which target cancer-specific pathways. It is hoped that these reagents will preferentially affect cancer cells and spare normal cells, thereby reducing the toxic side effects of chemotherapy, in addition to having an enhanced therapeutic effect. One such class of targeted agent are the PARP inhibitors (PARPi). These can be used as both an adjunct to conventional chemotherapy, or as a maintenance treatment after completion of conventional chemotherapy.

How the intervention might work

DNA repair inhibition

Cancers arise through a process of sequential mutations that lead to the development of dysfunctional and accelerated cellular growth. Whereby a driver mutation affects the normal molecular mechanisms that ensure DNA fidelity, these sequential mutations happen and are maintained at a faster rate, enabling a cancer to be more adaptive (Chiang 2008). Therefore, given this survival advantage, many cancer cells harbour mutations that render their ability to repair DNA damage less effectual. Although an evolutionary strength, this reduced ability to repair DNA damage also provides a potential therapeutic target. Indeed, many current therapies for cancer (cytotoxic chemotherapy and radiotherapy) work by damaging DNA. Noncancerous cells are, in the most part, able to utilise their functional DNA repair machinery to rescue themselves. However, due to their dysfunctional DNA repair machinery, cancer cells are unable to correct the damaged caused which, ultimately proves fatal to the cell (Parkinson 2008).

There are numerous mechanisms within a normal cell that ensure the maintained accuracy of newly synthesised DNA (necessary in cell division) and correction of damaged DNA, for example, the mismatch repair system or homologous recombination DNA repair (Chatterjee 2017). This redundancy means that a healthy cell is not

reliant on one particular mechanism for DNA repair and therefore can tolerate impairment of one or more its DNA repair pathways. However, a cancer cell is often overly reliant on one particular means of DNA repair, due to hereditary or acquired mutations. It is therefore possible to develop therapies that exploit this lack of redundancy and block the predominant DNA repair pathway in the cancer cell, leading to fatal DNA damage. This targeted therapy, should theoretically have minimal effect on healthy cells, as they are able to compensate with their remaining functional DNA repair machinery.

Such targeted therapies are already in clinical use, namely agents against PARP, DNA-dependent protein kinase (DNA-PK) and the ataxia-telangiectasia mutated gene protein kinase (ATM) (Bryant 2006). Of these DNA-repair inhibitors, PARP inhibitors have been most commonly used as anticancer therapy, so far.

Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi)

PARP proteins are a family of related enzymes involved in regulating various cellular processes, including DNA repair, cell death and inflammation. PARP inhibitors therefore have a potentially wide range of applications (Jagtap 2005).

PARP-1 is the most-studied of the PARP family. It is a nuclear enzyme, which binds to both single-stranded and double-stranded DNA breaks, either facilitating their repair by other enzymes (in the case of mild damage), or triggering cell-death pathways (in the case of more severe damage) (Curtin 2005; Peralta-Leal 2008; Ratnam 2007). Through its inhibition, cells lose their ability to effectively repair DNA damage and therefore die, via apoptosis or necrosis (Takaya 2020). This is of therapeutic benefit in cancers, whereby its targeted inhibition, through PARPi, leads to fatal genomic instability, as cancer cells often lack compensatory DNA repair mechanisms (Takaya 2020). The application of PARPi is of therapeutic interest in EOC as they often display pre-existing genomic instability (TCGA 2016). This is commonly as a result of abnormal BRCA protein expression (Takaya 2020).

The BRC*A* genes encode for DNA repair enzymes that function independently of the PARP pathway. Cells with *BRCA* pathogenic variants are very susceptible to PARPi, because both pathways to repair DNA are blocked. This then triggers cell cycle arrest and apoptosis specifically within cells that have the *BRCA* mutation (Bryant 2005; Farmer 2005). PARP inhibitors have been shown to be effective, when used alone in cell culture or in mouse models, at killing cells with pathogenic variants in the *BRCA1* and *BRCA2* genes (Bryant 2005; Farmer 2005), and have been used in clinical trials for breast cancer (Fong 2008). *BRCA* germline (inherited) mutations pre-dispose women to develop ovarian cancer. In addition, many ovarian cancers, in women who do not have germline *BRCA* pathogenic variants, have developed pathogenic variants in the *BRCA* genes within the tumour — called somatic mutations (Hennessy 2010)

EOC that demonstrates defective homologous recombination DNA repair are also amenable to PARPi (PRIMA). Homologous recombination is a DNA repair mechanism which corrects DNA double-stranded breaks. The homologous recombination repair pathway is often dysfunctional in EOC due to germline *BRCA1/2* pathogenic variants, somatic *BRCA1/2* pathogenic variants and *BRCA* gene promotor methylation (TCGA 2016). However, it is a complex system comprised of multiple proteins and therefore errors in other constituent proteins can lead to a similar molecular profile to those EOC resulting from pathogenic variants in *BRCA1/2*. This has led to the development of assays that can test for HRD to identify those EOC without *BRCA* pathogenic variants (either germline or somatic) that do display a homologously recombination deficiency phenotype and therefore could respond to PARPi (PRIMA). Indeed, this subgroup of EOC has been the focus of several recent trials exploring the use of PARPi in EOC (Takaya 2020).

Research into the anticancer applications of PARPi has focused on three main approaches.

- First, they can be used in isolation as the primary treatment for EOC either in the first-line or recurrent settings. (Zaremba 2007).
- Second, PARPi can be used in combination with conventional anticancer agents that act by damaging DNA, such as cytotoxic chemotherapy and radiotherapy, as PARPi block the DNA-repair mechanisms that cancer cells use to resist destruction. Again, this can either be in the first-line or recurrent setting.
- Finally, they can be used in a maintenance setting, in which they are used after definitive treatment in order to either reduce disease recurrence or delay disease recurrence.

All three modalities will be studied in this systematic review.

Why it is important to do this review

Targeted biological agents that work in different ways to conventional chemotherapy have been developed. It is therefore important to establish whether the addition of these new drugs to conventional chemotherapy regimens, as an alternative to conventional chemotherapy agents is beneficial, in terms of survival and, if so, at what cost and benefit, in terms of additional harmful effects. Furthermore, since these compounds may be less toxic compared to conventional chemotherapy agents, it may be feasible to use these new agents in patients who are not currently taking chemotherapy (so-called maintenance treatment), to reduce the chance of, or delay, the recurrence of their EOC. In this maintenance setting, where women would otherwise not be on treatment, there may be a difference balance in terms of harms and benefits of treatment.

OBJECTIVES

To determine the benefits and risks of poly (ADP-ribose) polymerase) inhibitors (PARPi) for the treatment of epithelial ovarian cancer (EOC).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Women ≥ 18 years old with histologically proven epithelial ovarian cancer (EOC) of any stage. We excluded women with other concurrent malignancies.

Types of interventions

- DNA-repair pathway inhibitors versus no treatment
- DNA-repair pathway inhibitors + conventional chemotherapy versus conventional chemotherapy
- DNA-repair pathway inhibitors versus conventional chemotherapy

Types of outcome measures

The primary and secondary outcomes of this review are as follows.

Primary outcomes

Overall survival (OS)

Secondary outcomes

Progression-free survival (PFS)

Objective response rate (ORR)

Quality of life, measured by a validated scale, e.g. QLQ-C30

Severe adverse events (SevAEs); all grades 3+ AEs according to a validated scale such as the Common Terminology Criteria for Adverse Events (CTCAE). Also, severe events according to:

- haematological (leucopenia, anaemia, thrombocytopenia, neutropenia, haemorrhage);
- gastrointestinal (nausea, vomiting, anorexia, diarrhoea, liver, proctitis);
- genitourinary;
- skin (stomatitis, mucositis, alopecia, allergy);
- neurological (peripheral and central);
- other side effects not categorised above.

Search methods for identification of studies

We sought papers in all languages and carried out translations where necessary.

Electronic searches

See: Cochrane Gynaecological Cancer Group methods used in reviews.

We searched the following electronic databases from 1990 to October 2020:

- Cochrane Gynaecological Cancer Group Trial Register (to October 2020);
- Cochrane Central Register of Controlled Trials (Central 2020, Issue 10);
- MEDLINE (1990 up to October week 2, 2020);
- Enbase (1990 up to week 42, 2020).

The CENTRAL, MEDLINE and Embase search strategies, based on terms related to the review topic, are presented in Appendix 1, Appendix 2 and Appendix 3.

Searching other resources

For the original review, we searched Physician Data Query, www.controlled-trials.com/rct, www.clinicaltrials.gov, www.cancer.gov/clinicaltrials and the National Research Register (NRR) for ongoing trials. We also sought details of ongoing or unpublished trials from the Food and Drug Administration (FDA) (www.fda.gov) and the European Medicines Agency (EMA) (www.ema.europa.eu), and from pharmaceutical company sources.

For this latest update, we relied on the electronic search to identify relevant ongoing trials from clinical trial registers. Where possible, we contacted the main investigators of unpublished trials for further information.

Data collection and analysis

Selection of studies

We downloaded all titles and abstracts retrieved by electronic searching to Covidence 2019 and removed duplicates. At least two review authors (IM, KH in the initial version of the review; a combination of AW, GC, JM and TL for the 2015 updated review; and a combination of JM, NR, AT and AW for the 2021 review) independently examined the remaining references. We excluded those studies that clearly did not meet the inclusion criteria, and obtained copies of the full text of potentially relevant references. At least two review authors (IM, KH for initial review; a combination of AW, GC, JM and TL for the 2015 update; and JM, NR, AT and AW) independently assessed the eligibility of retrieved papers. We documented reasons for exclusion.

Data extraction and management

For included studies, we abstracted data as follows.

- Author, year of publication and journal citation (including language)
- Country
- Setting
- Inclusion and exclusion criteria
- Study design, methodology
- Study population
  - Total number enrolled
  - Patient characteristics
  - Age
  - Co-morbidities
  - Previous treatment
- Total study duration
- Total number of intervention groups
- Ovarian cancer details at diagnosis
  - FIGO stage
  - Histological cell type
  - Tumour grade
  - Extent of disease
- Intervention details
  - Type of DNA-repair pathway inhibitor
  - Dose
  - Duration of treatment
  - Consolidation treatment or treatment of active disease
- Comparison details
  - Type of control: conventional chemotherapy or no treatment
  - Dose (if appropriate)
  - Duration (if appropriate)

- Deviations from protocol
- Risk of bias in a study (see below)
- Duration of follow-up
- Outcomes: overall survival OS), progression-free survival (PFS), quality of life, toxicity:
  - for each outcome: outcome definition (with diagnostic criteria if relevant);
  - unit of measurement (if relevant);
  - for scales: upper and lower limits, and whether a high or low score is good;
  - results: number of participants allocated to each intervention group;
  - for each outcome of interest: sample size; missing participants.

We extracted data on outcomes as below.

- For time to event (overall andPFS) data, we extracted the log of the hazard ratio (log(HR)) and its standard error (SE) from trial reports; if these were not reported, we attempted to estimate them from other reported statistics using the methods of Parmar 1998.
- For dichotomous outcomes (e.g. toxicity or deaths if it was not possible to use an HR), we extracted the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at an endpoint, in order to estimate a risk ratio (RR).
- For continuous outcomes (e.g. quality of life measures), we extracted the final value and standard deviation (SD) of the outcome of interest and the number of patients assessed at an endpoint in each treatment arm at the end of follow-up, in order to estimate the mean difference (MD) (if trials measured outcomes on the same scale) or standardised mean difference (SMD) (if trials measured outcomes on different scales) between treatment arms and its SE.

We extracted both unadjusted and adjusted statistics if reported. When we extracted adjusted results, we recorded the variables for which they were adjusted.

Where possible, all data extracted were relevant to an intention-to-treat analysis (ITT), in which participants were analysed in the groups to which they were assigned.

We noted the time points at which outcomes were collected and reported.

At least two review authors (a combination of AT, NR, AW, ER andJM for this review update) independently extracted data onto a data extraction form specially designed for the review update. We resolved differences between review authors by discussion or by appeal to a third review author (TL) if necessary.

Assessment of risk of bias in included studies

We assessed the risk of bias in included randomised controlled trials (RCTs) using Cochrane's risk of bias tool and the criteria specified in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This included assessment of:

- sequence generation;
- allocation concealment;
- blinding (of participants, healthcare providers and outcome assessors);
- incomplete outcome data:
  - we coded the satisfactory level of loss to follow-up for each outcome as:
    - yes, if fewer than 20% of patients were lost to follow-up and reasons for loss to follow-up were similar in both treatment arms;
    - no, if more than 20% of patients were lost to follow-up or reasons for loss to follow-up differed between treatment arms;
    - unclear if the loss to follow-up was not reported.
- selective reporting of outcomes;
- other possible sources of bias.

Two review authors (a combination of AT, NR, AW, ER andJM) independently applied the risk of bias tool and resolved differences by discussion or by appeal to a fifth review author (TL). We summarised results in a risk of bias' summary. We interpreted the results of meta-analyses in the light of the findings with respect to the risk of bias.

Measures of treatment effect

We used the following measures of the effect of treatment:

- For time to event data, we used the HR, if possible.
- For dichotomous outcomes, we used the RR.
- For continuous outcomes, we used the MD between treatment arms if all trials measured the outcome on the same scale, otherwise we used SMD.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

We did not impute missing outcome data; if only imputed outcome data were reported, we contacted trial authors to request data on the outcomes only among participants who were assessed.

Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage of heterogeneity between trials which cannot be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). If there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this.

Assessment of reporting biases

We did not produce funnel plots corresponding to meta-analysis due to the limited number of included studies. In future versions of this review, we will examine funnel plots for meta-analysis of the primary outcome to assess the potential for small-study effects. When there is evidence of small-study effects, we will consider publication bias as only one of a number of possible explanations. If these plots suggest that treatment effects may not be sampled from a symmetric distribution, as assumed by the

random-effects model, we will perform sensitivity analyses using fixed-effect models.

Data synthesis

Where sufficient clinically similar trials were available, we pooled their results in meta-analyses.

- For time-to-event data, we pooled HRs using the generic inverse variance facility of RevMan 5.4 (RevMan 2020).
- For dichotomous outcomes, we calculated the RR for each study and pooled these.
- No continuous data were synthesised for this review. In future versions of this review, for continuous outcomes (e.g. quality of life) we will pool the mean differences between the treatment arms at the end of follow-up if all trials measured the outcome on the same scale, otherwise, we will pool standardised mean differences.

We used random-effects models with inverse variance weighting for all meta-analyses (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

We considered factors such as type of intervention (e.g. use as early-stage consolidation therapy in chemo-sensitive cancers or used in late-stage chemo-resistant cancers) and stage of disease in the interpretation of any heterogeneity.

As planned *a priori* for subsequent updates at the time of the 2015 update of the review (Wiggans 2015), we analysed the effects of interventions in a number of comparisons, since there are a number of clinical scenarios where it may be appropriate to use PARPi, each of which is a separate clinical question. These comparisons, based on different situations encountered clinically, are separate, clinically relevant, questions. We, therefore, planned subgroup analyses by the line of treatment and by platinum sensitivity of disease at relapse.

Furthermore, increased knowledge about the biology of ovarian cancer, since the original protocol, concerning BRCA somatic and germline mutations and HRD status of the tumour were found to be biological markers of response to PARPi and may enable these drugs to be used more selectively, avoiding treatment of women less likely to respond to treatment. Analysis of results by BRCA and HRD status was therefore planned from the outset for this update.

Sensitivity analysis

There were too few studies to perform sensitivity analysis. In future versions of the review, we will perform sensitivity analysis excluding (i) studies at high risk of bias, and (ii) unadjusted results.

Summary of findings and assessment of the certainty of the evidence

Based on the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017a), we prepared a summary of findings table to present the results of the following outcomes.

- Overall survival (OS)
- Progression-free survival (PFS)
- Quality of life (QoL)
- Adverse events (AEs)

For each assumed risk cited in the tables, we provided a rationale and used the GRADE system to rank the quality of the evidence (Schünemann 2017b). Evidence was downgraded by -1 or -2 if the following limitations were present, according to their seriousness: study design limitations, inconsistency, imprecision, indirectness and publication bias. Where the evidence was based on single studies, or where there was no evidence on a specific outcome, we included the outcome in the 'Summary of findings' tables and graded or explained accordingly. We downgraded evidence of a clear effect derived from a single small study and resolved any differences by discussion. We reported and interpreted results based on the Cochrane Effective Practice and Organisation of Care and interactive GRADEpro Summary of Findings table guidance (EPOC 2015; Schunemann 2019).

RESULTS

Description of studies

For details of included, excluded and ongoing studies see Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

This review was first published in 2010 (Martinek 2010) when two ongoing randomised phase II clinical trials were identified from the clinical trials databases, which met our inclusion criteria, No preliminary data were available from an initial de-duplicated yield of 473 references. The 2015 update of the review (Wiggans 2015) identified four randomised controlled trials (RCTs) (ICEBERG 3 (Kaye 2012); Kummar 2015; Study 19 (Ledermann 2012); Oza 2015), two of which were the ongoing studies identified in the first version of the review. There were an additional four ongoing studies identified. In total, 14 papers were associated with the four included studies.

An updated search conducted on 30th July 2019 yielded the following.

- MEDLINE: April 2015 to July week 3 2019 – 519 references
- Embase: April 2015 to 2019 week 30 – 569 references
- Central 2019, Issue 7 – 229 references

Following preliminary de-duplication across the databases, the combined total yield was 1115 references.

A further search on the 20th October 2020 yielded the following.

- MEDLINE: July 2019 to October week 2 2020 – 244 references
- Embase: July 2019 to 2020 week 42 – 257 references
- Central 2020, Issue 10 – 38 references

Following preliminary de-duplication across the databases, the combined total yield for this search was 487 references, with an additional two published articles from two included studies found on handsearching after the search date.

Following sifting on title and abstract, these two 2019/2020 searches led to the retrieval of 255 full texts for assessment. Of this list, 143 papers related to 15 completed studies (including the four already included studies (ICEBERG 3 (Kaye 2012); Kummar 2015; Study 19 (Ledermann 2012); Oza 2015) (6232 participants in total) and 37 papers related to 17 ongoing studies were included;

after exclusion of review articles, commentaries and further duplicates, 48 papers were excluded with reasons (Characteristics of excluded studies) and another 27 were excluded as review articles/commentaries/duplicates after full text review (Figure 1).

Figure 1. Study flow diagram from updated searches to 19 October 2020.

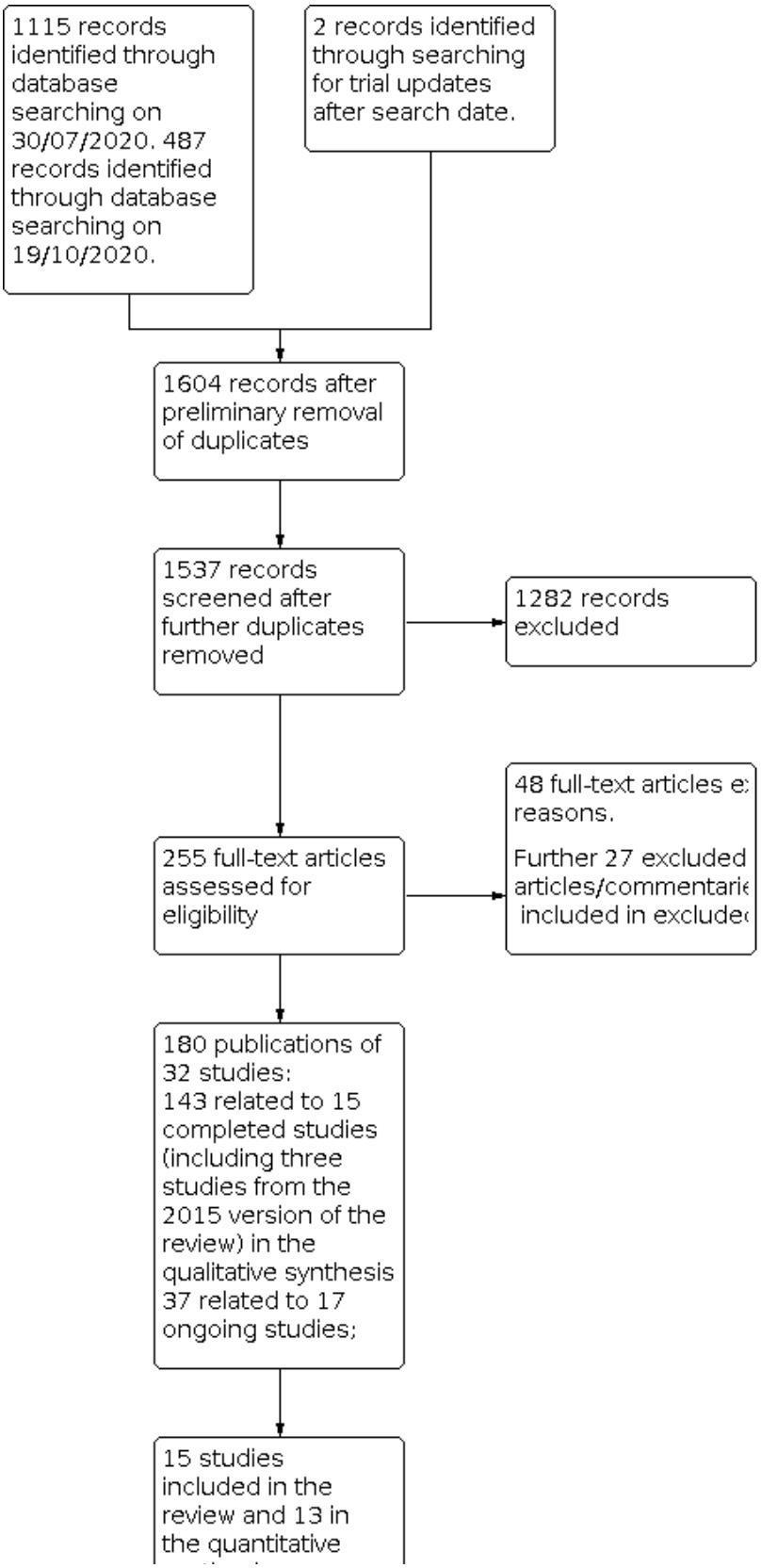
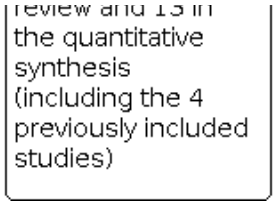


Figure 1. (Continued)



In total, we include 15 RCTs in this updated review:

ICEBERG 3 (Kaye 2012) (two references); Kummar 2015 (three references); Study 19 (Ledermann 2012) (12 references); Oza 2015 (six references); ARIEL3 (16 references); AVANOVA2 (one reference); NOVA (22 references); PAOLA-1 (13 references); PRIMA (eight references); SOLO 1 (18 references); SOLO 2 (26 references); SOLO 3 (three references); VELIA (five references), CLIO (four references) and NCT02446600 (two references).

The details of 17 ongoing studies can be found in the Characteristics of ongoing studies.

Included studies

For the details of the included studies, see the Characteristics of included studies and Table 1.

Newly-diagnosed epithelial ovarian cancer (EOC)

Four included studies evaluated the effect of PARP inhibitors (PARPi) in newly-diagnosed EOC (PAOLA-1; PRIMA; SOLO 1; VELIA). All trials were industry-funded international, multicentre trials.

Participants

All trials included women with newly-diagnosed advanced (International Federation of Gynecology and Obstetrics stage 3 or 4) EOC with a complete or partial response to first-line treatment (PAOLA-1; PRIMA; SOLO 1; VELIA). In the SOLO 1 study, women also had to have a mutation in *BRCA1*, *BRCA2,* or both (*BRCA1/2*). In other trials, the proportion of women with *BRCA* mutation was around 30%. The highest proportion of participants with homologous recombination deficiencies (HRD) mutation was in the VELIA study (63%), followed by PAOLA-1 and PRIMA studies (approximately 50%). The proportion of participants with HRD mutation in the SOLO 1 study is unknown. The median age of participants in the SOLO 1 study was also lower (median 53 years) than in the other three studies included in this comparison (median range 60 to 62 years).

Interventions

Two studies included in the comparison evaluated the effect of PARPi as maintenance therapy after platinum-based chemotherapy compared to placebo (PRIMA; SOLO 1). One study assessed the effect of PARPi in conjunction with intravenous bevacizumab and platinum–taxane chemotherapy compared to bevacizumab and chemotherapy alone (PAOLA-1); bevacizumab was given in a dose of 15 mg per kg of body weight every three weeks for a total duration of up to 15 months. The fourth study (VELIA) has a three-arm design where the PARPi in experimental arms was given as a part of first-line treatment in conjunction with chemotherapy and extended into the maintenance phase or not (placebo). The control intervention in the VELIA study was chemotherapy followed by placebo in the maintenance phase. The chemotherapy consisted of carboplatin (area under the curve of 6 mg per mL per minute, every three weeks) and paclitaxel (175 mg per square metre of body-surface area, administered every three weeks, or 80 mg per square metre, administered weekly). In two studies, the evaluated PARPi was olaparib 300 mg twice daily (PAOLA-1; SOLO 1). In the other two, niraparib 300 mg (once a day for 28 days) (PRIMA), and veliparib (VELIA) were given at a dose of 150 mg twice a day during the chemotherapy phase. The amount of veliparib was increased to 300 mg (twice a day) for two weeks during a transition phase and then subsequently raised to 400 mg if there were no concerning side effects during the transition phase.

Outcomes

The overall survival data were reported as immature in all studies included in this comparison; however, despite data immaturity, authors of PRIMA and SOLO 1 studies reported the effect estimates for the evaluated comparisons. Progression-free survival (PFS) was a primary outcome in all four studies; however, assessed by a blinded independent review only in one (PRIMA). Overall, the survival data were immature in all studies. The objective response rate (ORR) as per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 was reported only in the VELIA study. The quality of life in the included studies was captured using various tools: the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire QLQ-C30 (PAOLA-1; PRIMA), the Trial Outcome Index (TOI) score on the Functional Assessment of Cancer Therapy–Ovarian Cancer (FACT-O) questionnaire (SOLO 1); the European Quality of Life five-dimension, five-level questionnaire (EQ-5D-5L) (PRIMA), the Functional Assessment of Cancer Therapy–Ovarian Symptom Index (PRIMA), and the EORTC Quality of Life Questionnaire Ovarian Cancer module (EORTC-QLQ-OV28) (PRIMA)(Table 2). Adverse events were reported as graded by the National Cancer Institute Common Toxicity Criteria (NCI-CTC) versions 4.0 (SOLO 1) and 4.03 (PAOLA-1; PRIMA; VELIA).

Recurrent, platinum-sensitive EOC

Three studies compared PARPis with chemotherapy to treat recurrent EOC(ICEBERG 3 (Kaye 2012); NCT02446600; SOLO 3). All trials were international, multicentre trials. ICEBERG 3 (Kaye 2012) and SOLO 3 were industry-funded, and NCT02446600 was funded from public resources by the National Cancer Institute. In four studies PARP inhibitor was compared with placebo in the maintenance phase after chemotherapy (ARIEL3; NOVA; SOLO 2; Study 19 (Ledermann 2012)). All of these trials were industry-funded, international, and multicentre. Three further studies evaluated the effect of PARPi alongside chemotherapy; in two the comparison was made with chemotherapy alone (Kummar

2015; Oza 2015), in one with PARPi monotherapy (AVANOVA2). The Kummar 2015 study was government-funded, Oza 2015 study was industry-funded, and the AVANOVA2 study received mixed funding from a non-profit organisation and a pharmaceutical company. In Kummar 2015, participants were recruited only in North America (the USA and Canada); Oza 2015 study was an international, multicentre trial; and the AVANOVA2 study recruited participants in the USA and Scandinavian countries.

Participants

All studies included participants with recurrent, platinum-sensitive EOC. In ICEBERG 3 (Kaye 2012) and SOLO 3 studies included participants who had *BRCA* mutation and measurable disease according to RECIST. Additionally, approximately 50% of the participants in ICEBERG 3 (Kaye 2012) had relapsed within six months of platinum-based chemotherapy (platinum-resistant disease). NCT02446600 study enrolled participants with (23.7%) and without *BRCA* mutation. The proportion of participants with HRD mutation was not declared in all three studies. The age of participants was comparable in ICEBERG 3 (Kaye 2012) and SOLO 3 and unknown in NCT02446600. In Study 19 (Ledermann 2012), 40% had the measurable disease by RECIST and around 22% had a *BRCA* mutation. NOVA study included two populations with (203 participants) and without (350 participants) a g*BRCA*m. The proportion of participants with *BRCA* mutation in NOVA and ARIEL3 studies was comparable (37% and 35%, respectively). In ARIEL3, around 37% of participants had a measurable disease (as assessed by the investigator). All participants in the SOLO 2 study had a g*BRCA*m. In Kummar 2015 and AVANOVA2 studies majority of participants had a measurable disease according to RECIST criteria version 1.1. The proportion of women with BRCA mutation in Kummar 2015 and AVANOVA2 studies was around 40%. In Oza 2015 study, approximately 15% of the randomised participants had a *BRCA* mutation. The proportion of participants with HRD mutation was only reported in the AVANOVA2 study (60%). The median age of participants in Kummar 2015 and Oza 2015 studies was around 60. In the AVANOVA2 study, the median age of the participants was 66 years of age.

Interventions

ICEBERG 3 (Kaye 2012) has a three-arm design with both experimental arms containing PARPi (olaparib) in different dosages. In one arm, the dose was 200 mg, and in another, 400 mg was administered twice a day. The participants in the control arm received chemotherapy (50 mg/m2 of pegylated liposomal doxorubicin). NCT02446600 was another three-arm study in this comparison. One experimental arm received a PARP inhibitor (olaparib) 300 mg twice a day. In the other, a PARP inhibitor (olaparib 200 mg twice a day) was given in combination with cediranib maleate (30 mg daily). Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity. The control arm received standard of care, i.e. one of three types of chemotherapy: intravenous paclitaxel and carboplatin; intravenous carboplatin with gemcitabine hydrochloride; or intravenous carboplatin with liposomal doxorubicin hydrochloride. In SOLO 3, PARP inhibitor was compared with non-platinum based chemotherapy. The evaluated PARP inhibitor was olaparib in a dose of 300 mg twice a day. The chemotherapy in the control arm was tailored to individual single-agent chemotherapeutic (pegylated liposomal doxorubicin 50 mg/m2; paclitaxel 80 mg/m2; gemcitabine 1000 mg/m2; or topotecan 4 mg/m2). Out of four studies evaluating PARPi as maintenance therapy, two evaluated olaparib (300 mg twice a day)(Study 19 (Ledermann 2012), SOLO 2), and two single studies rucaparib (600 mg twice a day) (ARIEL3) and niraparib (300 mg daily)(NOVA). In Oza 2015 study, PARPi combined with platinum-based chemotherapy followed by PARPi in the maintenance phase was compared with chemotherapy alone (no treatment in the maintenance phase). The experimental arm contained olaparib (200 mg twice a day) combined with chemotherapy (intravenous paclitaxel 175 mg/m^2 with intravenous carboplatin the area under the curve 4 mg/mL per minute according to the Calvert formula). In the maintenance phase, olaparib was continued in a dose of 400 mg twice a day. The chemotherapy in the control arm comprised paclitaxel (175 mg/m^2) and carboplatin (area under the curve 6 mg/mL per minute). In Kummar 2015 study, the effect of PARPi (veliparib 60 mg once a day in a 21-day cycle) in combination with chemotherapy (cyclophosphamide 50 mg once a day) was compared with chemotherapy alone. The AVANOVA2 study is a proof-of-concept trial that aimed to identify a more active regimen for phase 3 evaluation. One of the arms contained niraparib alone (starting dose of 300 mg three times a day) and the other in combination with intravenous bevacizumab (15 mg/kg every three weeks).

Outcomes

The overall survival data were collected and reported in five studies in this population; however, in three studies data were immature at the point of analysis (SOLO 2, SOLO 3, Study 19 (Ledermann 2012)). In NCT02446600, the conference abstract contains a statement of no difference in overall survival (OS), but without further details. The outcome was not collected in Kummar 2015 and not reported due to data immaturity in AVANOVA2. Progression-free survival (PFS) was a primary outcome in all nine studies (ICEBERG 3 (Kaye 2012), NCT02446600, ARIEL3, NOVA, SOLO 2, Study 19 (Ledermann 2012), AVANOVA2; Oza 2015; Kummar 2015). In ICEBERG 3 (Kaye 2012), NCT02446600) and Kummar 2015 it is unclear who assessed PFS (investigator or blinded, independent reviewer). In ARIEL3, SOLO 2 and AVANOVA2, PFS was assessed by the investigator and in the NOVA study by blinded central radiological and clinical review. In Study 19 (Ledermann 2012), PFS was assessed by the site investigator and by a blinded independent central review, and in Oza 2015 by a blinded independent review. The objective response rate (ORR) assessed according to the RECIST was reported in seven studies (ICEBERG 3 (Kaye 2012), NCT02446600, SOLO 3, ARIEL3, Study 19 (Ledermann 2012), AVANOVA2; Oza 2015). The quality of life in the ICEBERG 3 (Kaye 2012) study was evaluated using various tools: Best Quality of Life (QoL) Response for the Trial Outcome Index, Best QoL Response for Total FACT-O, Best QoL Response for FOSI. In SOLO 3, it was assessed using the TOI score on the FACT-O questionnaire. In the NOVA study, the quality of life was evaluated using EQ-5D-5L and FOSI with the results of the latter one being reported in insufficient detail. Only the quality of life reported in SOLO 3, SOLO 2 and NOVA could have been incorporated in this review (Table 2). Adverse events reported in SOLO 3 (NCI-CTC version 4.0), Study 19 (Ledermann 2012)(NCI-CTC version 3.0), SOLO 2 (NCI-CTC version 4.0), NOVA and (Oza 2015 studies (version 4.02) could be used in the quantitative analysis. The version of the grading system in ARIEL3 study was not reported.

Recurrent, platinum-resistant EOC

A single study (CLIO) evaluated the effect of PARPi with chemotherapy as a treatment for recurrent platinum-resistant EOC. CLIO is an industry-funded, single country, multicentre trial. Additionally, around half of the participants in the ICEBERG 3 (Kaye 2012) were platinum-resistant. However, we decided not to include the ICEBERG 3 (Kaye 2012) study in this comparison.

Participants

CLIO study included women with recurrent, platinum-resistant advanced (International Federation of Gynecology and Obstetrics stage 3 or 4) EOC Information about participants' characteristics is limited as the study is available only as a conference abstract.

Interventions

CLIO study evaluated the effect of PARPi in comparison to chemotherapy - olaparib 300 mg twice a day for 28 days in 28-day cycles versus individually-tailored chemotherapy (carboplatin with gemcitabine, or carboplatin with paclitaxel, or carboplatin with liposomal doxorubicin, or liposomal doxorubicin 4-weekly, or topotecan, or weekly paclitaxel).

Outcomes

Neither overall survival (OS) nor progression-free survival (PFS) were reported in CLIO. The main trial outcome was the objective response rate (ORR). It is unclear who was assessing ORR and what criteria were used (investigator or blinded, independent reviewer). Quality of life was also not reported in this trial. Adverse events were graded using the National Cancer Institute Common Toxicity Criteria version 4.03.

Excluded studies

After removal of 27 review articles, further duplicates and commentaries, we excluded 48 references after obtaining the full text, for the following reasons:

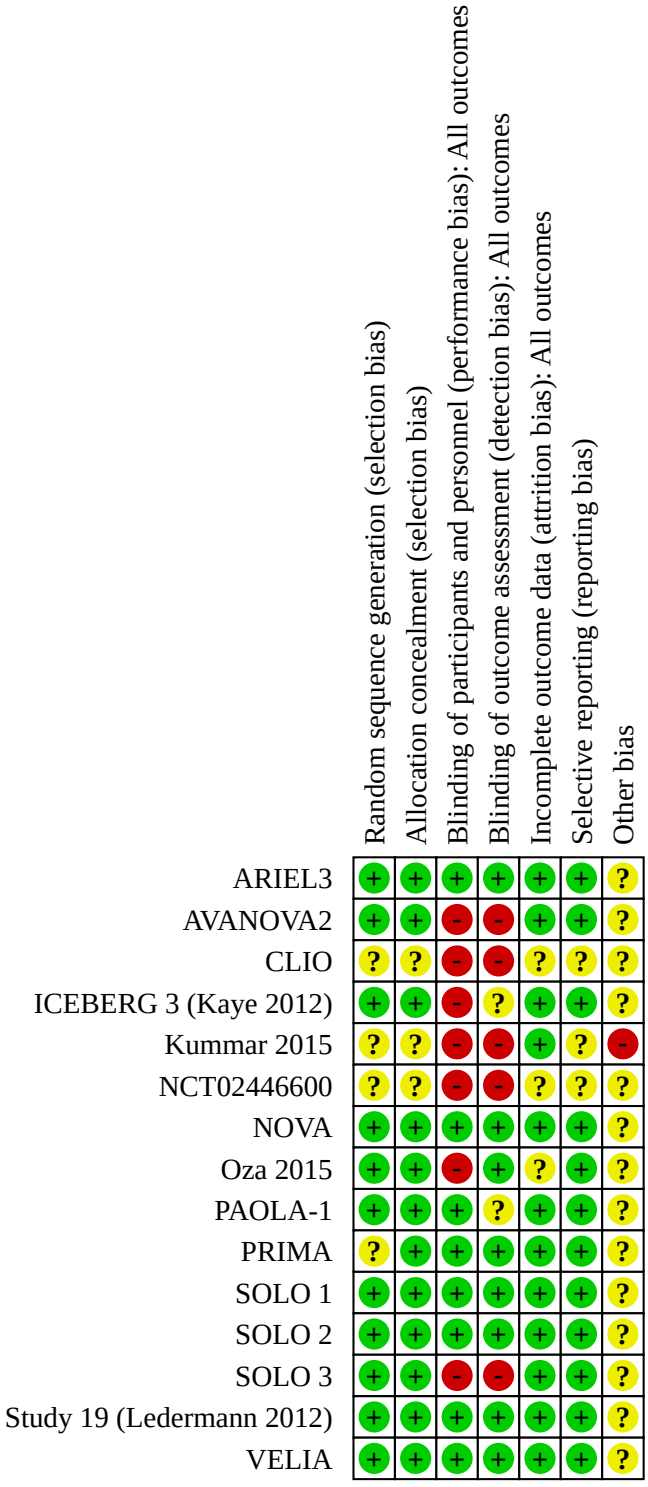
- wrong study design (27);
- irrelevant intervention (3);
- irrelevant comparison (8);
- systematic review/meta-analysis (12)

For details of these 47 excluded studies see Characteristics of excluded studies.

Risk of bias in included studies

Information on potential sources of risk of bias in two unpublished trials (CLIO; NCT02446600) was limited, resulting in a judgement 'unclear' for most of the assessed domains except blinding (performance bias and detection bias). For assessment of the risk of bias items for individual studies see Figure 2.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The majority of included studies were randomisation list was computer-generated and provided by a third party by a web-based or voice response system. The method of randomisation was insufficiently described in two studies (Kummar 2015; PRIMA). and for Kummar 2015, the allocation method was also unclear.

Blinding

In seven included studies (AVANOVA2; CLIO; ICEBERG 3 (Kaye 2012); Kummar 2015; NCT02446600; Oza 2015; SOLO 3), interventions were not concealed (open-label design); thus, the participants and personnel were aware of the group allocation. The primary outcome in the studies was often progression-free survival (PFS) (12/15 studies) assessed by an investigator (ARIEL3, AVANOVA2, SOLO 1, SOLO 2, VELIA, PAOLA-1) or by a blinded independent reviewer (NOVA; PRIMA; Oza 2015). In Study 19 (Ledermann 2012), the primary outcome was assessed by the investigator and blinded independent reviewer. In NCT02446600 and ICEBERG 3 (Kaye 2012) it was not clear who assessed progression-free survival. The primary outcome in the remaining three studies (Kummar 2015, SOLO 3, CLIO) was the objective response rate which was clearly described as assessed by a blinded independent reviewer only in SOLO 3.

Incomplete outcome data

Attrition was not considered an issue in most studies except Oza 2015 where there was insufficient information to judge this domain.

Selective reporting

Selective reporting of outcomes was not considered an issue in most studies except Kummar 2015 where there was insufficient information to judge this domain.

Other potential sources of bias

Kummar 2015 was judged as at high risk of bias in this domain due to concern over lack of clarity over reasons for earlier termination of the trial. The majority of included studies were industry-sponsored trials with several authors disclosing a financial conflict of interest hence judged as unclear risk of bias in this domain.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Newly-diagnosed EOC: PARPi with chemotherapy compared with chemotherapy alone; **Summary of findings 2** Summary of findings table - Newly-diagnosed EOC: PARPi monotherapy compared with placebo (maintenance therapy); **Summary of findings 3** Summary of findings table - Platinum-sensitive recurrent EOC: PARPi monotherapy compared with chemotherapy; **Summary of findings 4** Summary of findings table - Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy); **Summary of findings 5** Summary of findings table - Platinum-sensitive recurrent EOC: PARPi with chemotherapy compared with chemotherapy alone; **Summary of findings 6** Summary of findings table - Platinum-resistant recurrent EOC: PARPi monotherapy compared with chemotherapy

The effects of interventions are described in a number of comparisons since there are a number of clinical scenarios where it may be appropriate to use poly (ADP-ribose) polymerase) inhibitors (PARPi), each of which is a separate clinical question. This review, therefore, represents an umbrella review of different theoretical clinical scenarios. The summary of findings tables are presented for the most clinically relevant comparisons.

Newly-diagnosed epithelial ovarian cancer (EOC)

Four included studies evaluated the effect of PARPi in newly-diagnosed EOC (PAOLA-1; PRIMA; SOLO 1; VELIA). We graded certainty of the evidence of the two most clinically relevant comparisons (see Summary of findings 1 and Summary of findings 2). As bevacizumab is increasingly part of standard care, we classified comparison PAOLA-1 trial as chemotherapy with PARPi compared to PARPi. The median OS and PFS times are available in Table 3 and Table 4, respectively.

1. PARPi with chemotherapy compared with chemotherapy alone

See Summary of findings 1.

Survival outcomes

Overall survival (OS)

OS data were not reported.

Progression-free survival (PFS)

PARPi with chemotherapy compared with chemotherapy alone may have little or no effect on PFS (two studies, 1564 participants; hazard ratio (HR) 0.82, 95%confidence interval (CI) 0.49 to 1.38; *very low-certainty evidence;* Analysis 1.1). Analysis restricted only to data from VELIA trial (chemotherapy without bevacizumab) showed no change in conclusion regarding the effect of PARPi (one study, 758 participants; HR 1.07, 95%CI 0.90 to 1.28). We did not observe a statistically significant difference in the effect according to BRCA (Chi^2 = 0.22, P = 0.64; Analysis 1.2) or homologous recombination deficiencies (HRD) status (Chi^2 = 0.73, P = 0.39; Analysis 1.3).

Objective response rate (ORR) - no response

There may be little to no difference in ORR (rate of no evidence of response (i.e. no demonstrable complete response/partial response (CR/PR))) between PARPi with chemotherapy (one study, 192 participants; risk ratio (RR) 0.82, 95%CI 0.49 to 1.37; Analysis 1.4) and chemotherapy alone.

Quality of life (QoL)

PARPi combined with chemotherapy compared with chemotherapy alone was likely to result in little to no difference in the QoL measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire QLQ-C30 (one study; 744 participants, mean difference (MD) 1.56 95% CI -0.42 to 3.54]*; moderate-certainty evidence;* Analysis 1.5). The findings were described as not clinically meaningful.

Adverse events

There was probably an increased risk of experiencing any severe adverse event (grade 3 or higher) with a combination of PARPi and chemotherapy compared with chemotherapy alone (two studies, 1549 participants, RR 1.13, 95% CI 1.07 to 1.20; *high-certainty evidence;* Analysis 1.6). Analysis restricted only to data

from VELIA trial (chemotherapy without bevacizumab) showed no change in conclusion regarding the effect of PARPi (one study, 747 participants; HR 1.14, 95%CI 1.06 to 1.22).

2. PARPi with chemotherapy and as maintenance therapy compared to chemotherapy alone

Survival outcomes

Overall survival (OS)

OS data were not reported.

Progression-free survival (PFS)

PARPi with chemotherapy followed by PARPi monotherapy as a maintenance therapy resulted in a longer PFS compared to chemotherapy alone (one study, 757 participants; HR 0.68, 95%CI 0.56 to 0.83; Analysis 2.1). We did not observe a statistically significant difference in the effect of PARPi throughout according to *BRCA* (Chi^2 = 5.57, P = 0.02; Analysis 2.2) but not HRD status (Chi^2 = 2.79, P = 0.10; Analysis 2.3).

Objective response rate (ORR) - no response

There may be little to no difference in ORR (rate of no evidence of response (i.e. no demonstrable CR/PR)) between PARPi with chemotherapy and as maintenance therapy (one study, 191 participants; RR 0.63, 95%CI 0.36 to 1.11; Analysis 2.4) compared with chemotherapy alone.

Quality of life (QoL)

PARPi monotherapy probably results in little to no clinically meaningful difference in the QoL measured using the Functional Assessment of Cancer Therapy Ovarian Symptom Index–18 (one study; 362 participants; MD-3.00, 95% CI -4.48 to -1.52; *moderate-certainty evidence;* Analysis 3.6).

Adverse events

There was probably an increased risk of experiencing any severe adverse event (grade 3 or higher) for the combination of PARPi with chemotherapy and as maintenance therapy (one study, 748 participants, RR 1.15, 95% CI 1.07 to 1.23; Analysis 2.5) compared with chemotherapy alone.

3. PARPi monotherapy compared with placebo (maintenance therapy)

See Summary of findings 2.

Survival outcomes

Overall survival (OS)

PARPi monotherapy as maintenance therapy after chemotherapy probably resulted in little to no difference in OS compared with placebo (two studies, 1124 participants; HR 0.81, 95%CI 0.59 to 1.13; *moderate-certainty evidence;* Analysis 3.1). We did not observe a statistically significant difference in the effect of PARPi monotherapy according to HRD status (Chi^2 = 0.11, P = 0.74; Analysis 3.2).

Progression-free survival (PFS)

PARPi monotherapy used in the maintenance therapy compared with placebo may improve PFS, irrespective of PARPi type (two studies, 1123 participants; HR 0.42, 95% CI 0.19 to 0.92); *low-certainty evidence;* Analysis 3.3). We noted some evidence for a subgroup difference in the effect of PARPi monotherapy according to HRD status (Chi^2 = 3.85, P = 0.05; Analysis 3.5), but none according to BRCA status (Chi^2 =1.90, P = 0.17; Analysis 3.4).

Quality of life (QoL)

PARPi monotherapy used in the maintenance therapy compared with placebo probably results in a slight reduction in the QoL measured using the Trial Outcome Index (TOI) score (FACT-O questionnaire)(one study, 362 participants; MD -3.00, 95%CI -4.48 to -1.52; *moderate-certainty evidence,* Analysis 3.6*).* The differences were described as not clinically meaningful.

Adverse events

PARPi monotherapy may increase/have little to no effect on the risk of experiencing any severe adverse event (grade 3 or higher) compared with placebo (two studies, 1118 participants, RR 2.87, 95% CI 1.65 to 4.99; *very low-certainty evidence;* Analysis 3.7) but the evidence is very uncertain.

Recurrent, platinum-sensitive epithelial ovarian cancer (EOC)

Ten studies evaluated the effect of PARPi in recurrent, platinum-sensitive EOC (ARIEL3; AVANOVA2; ICEBERG 3 (Kaye 2012); Kummar 2015; NCT02446600; NOVA; Oza 2015; SOLO 2; SOLO 3; Study 19 (Ledermann 2012)). Out of five comparisons reported in these studies, we report four and graded certainty of the evidence of the three most clinically relevant comparisons (see Summary of findings 3; Summary of findings 4; Summary of findings 5). As the AVANOVA2 is a proof-of-concept trial having a comparison not relevant to current clinical practice (PARPi with bevacizumab compared with the PARPi alone) we decided not to present its results.

4. PARPi monotherapy compared with chemotherapy alone

The summary of evidence can be seen in the Summary of findings 3. The median OS and PFS are available in Table 3 and Table 4, respectively.

Survival outcomes

Overall survival (OS)

PARPi monotherapy compared with chemotherapy probably resulted in little to no difference in OS (two studies, 331 participants; HR 0.95, 95%CI 0.62 to 1.47; *low-certainty evidence,* Analysis 4.1) regardless of inhibitor's dose. The evidence comes from the studies involving only participants with *BRCA* mutation.

Progression-free survival (PFS)

PARPi compared with chemotherapy may result in little or no difference in PFS (three studies, 739 participants; HR 0.88, 95%CI 0.56 to 1.38; *very low-certainty evidence,* Analysis 4.2), but the evidence is very uncertain. We did not observe a statistically significant difference in the effect of PARPi monotherapy according to BRCA status (Chi^2 = 0.69, P = 0.41; Analysis 4.3).

Objective response rate (ORR) - no response

PARPi compared with chemotherapy may result in little or no reduction in ORR (three studies, 696 participants; RR 0.97, 95%CI 0.56 to 1.67; Analysis 4.4) but the evidence is very uncertain.

Quality of life (QoL)

PARPi compared with chemotherapy may result in little or no change in the QoL measured using the TOI score (FACT-O questionnaire) (one study, 229 participants, MD 1.20, 95%CI -1.75 to 4.16; *low-certainty evidence,* Analysis 4.5).

Adverse events

PARPi compared with chemotherapy may result in little or no difference in the rate of any severe adverse event (grade 3 or higher) (one study, 254 participants; RR 1.06, 95%CI 0.80 to 1.39; *low-certainty evidence,* Analysis 4.6).

5. PARPi compared with placebo after chemotherapy (maintenance therapy)

For a summary of evidence for this comparison see Summary of findings 4. The median OS and PFS are available in Table 3 and Table 4, respectively.

Survival outcomes

Overall survival (OS)

There was little to no difference in OS between PARPi and placebo (two studies, 560 participants; HR 0.88, 95% CI 0.65 to 1.20; *moderate-certainty evidence*, Analysis 5.1).

Progression-free survival (PFS)

PARPi resulted in a large increase in PFS compared to placebo (four studies, 1677 participants; HR 0.34, 95% CI 0.28 to 0.42; *high-certainty evidence,* Analysis 5.2). We observed a statistically significant difference in the effect of PARPi according to *BRCA* (Chi^2 = 9.82, P = 0.02; Analysis 5.3), but not HRD status (Chi^2 = 3.21, P = 0.07; Analysis 5.4).

Objective response rate (ORR) - no response

PARPi, in comparison to the placebo, probably resulted in an improvement in ORR (two studies, 312 participants; RR 0.90, 95%CI 0.83 to 0.97; Analysis 5.5).

Quality of life (QoL)

PARPi monotherapy used in the maintenance therapy compared with placebo may result in little to no difference in the QoL measured using the European Quality of Life 5-dimensions questionnaire Health Utility Index score (first post-progression measure) (one study, 339 participants, MD 0.02, 95%CI -0.01 to 0.05;moderate-certainty evidence; Analysis 5.6). We did not observe a statistically significant difference in the effect according to BRCA status (Chi^2 = 0.38, P = 0.54; Analysis 5.6).

PARPi monotherapy used in the maintenance therapy compared with placebo may result in little to no difference in the QoL measured using the TOI score (FACT-O questionnaire)(one study, 279 participants, MD-0.03, 95% CI -2.16 to 2.10; Analysis 5.7).

Quality adjusted PFS and Time Without Symptoms of treatment toxicity

The aim of Quality-Adjusted PFS (QA-PFS) and Time Without Symptoms of treatment Toxicity (TWiST) is to assess a combination of treatment-emergent symptoms and disease progression. PARPi monotherapy used in the maintenance therapy compared with placebo showed an improved value of QA-PFS (two studies, 858 participants, MD 6.41, 95% CI 5.37 to 7.44; Analysis 5.8) and TWiST (two studies, 858 participants, MD 6.52, 95% CI 5.69 to 7.35; Analysis 5.10). For both outcomes, we observed a statistically significant difference in the effect of PARPi according to *BRCA* status (Analysis 5.9; Analysis 5.11). These were post hoc analyses in both studies contributing to these analyses (see Table 2); however, both measures appear to be increasingly used in the context of studies evaluating maintenance treatments.

Adverse events

There may be a large increased risk of experiencing any severe adverse event (grade 3 or higher) with a PARPi compared to placebo (four studies, 1665 participants, RR 2.62, 95%CI 1.85 to 3.72; *low-certainty evidence,* Analysis 5.12).

6. PARPi with chemotherapy compared with chemotherapy alone

For a summary of evidence for this comparison see Summary of findings 5. The median PFS times are available in Table 4.

Survival outcomes

Overall survival (OS)

OS data were not reported.

Progression-free survival (PFS)

PARPi with chemotherapy compared with chemotherapy alone may have little or no effect on PFS (one study, 75 participants; HR 1.02, 95%CI 0.69 to 1.51; *very low-certainty evidence*, Analysis 6.1), but the evidence is very uncertain.

Objective response rate (ORR) - no response

The combination of PARPi with chemotherapy, compared to chemotherapy alone, may have little to no effect on ORR (one study, 70 participants; RR 1.10, 95%CI 0.89 to 1.34; Analysis 6.2), but the evidence is very uncertain.

Quality of life (QoL)

No QoL data available.

Adverse events

There may be little to no difference in any severe adverse events (grade 3 or higher) with a combination of PARPi and chemotherapy compared to chemotherapy alone (one study, 156 participants; RR 1.14, 95%CI 0.89 to 1.47; Analysis 6.3).

7. PARPi with chemotherapy followed by PARPi as maintenance compared with chemotherapy alone

The median OS times are reported in Table 3.

Survival outcomes

Overall survival (OS)

PARPi with chemotherapy followed by PARPi as maintenance may result in little to no difference in OS compared to chemotherapy alone (one study, 162 participants; HR 1.17, 95%CI 0.79 to 1.74; Analysis 7.1).

Progression-free survival (PFS)

PARPi combined with chemotherapy followed by PARPi as maintenance therapy probably resulted in a longer PFS compared to chemotherapy alone (one study, 162 participants; HR 0.51, 95%CI 0.34 to 0.77; Analysis 7.2). We observed a statistically significant difference in the effect of PARPi according to *BRCA* status ($Chi^2 = 4.90$, P = 0.03; Analysis 7.3).

Objective response rate (ORR) - no response

PARPi combined with chemotherapy followed by PARPi as maintenance therapy compared with chemotherapy alone may result in little to no difference in ORR (one study, 162 participants; RR 0.85, 95%CI 0.58 to 1.26; Analysis 7.4).

Quality of life (QoL)

No QoL data available.

Adverse events

There may be an increased risk of experiencing any severe adverse events (grade 3 or higher) with PARPi continued into the maintenance phase after combined treatment with PARPi and chemotherapy compared to placebo after chemotherapy alone (one study, 111 participants; RR 2.07, 95%CI 1.03 to 4.18; Analysis 7.5).

Recurrent, platinum-resistant epithelial ovarian cancer (EOC)

8. PARPi monotherapy compared with chemotherapy

For the summary of evidence for this comparison see Summary of findings 6.

Survival outcomes

Overall survival (OS)

OS data were not reported.

Progression-free survival (PFS)

PFS data were not reported.

Objective response rate (ORR) - no response

PARPi monotherapy compared to chemotherapy may have little to no effect on ORR (one study, 100 participants; RR 2.96, 95%CI 0.70 to 12.44; Analysis 8.1), but the evidence is very uncertain.

Quality of life (QoL)

No QoL data available.

Adverse events

PARPi monotherapy compared with chemotherapy may have little to no effect on the rate of any severe adverse event (grade 3 or higher) (one study, 100 participants; RR 1.16, 95%CI 0.79 to 1.70; *very low-certainty evidence,* Analysis 8.2), but the evidence is very uncertain.

DISCUSSION

Summary of main results

In total, 6109 women with epithelial ovarian cancer (EOC) were included from 15 studies (four with primary (3070 participants) and 11 (3039 participants) with recurrent EOC). Eight of these studies were deemed at low risk of bias across most of the assessed domains. Studies included used various poly (ADP-ribose) polymerase) inhibitors (PARPi) (olaparib n = 9; niraparib n = 3; veliparib n = 2; rucaparib n = 1). In addition, studies either used PARPi in isolation or in combination with a vascular endothelial growth factor agent (bevacizumab n=2 or cediranib n = 1). Comparisons were performed across six clinically relevant subgroups:

1. PARPi in newly-diagnosed EOC versus chemotherapy alone (n = 1);
2. PARPi monotherapy (maintenance) in advanced newly-diagnosed EOC versus placebo (n = 2);
3. PARPi monotherapy compared with chemotherapy in recurrent platinum-sensitive EOC (n = 3).
4. PARPi compared with placebo after chemotherapy in EOC (maintenance therapy) (n = 4);
5. PARPi monotherapy in recurrent EOC versus chemotherapy alone (n = 1);
6. PARPi monotherapy compared with chemotherapy in recurrent platinum-resistant EOC (n = 1).

In addition, one study compared PARPi and chemotherapy with chemotherapy alone. The certainty of the evidence was graded as very low.

Meta-analysis of these subgroups found that the progression-free survival (PFS) may be increased (*low-certainty evidence*) with the use of PARPi monotherapy when used as a maintenance treatment after first-line chemotherapy in newly-diagnosed EOC. This effect is more pronounced when used as maintenance therapy in recurrent platinum-sensitive EOC (*high-certainty evidence*). However, in both instances, little to no difference was seen in overall survival (OS), although these data are immature and may change with further follow-up. The results for the subgroup of participants with *BRCA* pathogenic variants were consistent with those reported to have *BRCA* wild type, although the majority of those recruited, where stated, had either germline or somatic *BRCA* mutations or HRD, so there are relatively few without some form of HRD for comparison.

Regarding adverse events, the use of PARPi led to an increase in the reported number of any serious adverse events (grade 3 or higher) when used in addition to chemotherapy versus chemotherapy alone in the treatment of advanced primary chemotherapy. This was also the case when PARPi was used as maintenance therapy in either first-line treatment or recurrent platinum-sensitive EOC. However, there may be little to no difference (*low-certainty evidence*) in the rate of serious adverse events seen in PARPi

monotherapy compared with chemotherapy when used to treat recurrent platinum-sensitive EOC.

The quality of life data were generally not well-reported, compared to efficacy data, and heterogenous so not all available for meta-analysis (see Table 2 for details). Quality of life (QoL) outcomes in trials exploring the use of PARPi in women with newly-diagnosed EOC is based on the secondary outcome reporting of four studies (PAOLA-1; PRIMA; SOLO 1; VELIA). Analyses were limited and there are no separate published reports detailing QoL outcomes. Heterogenous QoL measures were used, making data synthesis challenging. All of these studies reported no significant difference in their respective QoL measures between their PARPi arm and placebo arm. VELIAalso found no difference in QoL measure in their intention-to-treat, BRCA or homologous recombination deficient (HRD) populations.

The evidence base for QoL outcomes for PARPi use in the recurrence setting is more robust. Four studies reported QOL data as secondary outcomes (ARIEL3; NOVA; SOLO 2; SOLO 3). Meta-analysis was challenging due to the use of different measures and conditions between studies. Three studies have separately published comprehensive QoL data. SOLO 2utilised the Quality Time Without Significant Symptoms of Toxity (Q-TWIST) score and Quality Adjusted Progression Free Survival (QA-PFS). These are post-hoc analyses, which measure time without symptoms from a combination of treatment and disease progression, and so are affected by PFS, as well as adverse effects from treatment. The authors concluded there were clinically meaningful patient-centred benefits in both Q-TWiST and QA-PFS, despite the adverse effects associated with olaparib. NOVA have also published separate QoL data which was derived from the Functional Assessment of Cancer Therapy – Ovarian Symptoms Index (FOSI) score. Their results suggest that women who receive niraparib as maintenance treatment for recurrent ovarian cancer after responding to platinum treatment can maintain QoL during their treatment when compared with placebo. Finally, ARIEL3 conducted and published a specific QoL analysis. The authors measured QoL outcomes with the European QoL Five-dimension five level questionnaire (EQ-5D-5L) and did a post-hoc analysis of Q-TWiST and QA-PFS. Their data supported the use of rucaparib; those treated with it, including those without g*BRCA* or s*BRCA*, had longer periods without clinically-relevant symptoms.

Overall completeness and applicability of evidence

We are confident that we have captured studies assessing PARPi in ovarian cancer, having identified ongoing studies in a previous review update and compared included studies to subsequent systematic reviews.

Evidence is most robust for olaparib, with less complete data for veliparib, niraparib and rucaparib. Data are also heavily skewed to the germline *BRCA*m populations, which makes up 16% of patients with high-grade serous EOC (depending on population) (Risch 2001). However, subgroup data suggest that PARPi responses are also seen in those with somatic (tumour) *BRCA*m and HRD. Since the last update of the review (Wiggans 2015), tumour testing for *BRCA*m and access to germline testing for *BRCA*m in those with *BRCA*m tumours is routine in the UK. This was driven initially by pharmaceutical company testing, but supported by updated National Institute for Clinical Excellence(NICE) guidance, which recommends *BRCA* testing for breast cancer (NICE [CG164] 2019).

In terms of applicability, patients in studies tend to be younger and fitter than the general cohort of patients with ovarian cancer. The increased risk of severe adverse events and effects on the quality of life of long-term maintenance treatment may therefore be different in the wider population of patients with ovarian cancer.

From the available data, it is still not clear whether PARPi only delays the onset of recurrent disease, or whether there is an OS benefit for certain subgroups of women. Overall survival endpoints are harder to obtain since they require longer for the data to mature. Furthermore, OS was a secondary outcome in many of the studies, so studies were not powered for OS effects. In addition, the effects of individual therapeutic agents can be obscured due to the effects of other treatments, especially in EOC where women often have multiple rounds (or lines) of treatment over what can be several years. We hope a more complete picture will emerge with longer-term follow-up data from randomised controlled trials (RCTs), but have concerns that there is an over-emphasis on PFS outcomes (see Authors' conclusions for further discussion).

Serious adverse events, which were more common in women receiving PARPi maintenance treatment, which may have a significant impact on quality of life. We were unable to adequately evaluate the quality of life due to insufficient data and more evidence on this is needed.

Quality of the evidence

Many studies appear to be well conducted with pre-defined outcome criteria and robust randomisation systems. Eight of the 15 studies were at low risk of bias for the majority of assessment criteria, whereas eight studies were open-label studies and therefore at risk of bias of many outcome measures, although OS is unlikely to have been affected (Figure 2). The evidence is of moderate certainty for studies looking at the affects of olaparib and estimates of effect may change with further research. There was low-certainty evidence for veliparib, and we are very uncertain about the effects of the treatment.

Potential biases in the review process

We are not aware of any biases in the review process. We conducted this review using standard Cochrane methodology, which aims to reduce bias through double sifting, double data extraction and transparent grading of evidence. None of the authors have any links to drug companies, a financial interest in the prescription of chemotherapeutic agents, nor were they involved in the conduct of the included studies.

Agreements and disagreements with other studies or reviews

In the previous update of the review, we found one review article of PARPi in gynaecological cancers, including epithelial ovarian cancer, that did not identify any additional studies (Reinbolt 2013) and did not include a meta-analysis of the results. However, a PubMed search in July 2021 (using the broad terms “PARP” “ovarian” and “systematic review”) revealed 26 systematic reviews, subsequent to the last version of this Cochrane Review, reflecting the importance and growth of this topic since the last update of the review in 2015 (Al Hadidi 2018; Bartoletti 2020; Cheng 2021; Gong 2020; Gu 2020; Hao 2021; Jiang 2020; Kaneko 2021; Lee 2021; Li 2021; Lin 2021; Liu 2018; Mohyuddin 2020; Morice 2021; Morice 2021a; Ruscito 2020; Shao 2020; Shao 2021; Staropoli 2018;

Stodtmann 2021; Sun 2021; Tomao 2019; Wang 2020; Xu 2020; Yang 2020; Yi 2019).

Al Hadidi 2018 assessed studies of maintenance treatment in platinum-sensitive relapsed EOC. They included four studies with a total of 1264 patients (PARP n = 780). They determined that PFS was better in the PARPi group in both BRCA-positive patients (hazard ratio (HR) 0.24, 95% confidence interval (CI) 0.19 to 0.30; P < 0.00001) and BRCA-negative patients (HR 0.52, 95% CI 0.36 to 0.75; P < 0.00001). They also found a difference in overall survival (OS) between the two groups in BRCA-positive patients (HR 0.72, 95% CI 0.53 to 0.97, P= 0.03). This study is one of the excluded studies in this review (Excluded studies).

Bartoletti 2020 conducted a network meta-analysis comparing PARPi with bevacizumab in EOC platinum-sensitive recurrent EOC. They concluded that PARPi improved PFS compared with bevacizumab, especially in *BRCA*m patients who had not previously received PARPi. They calculated PFS for participants with *BRCA*m was HR = 0.46 (95% CI 0.36 to 0.59), whereas those with wild type *BRCA h*ad an HR = 0.87 (95% CI 0.63 to 1.20);. They performed a Surface Under the Cumulative RAnking curve analysis**(**SUCRA) analysis and estimated that PARPi "had the highest probability of being ranked as the most effective therapy (90% and 60%, for [sic] PARP inhibition and bevacizumab, respectively)". It should be noted that authors declared fees from pharmaceutical companies, including Amgen, Eli Lilly, Eisai, Ipsen, MSD, Novartis, Pfizer, Roche and Takeda.

Cheng 2021 looked at maintenance therapy in women with newly-diagnosed ovarian cancer, comparing PARPi with placebo. They identified four RCTs with a total of 3070 participants. In the HRD population they found that PFS was improved with PARPi (HR 0.39; 95% CI, 0.29 to 0.53), but 'no clear difference' in the homologous recombination proficient population (HR 0.83, 95% CI 0.67 to 1.03) and agreed 'no clear difference' between the groups in terms of other outcomes of OS, health-related quality of life and adverse events. They also concluded that results were probably not affected by stage, response to first-line chemotherapy and residual disease after debulking surgery.

Gong 2020 compared different PARPi regimens in *BRCA*m EOC in the first-line treatment of EOC (bevacizumab and olaparib versus veliparib and chemotherapy versus olaparib) and in a platinum-sensitive relapsed setting (olaparib, rucaparib, niraparib) in a network meta-analysis, and did not find a difference between different PARPi in terms of PFS. Toxicity of PARPi regimens was less in the first-line setting than at relapse. In an analysis of cost-effectiveness, they determined that adding bevacizumab to olaparib (US $353.72) increased the cost per unit net health benefit for patients compared with olaparib monotherapy (US $260.57).

Gu 2020 performed a meta-analysis of PARPi in solid tumours, not just EOC. They demonstrated an improvement in PFS and OS in participants with *BRCA*1/2 mutations (PFS = HR 0.32 (P < 0.001) and OS = HR 0.74 (P < 0.001) and concluded that quote: “PARP inhibitors may prolong survival" and that “PARP inhibitors were more [sic] favourable for BRCA1/2 mutations in ovarian cancer patients".

Hao 2021 looked at PARPi in patients with advanced EOC and, with a search date of January 2020, they found 10 phase II and III studies for inclusion, with a total of 4,21 participants included in survival analyses. The pooled HR (PARPi versus control group) for PFS was 0.41 (95 % CI, 0.35 to 0.50) in all included patients. The PFS had an HR of 0.51 (95 % CI, 0.40 to 0.64) in studies that included participants with both *BRCA*m and wild type; the HR for PFS was 0.32 (95 % CI, 0.26 to 0.39) in participants with a *BRCA*m, and 0.57 (95 % CI, 0.41 to 0.78) in patients with *BRCA* wild-type. They agreed that PARPi use conferred increased risks of all-grade and high-grade haematological toxicities (P < 0.05) and all-grade gastrointestinal side effects and high-grade nausea and vomiting (P < 0.05).

Jiang 2020, with a search date to April 2020, included a total of 12 studies with 5,347 participants with advanced EOC. Compared with the control group, PARPi improved PFS (HR 0.51; 95% CI, 0.40 to 0.65; P < 0.00001) and ORR (RR, 1.26; 95% CI, 1.11-1.43; P = 0.0003) this was regardless of *BRCA* and HRD status. They also found no difference in OS, in the seven studies which reported this outcome, with a pooled HR of 0.86 (95% CI, 0.73-1.01; P = 0.06). PARP inhibitors use was associated with a higher risk of haematologic events and different PARPi had differing toxicity profiles. This outcome held regardless of *BRCA* mutation status and first-line/ relapsed settings. Despite the lack of OS effect, they concluded that "PARP inhibitors are an effective and well-tolerated treatment for patients with advanced-stage epithelial ovarian cancer". The authors declared that they had no commercial conflict of interest.

Kaneko 2021 was a single-author meta-analysis of maintenance PARPi treatment in relapse platinum-sensitive EOC. With a search date of the end of July 2020, they included four studies with a total of 1079 participants and evaluated differences in restricted mean survival times (RMST). The RMST difference for up to 360 days for PARP inhibitors versus placebo for all participants was 87 days (95% CI 71 to 102 days). For those with *BRCA* mutations, the RMST was 112 days (95% CI 96 to 129 days), for those with HRD tumours the RMST was 99 days (95% CI 80 to 119), and for those with BRCA wild-type cancers, the RMST was 69 days (95% CI = 47, 92), respectively.

Lee 2021 performed a meta-analysis of PARPi in patients with EOC and a platinum-sensitive relapse. They analysed results by the following subgroups: germline *BRCA* mutation (g*BRCA*m), somatic *BRCA* mutation (s*BRCA*m), wild-type *BRCA* but HRD; and those with homologous recombinant-proficient (HRP) tumours. They included four studies with 972 participants who received a PARPi and 530 who received placebo. PFS results were as follows: g*BRCA1*m (n = 471 participants) HR = 0.29 (95% CI 0.23 to 0.37); g*BRCA2*m (n = 236 participants) HR = 0.26 (95% CI 0.17 to 0.39); sBRCAm (n = 123 participants) HR = 0.22 (95% CI 0.12 to 0.41); wild-type *BRCA* HRD tumours (n = 309 participants) HR = 0.41 (95% CI 0.31 to 0.56); wild-type *BRCA* HRP tumours (n = 346 participants) HR = 0.64 (95% CI 0.49 to 0.83). Most authors had declared a financial conflict of interest (Amgen, Arcagy Research, AstraZeneca, Boehringer Ingelheim, Clovis Oncology, GlaxoSmithKline/Tesaro, Novartis, Pfizer, Roche, Takeda, and Yuhan), including three authors who were employees of AstraZeneca, Clovis Oncology, and GlaxoSmithKline; the meta-analysis included unpublished subgroup data from AstraZeneca, Clovis Oncology, and GlaxoSmithKline.

Li 2021 was a meta-analysis specifically looking at fatigue in cancer patients caused by PARPi. They included 29 RCTs with a total of 9479 participants. PARPi increased the risk of developing all-grade (RR 1.25, 95%CI 1.20 to 1.31; P < 0.00001; I^2 = 48%) and high-grade (G3+) fatigue (RR 1.92, 95%CI 1.51 to 2.45; P < 0.00001; I^2 = 11%). Veliparib had a lower risk of fatigue and participants with ovarian cancer may

have a higher risk of fatigue than those with non-ovarian cancer. No potential conflict of interest was reported by the authors.

Lin 2021 assessed PARPi maintenance treatment in patients with newly-diagnosed advanced EOC. Four RCTs met the inclusion criteria, including 2,687 participants. PARPi were associated with improved PFS (HR = 0.53, 95% CI 0.40-0.71; P < 0.0001). The subgroup analysis for PFS by *BRCA* status were: *BRCA*m (HR = 0.35, 95% CI 0.29 to 0.42; P < 0.00001) and HRD (HR = 0.43, 95% CI 0.32 to 0.60; P < 0.00001); *BRCA*wt tumours (HR = 0.72, 95% CI 0.63-0.82; P < 0.00001) ; and HRP tumours (HR = 0.83, 95% CI 0.70-0.99; P = 0.04). OS data were not presented. The authors reported no conflicts of interest.

Liu 2018 looked specifically at gastrointestinal (GI) adverse effects of PARPi. They included 2286 participants with EOC patients from 12 studies. All-grade GI adverse events were common: nausea 68.8% (95% CI 63.5 to 73.6%); vomiting 36.2% (95% CI 30.9 to 41.8%); diarrhoea 25.3% (95% CI 21.2 to 29.8%); and constipation 25.3% (95% CI 17.9 to 34.5%). However, G3+ adverse events were uncommon; nausea 3.4% (95% CI 2.6 to 4.5%); vomiting 2.0% (95% CI 1.4 to 3.0%); diarrhoea 1.7% (95% CI 1.0 to 3.0%), and constipation 1.4% (95% CI 0.9 to 2.3%). The relative risks (RR) of all-grade adverse events were: nausea = RR 2.00 (95% CI: 1.79 to 2.24; P<0.001); vomiting = RR 2.12 (95% CI: 1.75 to 2.58; P<0.001); diarrhoea = RR 1.20 (95% CI 1.01 to 1.44; P=0.044); and constipation = RR 1.20 (95% CI: 0.88-1.80; P=0.21). The RR of G3+ adverse events were: nausea = 3.74 (95% CI: 1.50-9.36; P=0.005); vomiting = 2.81 (95% CI: 1.17-6.74; P=0.02); diarrhoea = 0.56 (95% CI: 0.22-1.43; P=0.23); and constipation = 0.92 (95% CI: 0.34-2.49, P=0.87). The authors reported no conflicts of interest.

Mohyuddin 2020 was a systematic review comparing responses to PARPi in patients with genetic and somatic *BRCA*m, not limited to ovarian cancer. They found 18 studies for inclusion, although only eight detailed response rates separately for participants with germline and somatic *BRCA*m, which were found to be similar (55.8% response versus 43.9% response for somatic and germline *BRCAm*, respectively; P= 0.003)

Morice 2021a conducted a meta-analysis specifically to look at the risk of myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) associated with PARPi, not restricted to patients with EOC. They extracted data from ClinicalTrials.gov and went next to published manuscripts, or subsequently contacted corresponding authors or sponsors to provide data, if not available. They also conducted an observational, retrospective, cross-sectional pharmacovigilance study of VigiBase. They included 28 RCTs (18 placebo and ten non-placebo RCTs), with 5693 participants in PARPi groups and 3406 participants in control groups. Data from the 18 placebo RCTs (n=7307 participants) demonstrated that PARPi increased the risk of MDS and AML compared with placebo treatment (OR 2.63, 95% CI 1.13 to 6.14, P = 0.026; I^2 = 0). The incidence of MDS and AML in PARPi groups was 0.73% (95% CI 0.50 to 1.07; I^2 = 0%; 21 events in 4533 participants) compared with an incidence of 0.47% (95% CI 0.26 to 0.85; I^2 = 0%; three events in 2774 participants) in the placebo groups. These findings were supported by the pharmacovigilance study where 99 cases of MDS and 79 cases of AMD related to PARPi therapy were extracted. In 58 patients, where data were available, the median latency period from first exposure to a PARPi to developing MDS or AML was 17.8 months (8.4 to 29.2 months; n = 58) and in the 104 cases with reported outcomes, there were 47 deaths.

Morice 2021 has only been published online, ahead of print, no abstract is available and we have not yet been able to access the full text.

Ruscito 2020 performed a systematic review with a search date of December 2019. They included 12 RCTs, including 5171 participants. They concluded that PARPi maintenance inhibitors improved PFS in both recurrent and first-line treatment for EOC, which was independent of *BRCA* mutational status. For the recurrent platinum-sensitive cohort, pooled data for PFS for PARPi versus placebo demonstrated benefit (HR 0.37, 95% CI 0.32 to 0.42) with pooled data for the first-line cohort showing similar results (HR 0.62, 95% CI 0.50 to 0.76). Interestingly, no data were presented in the abstract, nor were any OS data reported, with what appears to be reporting bias in the systematic review. They reported that severe adverse events, including haematological and fatigue, were more common with PARPi treatment. There was no conflict of interest statement that we have been able to discern in the published version, although one author is a lead author on a PARPi study. This study is one of the excluded studies in this review (Excluded studies).

Shao 2020 was a systematic review of PARPi maintenance treatment in participants with ovarian cancer, both in newly-diagnosed and in platinum-sensitive and platinum-resistant relapse and compared PARPi treatment with placebo or other chemotherapy drugs. They included nine studies in the meta-analysis, five in newly-diagnosed participants and four in recurrent disease. In total there were 4526 participants. The pooled OS data across all the studies, despite different treatment settings, and found an OS of HR = 0.78 (95%CI 0.61 to 1.01; *P* = 0.06). Similarly, they pooled PFS data across both newly diagnoses and recurrent settings and found an improvement in PFS for PARPi (HR = 0.53, 95%CI 0.43 to 0.68, *P* < 0.00001). They found an incidence of G3+ adverse events of 55.19% and "serious adverse events" of 26.29%. What constitutes “serious” was not defined. They concluded that “[PARPi] therapy can significantly improve PFS in ovarian cancer patients, but it has no benefit in OS. However, the therapy is associated with a significant increase in the risk of AEs of grade >/= 3 and serious AEs”. The authors declared that they had no competing interests and the work was funded by a national grant.

Shao 2021 was another systematic review of PARPi from the same team as Shao 2020, but focused on the treatment of participants with breast and ovarian cancer who had a *BRCA*m. They found that PFS improved for participants with both *BRCA*m breast (HR 0.64, 95% CI 0.55 to 0.75, P<0.001) and ovarian cancer (HR 0.33, 95% CI 0.27 to 0.42, P < 0.001). They agreed with our findings that OS of patients was not significantly increased (breast cancer: HR 0.87, 95% CI 0.76 to 1.01, P = 0.065; ovarian cancer: HR 0.78, 95% CI 0.61 to 1.01, P = 0.058). They concluded that [PARPi were "most beneficial to the ovarian cancer subset when administered early after diagnosis, rather than after recurrence”. Details about the number of studies and number of participants included were not stated in the abstract, but the results state that 15 RCTs were included for *BRCA*m-positive participants with breast and ovarian cancer (11 RCTs in ovarian cancer), with a total of 3,756 *BRCA*m positive patients (40% breast cancer participants and 60% ovarian cancer patients).

Staropoli 2018 included search dates of January 2008 to April 2018. PFS and adverse events were primary and secondary end-points, OS data were not presented. They included five RCTs with 1839 participants. PFS in the *BRCA*m cohort was HR 0.25 (95%CI 0.21 to 0.31; 871 participants) and for the *BRCA*wt cohort was HR 0.41 (95%CI 0.31 to 0.55; 836 participants). More severe (G3+) GI toxicities were noted with rucaparib and G3+ haematological toxicities with niraparib. Despite the lack of OS data, they concluded that "We confirm a significant benefit in survival outcome of [sic] PARPis for EOC patients". The disclosures section (after acknowledgements) was not completed and the work was performed as part of a PhD programme and funded by an academic institution.

Stodtmann 2021 was a meta-analysis of pharmacokinetic outcomes for veliparib from phase I to III trials in patients with a range of cancers, so outcomes were not relevant to this review.

Sun 2021 was a meta-analysis of GI toxicities with PARPi in a range of cancers. They found that PARPi increased the risk of "high-grade" (presumed G3+) nausea (RR 1.99, 95% CI 1.44 to 2.74), vomiting (RR 1.54, 95% CI, 1.11 to 2.14) and decreased appetite (RR 2.03, 95% CI 1.22 to 3.40). Pooled incidence rates of severe adverse events were: nausea 2.3%; vomiting 2.0%; diarrhoea 1.7%; reduced appetite 1.0%; and constipation 0.5%. Incidence of less severe GI adverse events were not given and natural frequency data relatively were difficult to find compared to RR. The authors declared that they had no conflict of interests.

Tomao 2019 was an update of a systematic review of PARPi for platinum-sensitive recurrent EOC. The number of included studies and participants was not included in the abstract, but was stated as four in the full text version (five articles), including 1677 participants (1079 PARPi and 598 placebo). Outcomes focused on PFS data, which were improved for both patients with germline *BRCA*m (0.26, 95% CI 0.21 to 0.31) and somatic *BRCA*m (HR 0.24, 95% CI 0.12 to 0.48), as well as the overall population (HR 0.49, 95% CI 0.41 to 0.59), although *BRCA*m rates and HRD across the studies may be higher than in the general EOC population. The authors declared that they had no conflict of interest.

Wang 2020 performed a systematic review of PARPi as maintenance treatment in patients following first-line treatment of EOC. They included three RCTs (all included in this review), with 1881 participants. The authors declared that there was "absence of any commercial or financial relationships that could be construed as a potential conflict of interest". Overall PFS was improved with PARPi (HR, 0.51; 95% CI, 0.33–0.80). OS data were not presented. These findings were robust for subgroup analyses by age group, stage, timing of surgery (upfront versus interval debulking). Improvement in PFS was not significant for those without a *BRCA*m (HR 0.67, 95% CI 0.43 to 1.04), but was for the subset of participants where data were reported by HRD status (HRD cohort (HR 0.5, 95% CI 0.38 to 0.66) and for those with HRP (0.75, 95% CI 0.60 to 0.93). They reported some adverse events in a narrative review by study/individual PARPi. The link to the meta-analysis data in figures is limited to PFS data, not SAE or QoL data.

- In SOLO 1 (olaparib) anaemia was the most common G3+ adverse event (22% in PARPi group versus 2% in control);
- In VELIA (veliparib) G3+ thrombocytopaenia was most common (28% in PARPi group versus 8% in control);
- In PRIMA (niraparib) any G3+ adverse events were common in the study arm (70% in PARPi group versus 18.9% in control), with haematological toxicities being the most common.

Xu 2020 was a network meta-analysis of PARPi treatment, in patients with platinum-sensitive EOC, with a primary end-point of PFS, with analysis by *BRCA*m and HRD status. PFS was improved with PARPi maintenance treatment in participants and was similar in participants with *BRCA*m and HRD. They presented data by treatment: chemotherapy plus olaparib followed by olaparib maintenance (olaparib-throughout) (HR 0.51, 95% CI 0.34 to 0.76); rucaparib maintenance (HR 0.37, 95% CI 0.30 to 0.45); olaparib maintenance only (HR 0.35, 95% CI 0.25 to 0.49); and niraparib maintenance (HR 0.38, 95% CI 0.30 to 0.4). The rank probability (SUCRAs) of PFS in participants was: olaparib (79.1%) > rucaparib (72.5%) > niraparib (66.7%) > olaparib-throughout (31.6%) > Placebo (0.016%), which were similar in BRCAm and HRD participant subgroups. Discontinuation of treatment due to adverse events was commoner in the PARPi groups in the whole population. All had an increase in G3+ adverse events compared to placebo in maintenance treatment (rucaparib (RR 3.8, 95% CI 2.8 to 5.6); olaparib (RR 2, 95% CI 1.5 to 2.6); and niraparib (RR 3.3, 95% CI 2.5 to 4.4)). G3+ adverse events were commoner in the rucaparib and niraparib groups than for olaparib (SUCRAs = placebo (100.0%) > olaparib (66.4%) > niraparib (25.7%) > rucaparib (7.8%). They concluded that "clinicians should consider adverse events" but that these were "generally manageable". The authors stated that there was an "absence of any commercial or financial relationships that could be construed as a potential conflict of interest".

Yang 2020 was a systematic review of PARPi in EOC with a search date to February 2020. They excluded treatments that included neoadjuvant chemotherapy. They included three phase II RCTs and seven phase III RCTs with 5006 participants in total. They included both PFS and OS outcomes and concluded that both PFS and OS were improved across all cohorts (PFS = HR 0.44 95% CI, 0.34 to 0.53; and OS = HR 0.79, 95% CI 0.65 to 0.94), and were similar by *BRCA*m and HRD status. However, the forest plots are difficult to interpret, with more than one data point from each study in each forest plot with no explanation as to the difference between the data points. There were no conflicts of interests declared.

Yi 2019 was a systematic review of PARPi in a variety of cancers cancer comparing outcomes in participants with HRD and HRP tumours. They included 13 studies. Eight were studies of participants with ovarian cancer and six were studies including other cancers: breast cancer (1 study); gastric cancer (2 studies); colorectal cancer (2 studies); and prostate cancer (1 study). One study included participants with breast and ovarian cancer. Outcomes included PFS and OS. Participant cohorts were as follows: *BRCA*m HRD, n = 697; *BRCA*wt HRD, n = 478; and HRP (n = 1417). They reported PFS at 6- and 12-months and found that the BRCAm/HRD population had an increased PFS at 6 months (OR 2.29, 95% CI 1.03 to 5.08) and 12 months (OR 1.95, 95% CI 1.26 to 3.01) compared with *BRCA*wt/HRD participants. BRCAwt/HRD participants had a higher PFS at 6 (OR 1.72, 95% CI 1.27 to 2.43) and 12 months (OR 1.85, 95% CI 1.31 to 2.62) than HRP patients. There were no conflicts of interests declared.

It should be noted that some of these systematic reviews were at risk of bias since authors had stated (or sometimes not) conflicts of interest, for others conflict of interest statements, were not apparent. Few, if any, of the studies reported an assessment of the

quality of the included studies, and certainty of the results, with a GRADE assessment or similar. Data presented in abstracts were often incomplete and did not all meet reporting guidance (PRISMA and EQUATOR). Some studies included questionable comparisons of different groups and the conclusions, in some cases, overly promoted the benefits of PARPi treatment, especially those that only included PFS data. It is of concern that some systematic reviews make strong recommendations supporting PARPi use, despite the lack of reporting of OS data.

AUTHORS' CONCLUSIONS

Implications for practice

Patients with epithelial ovarian cancer (EOC) of high-grade serous and endometrial serotypes have a relatively high risk of germline *BRCA* mutation and national guidelines recommend that these patients should be offered genetic screening (NICE [CG164] 2019; Risch 2001). This would be irrespective of whether poly (ADP-ribose) polymerase) inhibitors (PARPi) are effective, since it has implications for patients and their families.

These data suggest that the use of PARPi as a maintenance therapy is of benefit in terms of slowing initial disease progression. Progression-free survival (PFS) was improved in those who received PARPi, regardless of the type of PARPi used, as maintenance therapy, when compared to those who received a placebo in both the primary and recurrence setting (Analysis 3.3; Analysis 5.2). However, it is less clear if maintenance PARPi treatment, in either setting, leads to an improvement in overall survival (OS). Improvement in PFS comes at the expense of an increase in adverse events (Analysis 3.7; Analysis 5.12). We did not find that the use of PARPi as a monotherapy alternative to other chemotherapy, or in combination with chemotherapy, improved PFS or OS in either the primary treatment or recurrence setting. Combination of a PARPi with chemotherapy increased rates of adverse events (Analysis 1.6; Analysis 2.5; Analysis 7.5). In contrast, the addition of PARPi to chemotherapy that includes bevacizumab did lead to improved PFS; this finding, however, is limited to one study (PAOLA-1). These findings continue into our subgroup analysis of those with known pathogenic variants in *BRCA1/2* or homologous recombination DNA repair deficiency (HRD).

Due to increasing ability to salvage women with recurrent disease with further treatment options, and a significant risk of cross-over for those who did not have a PARPi after first-line treatment, the correlation between PFS and OS in first line treatment of EOC has weakenedSjoquist 2018. In their systematic review of studies comparing PFS and OS for first-line treatment of advanced EOC, Sjoquist 2018 found that there was was only a moderate correlation (r^2 = 0.52) between PFS and OS, which has weakened over time with the introduction of biological agents.They speculated reasons for this, which may include a difference in the definition of progression and increasing cross-over and other salvage therapies postprogression. They found that fhat few studies detail post-progression therapies.

PARPi can be considered as a maintenance therapy after either primary treatment or treatment of recurrent disease, in those who have not previously received a PARPi, for the improvement of PFS. However, beneficial effects in terms of overall survival (OS) have not been established and therefore PARPi maintenance treatment should be carefully discussed with patients, so they are able to make an informed choice, weighing up the benefits against increased risks of side effects and potential impact on quality of life. This is echoed in the current National Institute of Health and Care Excellence (NICE) guidance on the use of PARPi in EOC, which currently makes PARPi (or olaparib plus bevacizumab) available via the cancer drug fund, rather than officially endorsing, until further data are available (NICE [CG164] 2019; NICE [TA598] 2019 ; NICE [TA611] 2019; NICE [TA620] 2020; NICE [TA673] 2021; NICE [TA693] 2021).

Treatment in EOC is becoming highly complex, with an ever-increasing number of biological agents, used in multiple combinations. Further updates of this review should consider a network meta-analysis approach, combining different biological agents used alongside chemotherapy and as maintenance treatment, with separate reviews for treatment at diagnosis, and in platinum-sensitive and platinum resistant/refractory disease settings, in order to further inform patient care.

Implications for research

Our data indicate that the use of PARPi in the maintenance setting improves PFS survival in women with EOC. Data do not demonstrate a similar improvement in OS, however, although these data are immature. These new data have answered some of the questions that remained from our previous version of this review (Wiggans 2015. Despite improvement in PFS, many women will progress on PARPi and will ultimately succumb to their disease. The mechanisms that lead to PARPi resistance within EOC of acute interest. It is evident that EOC has the ability to develop resistance to PARPi and overcome maintenance therapy (McMullen 2020). By describing these mechanisms, researchers may have the opportunity to originate novel adjuvant therapies that could prolong the effect of PARPi or prevent resistance. This should be seen as a funding priority.

Our data indicate that the combination of PARPi and bevacizumab may improve PFS. However, our analysis is based on data from one study AVANOVA2. Therefore, further studies would improve our confidence in this finding. What is more, it is not clear, if bevacizumab should be used in combination with PARPi, or if it would have more utility if used when those on PARPi relapse. In addition, there are limited data about the use of PARPi in combination with novel immune therapies. The JAVELIN study failed to show any benefit from the addition of avelumab. However, there has been some degree of criticism as to the selection criteria for this study (Yonemori 2019). Therefore, the use of immunotherapy in combination with PARPi remains an area of equipoise.

The impact of the timing of surgery, be it primary or interval debulking, and the use of PARPi is not clear from these data. The current literature has captured little regarding the timing of the surgery and the level of cytoreduction at surgery. Such granularity could help identify subgroups of patients with EOC who may be better suited to PARPi. Moreover, it could help identify optimal treatment regimens.

In these data, the risk of adverse events (grade three or higher) was increased when PARPi were used as a maintenance therapy. This was to clinically significant levels. This leads to women, not infrequently, choosing to stop a treatment. Future studies should therefore explore ways to mitigate adverse effects in those taking

PARPi as a maintenance therapy, or ways to better identify those who are more likely to benefit from PARPi, thereby sparing those who do not side effects that may limit quality of life.

Long-term harms data is sparse from the use of PARPi as a maintenance therapy in patients with EOC. Given that PARPi impede DNA repair, concerns have been raised as to wether or not they increase the risk of subsequent malignancies, especially haematological malignancies, such as MDS and AML (Morice 2021). *In vivo* data would suggest that their long term use is relatively safe (Póti 2018), but this needs to be collaborated with long-term data from clinical trials and population-level data from registries and good post-market surveillance.

Finally, and most importantly, any studies of maintenance treatment in ovarian cancer, which for many is a life-limiting illness, should assess both OS and the long-term effects on quality of life, not just a surrogate outcome of PFS, which may have little real benefit to patients. Kovic 2018 performed a systematic review and quantitative analysis examining how PFS correlated with health-related quality of life (HRQoL) in oncology studies. They noted that PFS was designed as a measurement tool to identify signals of clinical activity on drug development studies and observed that this has now become the primary outcome measure in many cancer studies. They speculated that PFS is an appealing outcome, especially for pharmaceutical companies, as PFS require reduced numbers of participants for statistical power, and further reduce costs as studies with PFS as the primary outcome require shorter follow-up than studies reporting OS. Arguments for using PFS as the primary outcome include the avoidance of confounders from cross-over designs and subsequent variation in treatment after progression. They argued that PFS is only a valid surrogate end-point if: (1) PFS is a valid predictor of OS differences; and (2) if patients who live longer without disease progression have a better overall HRQoL.

Kovic 2018 conducted a systematic review of human cancer RCTs published from January 2000, to May 2016 and identified 52 articles reporting on 38 RCTs, of which only 24 reported both PFS and HRQoL data in a single article. Although many studies included HRQoL outcomes, many failed to publish or report these data in formats that allowed quantitative analyses, and so were excluded from their analysis. Of 2351 potentially includable articles, 2303 were excluded, including for the following reasons: 811 only included PFS data; 490 had insufficient HRQoL data for analysis; 145 had PFS/HRQoL data missing; and 44 only included HRQoL data. Interestingly, 24/38 (60%) of the studies had shorter HRQoL follow-up than median PFS. Using simple regression analysis, they failed to find an association between PFS and HR QoL outcomes. They concluded that their findings "...raise questions regarding the assumption that interventions prolonging PFS also improve HRQoL in patients with cancer....clinical trial investigators should measure HRQoL directly and accurately, ensuring adequate duration and follow-up." Their findings also demonstrate how poorly HRQol data are reported in cancer studies generally, despite this being one of the most significant outcomes for patients.

Sjoquist 2018 cautioned the reliance upon PFS as a surrogate outcome, given the weakening correlation with OS in first-line studies of EOC. They suggested supporting PFS data with additional end points, including patient-reported outcome measures (including QoL), time to second disease progression (PFS2), and time to first and second subsequent treatments(Herzog 2014). Alternative primary outcomes, which may be of greater relevance for patient decision-making, as well as regulatory approval, include quality-adjusted PFS (QA-PFS) (Glasziou 1990) and Q-TWiST, as these may be a measure of net clinical benefit and, hopefully, lead to an improvement in the recording of patient-reported outcomes. These outcomes should, however, be pre-specified in studies to reduce the risk of selective outcome reporting bias and, it should be acknowledged.

Without mature OS and good quality of life data, patients are making decisions based on the hope of improvement in survival, which may be at the expense of significant symptoms. This is inappropriate and adequate reporting of outcomes important to patients, including OS, quality of life and other patient-reported outcomes, should be mandatory in this treatment setting, as for many this may turn out to be palliative chemotherapy. Concerns regarding publishing surrogate end-point PFS, without adequate HRQoL data, raised by Kovic 2018, should be addressed by those who lead clinical trials, reviewers and publishers. Consistent and comprehensive reporting of high-quality HRQoL data, using recognised scoring systems and reporting of data in formats that are openly available and extractable, is highly recommended.

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Wiggans 2015

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ARIEL3

Study characteristics	
Methods	**Study design**: a randomised, double-blind, placebo-controlled, phase 3 trial **Accrual**: 7 April, 2014 to 19 July 2016. **Location of recruitment sites**: multi-country (11 countries) **Funding**: Clovis Oncology **Median follow-up time**: 28.1 months (IQR 22 to 33.6) The randomisation ratio was 2:1 stratified by homologous recombination repair gene mutation status, progression-free interval after the penultimate platinum-based regimen, and best response to the most recent platinum-based regimen.
Participants	564 pts meeting the following criteria underwent randomisation to trial arms: • 18 years or older; • platinum-sensitive high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube carcinoma; • completion of at least two previous platinum-based chemotherapy regimens (previous treatment with bevacizumab was permitted with the exception of bevacizumab maintenance treatment after the most recent platinum-based regimen).

ARIEL3 *(Continued)*

	The median age of pts was 61 years (IQR 53 to 67) in rucaparib arm (RUC) and 62 years (IQR 53 to 67) in the placebo (PLB) arm. High-grade serous type tumour: RUC none, PLB 1 (1%) BRCA mutation: RUC 130 (35%), PLB 66 (35%) BRCA1: RUC 80 (21%), PLB 37 (20%) BRCA2: RUC 50 (13%), PLB 29 (15%) The ECOG performance status (PS) was known for all randomised pts: ECOG 0: RUC 280 (75%), PLB 136 (72%) ECOG 1: RUC 95 (25%), PLB 53 (28%) The number of pts with measurable disease assessed by the investigator was 141 (38%) in RUC arm and 66 (35%) in PLB arm. The proportion of participants with HRD mutation was not given.
Interventions	The experimental arm (375 pts) included oral RUC (600 mg twice daily) in continuous 28-day cycles. The comparator arm (189 pts) included matching PLB also in continuous 28-day cycles. Both options were administered until disease progression, death, or other reason for discontinuation.
Outcomes	**PRIMARY:** investigator-assessed PFS **SECONDARY:** PFS according to blinded independent central review, patient-reported outcomes (the FOSI-18 disease-related symptoms–physical subscale), OS, safety (grading system not specified) and population pharmacokinetic modelling
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated sequence (block size of six, stratified by homologous recombination repair gene mutation status, progression-free interval after the penultimate platinum-based regimen, and best response to the most recent platinum-based regimen).
Allocation concealment (selection bias)	Low risk	Patients were assigned to the rucaparib or placebo group in a masked manner with use of Almac Clinical Technologies' interactive web and voice response system (IXRS); To ensure masking was maintained, rucaparib and placebo tablets were manufactured to have identical appearances.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, investigators, site staff, assessors, and the funder were masked to assignments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients, investigators, site staff, assessors, and the funder were masked to assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy and safety data: ITT population Discontinued treatment RUC 282 (75%), PLB 180 (95%)

ARIEL3 *(Continued)*

		Reasons for discontinuation were given.
Selective reporting (reporting bias)	Low risk	OS immature Patient-reported health outcomes will be shown in a secondary publication (Coleman 2017) No concern over selective reporting
Other bias	Unclear risk	• Industry-sponsored trial with several authors disclosing a financial conflict of interest.

AVANOVA2

Study characteristics	
Methods	**Study design**: a two-arm, open-label, phase II, randomised study (inferiority) **Accrual:23** May 2016 to 6 March 2017 **Location of recruitment sites**: USA, Denmark, Sweden, Finland and Norway **Funding**: Nordic Society of Gynaecological Oncology and Tesaro, Inc. **Median follow-up time:** 16.9 months (IQR 15.4 to 20.9) The randomisation ratio was 1:1 stratified by homologous recombination deficiency status and chemotherapy-free interval.
Participants	97 participants meeting the following criteria underwent randomisation to trial arms: • 18 years or older, • recurrent platinum-sensitive epithelial ovarian, fallopian tube, or peritoneal cancer • high-grade serious or high-grade endometrioid histology, • prior line of platinum-containing therapy for primary disease (up to one non-platinum-based line of therapy in the recurrent setting), • ECOG PS 0 to 2, • life expectancy of at least 12 weeks. The median age of pts was 67 years (IQR 59 to 70) in niraparib with bevacizumab arm (NIR+BEV) and 66 years (IQR 58 to 70) in niraparib (NIR) only arm. HRD mutations: NIR+BEV 28 (58%), NIR 30 (61%) BRCA positive: NIR+BEV 15 (31%), NIR 18 (37%) 94% of pts (91 of 97) had at least one post-baseline tumour evaluation according to RECIST. The proportion of pts with high-grade serous type, BRCA1, BRCA2 and by the grade of ECOG PS were not given.
Interventions	The experimental arm (48 pts) included oral NIR (starting dose of 300 mg) three capsules once a day for 21 days in combination with intravenous BEV (15 mg/kg on day 1 every 3 weeks). The comparator arm (49 pts) included only oral NIR (starting dose of 300 mg) given as three capsules once daily for 21 days.
Outcomes	**PRIMARY**: investigator-assessed PFS **SECONDARY**: Disease Control Rate (complete response, partial response, or stable disease for ≥12 weeks), ORR according to RECIST (v1.1), patient-reported outcomes, safety (NCI CTCAE v4.0) and tolerability. Overall response according to GCIG criteria will be reported separately.

AVANOVA2 *(Continued)*

Notes	AVANOVA is a proof-of-concept trial which aimed only to identify the more active regimen for phase 3 evaluation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients enrolled by investigators were randomised in a 1:1 ratio using random permuted block randomisation (block sizes three and six in the original three-group design; block sizes two and four in the amended two-group design) implemented by Sealed Envelope Ltd
Allocation concealment (selection bias)	Low risk	Patients enrolled by investigators were randomised in a 1:1 ratio using random permuted block randomisation (block sizes three and six in the original three-group design; block sizes two and four in the amended two-group design) implemented by Sealed Envelope Ltd
Blinding of participants and personnel (performance bias) All outcomes	High risk	No-one was masked to treatment assignment in this open-label trial and no independent review of tumour response was done in this proof-of concept trial, which aimed only to identify the more active regimen for phase 3 evaluation
Blinding of outcome assessment (detection bias) All outcomes	High risk	No-one was masked to treatment assignment in this open-label trial and no independent review of tumour response was done in this proof-of concept trial, which aimed only to identify the more active regimen for phase 3 evaluation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy and safety data: 97 of 103 randomised participants (94%) 103 patients were initially enrolled and the 6 patients assigned to bevacizumab alone (of those randomly assigned to interventions in the 3-arm trial) were then excluded following trial amendment. Discontinued treatment: 33/48 NIR+BEV, 44/49 NIR Reasons for discontinuation reported.
Selective reporting (reporting bias)	Low risk	OS immature No concern over selective reporting
Other bias	Unclear risk	• Industry-sponsored trial with several authors disclosing a financial conflict of interest

CLIO

Study characteristics

Methods	**Study design**: a randomised, phase II study **Study start**: August 2016 **Estimated study completion**: May 2019 (Source: ClinicalTrial.gov) **Location of recruitment sites**: Belgium **Funding**: AstraZeneca **Median follow-up time**: unknown

CLIO *(Continued)*

Participants	100 pts meeting the following criteria underwent randomisation to trial arms: • recurrent epithelial carcinoma of the ovary, fallopian tube or primary peritoneum; • platinum-sensitive disease; • at least 1 previous line of chemotherapy; • Measurable disease at study entry; • normal organ and bone marrow function measured within 28 days of randomisation; • WHO PS 0 to 2. No details of participants characteristics were available.
Interventions	The experimental arm (67 pts) included oral olaparib (OLA)(300 mg twice daily) for 28 days in 28-day cycles. The comparator arm (33 pts) included physician's choice chemotherapy (chemotherapy): carboplatin with gemcitabine or carboplatin with paclitaxel or carboplatin with liposomal doxorubicin or liposomal doxorubicin 4-weekly or topotecan or paclitaxel weekly.
Outcomes	**PRIMARY**: Overall Objective Response [Time Frame: 1 year after end inclusion] (source: ClinicalTrials.gov)
Notes	• Data for this trial are available only from a conference abstract. • Possibility of crossover at the time of progression. • **Trial status:** unknown (Latest update on ClinicalTrials.gov: October 18, 2018)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Lack of sufficient information
Allocation concealment (selection bias)	Unclear risk	Lack of sufficient information
Blinding of participants and personnel (performance bias) All outcomes	High risk	open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	open-label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lack of sufficient information
Selective reporting (reporting bias)	Unclear risk	Lack of sufficient information
Other bias	Unclear risk	Industry-sponsored trial

ICEBERG 3 (Kaye 2012)

Study characteristics

ICEBERG 3 (Kaye 2012) *(Continued)*

Methods	**Study design**: a randomised, open-label, phase 2 study **Accrual**: not reported **Location of recruitment sites**: multi-country (9 countries) **Funding**: AstraZeneca **Median follow-up time**: not reported The randomisation ratio was 1:1:1 stratified by to BRCA1 or BRCA2 status and platinum sensitivity.
Participants	97 pts meeting the following criteria underwent randomisation to trial arms: • 18 years or older; • with histologically- or cytologically-confirmed recurrent epithelial ovarian, primary peritoneal or fallopian tube carcinoma; • confirmed BRCA1/2 mutation; • recurrence within 12 months of the most recent platinum-based chemotherapy regimen; • ECOG PS 0 to 2; • life expectancy > 16 weeks; • one or more measurable lesions according to RECIST criteria; • no previous exposure to pegylated liposomal doxorubicin. The mean age of pts was 57.2 years (range 45 to 77) in olaparib 200 mg arm (OLA 200), 53.8 years (range 35 to 76) in olaparib 400 mg (OLA 400), and 54.3 (range 43 to 81) in pegylated liposomal doxorubicin (chemotherapy) arm. Platinum-resistant disease: OLA200 18 (56.3%), OLA400 16 (50%), chemotherapy 14 (42.4%) High-grade serous type tumour: OLA200 25 (78.1%), OLA400 24 (75%), chemotherapy 26 (78.8%) BRCA1: OLA200 26 (81.3%), OLA400 28 (87.5%), chemotherapy 27 (81.8%) BRCA2: OLA200 6 (18.8%), OLA400 4 (12.5%), chemotherapy 6 (18.2%) The ECOG PS was known for all pts: ECOG 0: OLA200 16 (50%), OLA400 19 (59.4%), chemotherapy 19 (57.6%) ECOG 1: OLA200 13 (40.6%), OLA400 13 (40.6%), chemotherapy 13 (39.4%) ECOG 2: OLA200 3 (9.4%), OLA400 0, chemotherapy 1 (3%) The proportion of participants with HRD mutation was not given.
Interventions	The experimental arms included OLA in a dose of 200 mg twice a day (32 pts) and 400 mg twice a day (32 pts). The comparator arm (33 pts) included chemotherapy with intravenous pegylated liposomal doxorubicin 50 mg/m^2 every 28 days. NB. Eight women who progressed on chemotherapy crossed over from chemotherapy to OLA 400 mg group.
Outcomes	**PRIMARY:** PFS **SECONDARY:** ORR, disease control rate, overall duration of response, best percentage change in tumour size, best percentage change from baseline in CA-125 Levels, confirmed RECIST response and/or CA-125 response, OS, best quality of life (QoL) response for Trial Outcome Index (TOI), Best QoL response for total Functional Analysis of Cancer Therapy - Ovarian (FACT-O), best QoL response for FACT-O Symptom Index (FOSI).

ICEBERG 3 (Kaye 2012) *(Continued)*

Notes	The same study as the ICEBERG 3 (Kaye 2012) study identified as ongoing in an initial version of the review. Higher response rates in the pegylated liposomal doxorubicin group compared to other studies attributed to high proportion with BRCA mutation, as evidence from other studies that this improves response rate to pegylated liposomal doxorubicin. Clinical trial identifiers: ICEBERG 3; NCT00628251; D0810C00012; EUCTR2007-007622-22- GB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: ''randomisation assignment list was computer-generated using the Global Randomisation system (DRand)"
Allocation concealment (selection bias)	Low risk	Quote: "patients were randomly assigned sequentially using an Interactive Voice Response System"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "centrally reviewed tumour assessment for all patients with RESIST scans were used for sensitivity analysis" Correspondence with authors confirmed that central reviewers were blinded to treatment groups, which is of low risk, but other outcomes at unclear risk of bias, as open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients lost to follow-up and all accounted for in CONSORT flowchart
Selective reporting (reporting bias)	Low risk	Outcome measures as declared at trial registration on www.ClinicalTrials.gov
Other bias	Unclear risk	Several investigators disclosed financial links to AstraZeneca

Kummar 2015

Study characteristics

Methods	**Study design**: a randomised, open-label, phase 2 trial **Accrual**: not reported **Location of recruitment sites:** Canada and USA **Funding**: the National Cancer Institute (NIH) **Median follow-up time**: not reported The randomisation ratio was 1:1. The trial used a phase 2.5 design. Patient data were analysed with and without being stratified by known BRCA mutation status.
Participants	75 participants meeting the following criteria underwent randomisation to trial arms: • 18 years or older; • histologically-documented BRCA mutation-positive ovarian cancer (documented deleterious BRCA1/2 mutation or a BRCAPRO score of >=30%) and primary peritoneal cancer, fallopian tube cancer,

Kummar 2015 *(Continued)*

	or HGSOC (patients with pretreated primary peritoneal cancer, fallopian tube cancer, HGSOC, or BRCA-mutant ovarian cancer); • pts received at least one line of standard therapy; • have measurable disease; • Karnofsky PS >=70%; • Previous anticancer therapy or surgery must have been completed at least 4 weeks before enrolment. The median age of pts in the trial was 58 years (range 37 to 79). BRCA mutation was present in 31 pts (41%). Karnofsky PS was known for all pts with 23 pts scoring 100%, 33 pts scoring 90%, 17 pts scoring 80% and 2 pts scoring 70%.
Interventions	The experimental arm (37 pts) included veliparib with cyclophosphamide (VEL+CHemotherapy) administered orally 4x per day (C 50 mg, V 60 mg) at 21-day intervals until disease progression. The comparator arm (38 pts) included cyclophosphamide alone (chemotherapy) at 50 mg once daily. At progression, those in the comparator arm were able to cross over to experimental treatment.
Outcomes	**PRIMARY**: percentage of participants with an overall response rate, PFS **SECONDARY**: number of participants withaAdverse events, change in Poly-ADP Ribose (PAR) concentration levels from baseline, change in ϒH2AX- Positive Circulating Tumor Cells (CTCs) in whole blood, number of participants with deleterious mutations in DNA repair genes.
Notes	No HR for OS or PFS reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Pts were randomised to receive either C alone or V+C". No additional information provided by authors
Allocation concealment (selection bias)	Unclear risk	No additional information provided by authors
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label - not reported that assessors were blinded. No additional information provided by the authors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 75 patients accounted for at end of study
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Closed early at interim analysis as fewer responses in combination arm than pre-specified in power calculation but powered to only detect a 20% difference in response rates. The authors did not provide further data/clarification.

NCT02446600

Study characteristics	
Methods	**Study design**: a randomised, phase III study **Accrual**: 4 February 2016 to 13 November 2017 **Location of recruitment sites**: USA, Canada, Japan and South Korea **Funding**: National Cancer Institute **Median follow-up time: u**nknown The randomisation ratio was 1:1:1 stratified by *BRCA* mutation status, the platinum-free interval, and prior anti-angiogenic therapy.
Participants	565 pts (528 initiated treatments) meeting the following criteria underwent randomisation to trial arms: • platinum-sensitive recurrent high-grade serous or high-grade endometrioid ovarian, primary peritoneal, or fallopian tube cancers; • other ovarian cancers ware also eligible provided that the pts had a known deleterious germline BRCA1 or BRCA2 mutation, RECIST 1.1 measurable disease or evaluable disease; • a first-line platinum-based regimen with or without intravenous consolidation chemotherapy; • ECOG 0-2 (Karnofsky >= 60%). BRCA mutation was present in 134 pts (23.7%). No more details of participants characteristics were available.
Interventions	The experimental arms included oral olaparib (189 pts, OLA) 300 mg twice a day, and oral olaparib 200 mg twice a day with once a day 30 mg oral cediranib maleate (189 pts, OLA+CED). Cycles repeat every 28 days in the absence of disease progression or unacceptable toxicity. The comparator arm (187 pts) included standard of care chemotherapy (chemotherapy), i.e. platinum-based chemotherapy - carboplatin/paclitaxel; carboplatin/gemcitabine; or carboplatin/liposomal doxorubicin).
Outcomes	**PRIMARY**: PFS using RECIST v1.1 **SECONDARY**: OS, frequency and severity of adverse effects, patient-reported scores of disease-related symptoms as measured by the National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Ovarian Symptom Index-18 Disease-Related Symptom-Physical.
Notes	• Data for this trial are available only from a conference abstract. • Actual primary completion on ClinicalTrials.gov: 23 Feb 2020. • Out of 565 randomised,528 pts initiated their treatment (166 chemo, 183 OLA, 179 CED+OLA) • Trial status: active, not recruiting (latest update on ClinicalTrials.gov: 8 April 2020) • Results submitted to ClinicalTrials.gov: 23 February 2021.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Lack of sufficient information
Allocation concealment (selection bias)	Unclear risk	Lack of sufficient information

NCT02446600 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lack of sufficient information
Selective reporting (reporting bias)	Unclear risk	Lack of sufficient information
Other bias	Unclear risk	Lack of sufficient information

NOVA

Study characteristics	
Methods	**Study design**: a randomised, double-blind, placebo-controlled, phase 3 trial **Accrual**: 23 August 2013 to unspecified (database lock: 20 June 2016) **Location of recruitment sites**: Canada and USA **Funding**: Tesaro, Inc. **Median follow-up time (at the data cutoff)**: 16.9 months (IQR 13.8 to 21.4) The randomisation ratio was 2:1 stratified by the time to progression after completion of the penultimate platinum regimen, the use of bevacizumab in conjunction with the penultimate or last platinum regimen, and the best response during the last platinum regimen.
Participants	553 pts meeting the following criteria underwent randomisation to trial arms: • 18 years or older; • histologically-diagnosed recurrent ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with predominantly high-grade serous histological features; • sensitivity to platinum-based treatment; • received at least two platinum-based regimens. NB: The trialists enrolled two independent cohorts on the basis of the presence or absence of a germline BRCA (gBRCA) mutation. Patients were randomly assigned not later than 8 weeks after completing their last dose of platinum-based therapy. The median age of pts with gBRCA was 57 years (range 36 to 83) in niraparib (NIR) arm and 58 years (range 38 to 73) in placebo (PLB) arm. The median age of pts without gBRCA mutation was 63 years (range 33 to 84) in NIR arm and 61 years (range 34 to 82) in PLB arm. Overall, 210/533 (38%) pts had gBRCA mutation: 128 (23%) had BRAC1, and 69 (13%) had BRAC2. 40% of the patients in the non-gBRCA cohort were assumed to have an HRD-positive tumour. Overall 49.2% of pts had a partial response to the most recent platinum therapy. In the gBRCA mutation cohort, 48.6% were in NIR arm and 49.2% in PLB arm. In non gBRCA mutation cohort, 50% were in NIR arm, and 48.3% in PLB arm.

NOVA *(Continued)*

	The proportion of participants with high-grade serous type and by the grade of ECOG PS was not given.
Interventions	The experimental arm (372 pts) included oral niraparib (tablet, 300mg x daily, 28-day cycles). The comparator arm (181 pts) included placebo.
Outcomes	**PRIMARY:** PFS by blinded central radiological and clinical review. **SECONDARY:** patient-reported outcomes, chemotherapy-free interval, time to first subsequent therapy, PFS2, time to second subsequent therapy, OS and safety (NCI CTCAE v.4.02).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	From the trial's protocol: Quote: "Each patient who completes the study screening assessments meets all eligibility criteria and is accepted for the study will be assigned a unique identification number and will receive the corresponding treatment/sequence according to a randomization scheme generated by the IWRS vendor. The randomization schedule will be prepared by the IWRS vendor using a validated program. The IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment/sequence group and will specify a unique medication number for the investigational product to be dispensed to the patient." Randomisation was performed within each cohort separately.
Allocation concealment (selection bias)	Low risk	From the trial's protocol: Quote: "Each patient who completes the study screening assessments meets all eligibility criteria, and is accepted for the study will be assigned a unique identification number and will receive the corresponding treatment/sequence according to a randomization scheme generated by the IWRS vendor. The randomization schedule will be prepared by the IWRS vendor using a validated program. The IWRS will assign a randomization number to the patient, which will be used to link the patient to a treatment/sequence group and will specify a unique medication number for the investigational product to be dispensed to the patient. [...] “A separate randomization list will be created for each cohort."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study patients, Investigators, study personnel at sites, and the Tesaro study team and its representatives were blinded to the identity of the assigned treatment from the time of randomisation until final database lock. Patients who were ongoing in the study at the time of database lock remained blinded to their treatment assignments, as did the site investigators and study personnel (Methods in the Appendix)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent radiological review and central review by a clinician who was unaware of study-group assignments were used to define disease progression, with an identical schedule of assessments used in the two cohorts.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Efficacy data:** ITT population (defined as all the patients who underwent randomisation in each of the two cohorts). **Safety data:** the safety population (all the patients who had received at least one dose of niraparib or placebo). Discontinued treatment: gBRCA 89/138 NIR, 61/65 PLB non gBRCA 185/234 NIR, 102/116 PLB Reasons for discontinuation reported.

NOVA *(Continued)*

Selective reporting (reporting bias)	Low risk	OS immature (secondary outcome) Quote: "QTc not in the main manuscript but in the protocol, Chemo free interval and evaluation of clinical parameters also in the protocol but not the main manuscript." Missing outcomes are not primary ones.
Other bias	Unclear risk	• Industry-sponsored trial with several authors disclosing a financial conflict of interest

Oza 2015

Study characteristics	
Methods	**Study design**: a randomised, open-label, phase II trial **Accrual**: 12 February and 30 July, 2010 **Location of recruitment sites**: multi-country (12 countries) **Funding**: AstraZeneca **Median follow-up time**: PARP inhibitor (olaparib) with chemotherapy 33.4 months (IQR 20.4, 42.9), chemotherapy only 32.2 months (19.5–43.6) in chemotherapy only The randomisation (1:1) stratified by the number of platinum treatments and platinum-free interval.
Participants	162 participants meeting the following criteria underwent randomisation to trial arms: • 18 years or older; • platinum-sensitive recurrent high-grade serous epithelial ovarian cancer; • received no more than 3 previous platinum-based treatments; • were progression-free for at least 6 months following the end of the last platinum treatment; • ECOG 0-2 The median age was 59 (range 27 to) in olaparib (OLA) with chemotherapy and 62 in chemotherapy only arm (range 31 to 79). BRCA status was known for 12 (15%) of pts in OLA with chemotherapy arm and 12 (16%) in chemotherapy only arm. BRCA1: OLA with chemotherapy 7 (9%), chemotherapy 10 (12%) BRCA2: OLA with chemotherapy 5 (6%), chemotherapy 2 (2%) The ECOG PS was known for 160 pts: 0: OLA with chemotherapy 58 (72%), chemotherapy 63 (78%) 1: OLA with chemotherapy 21 (26%), chemotherapy 15 (19%) 2: OLA with chemotherapy 2 (2%), chemotherapy 1 (1%) The proportion of pts with high-grade serous type, HRD mutation and with RECIST measurable disease were not given.
Interventions	The experimental arm (81 pts) included oral olaparib (200 mg twice a day, 1 to 10 of a 21-day cycle) in combination with intravenous paclitaxel (175 mg/m^2 day 1 of a 21-day cycle) and carboplatin (AUC4 day 1 of a 21-day cycle) for at least 4 cycles. This was followed by olaparib monotherapy in the maintenance phase (400 mg twice a day continuous dosing).

Oza 2015 *(Continued)*

	The comparator arm (81 pts) included chemotherapy comprised of the intravenous paclitaxel (175 mg/m^2 day 1 of a 21-day cycle) and carboplatin (AUC6 day 1 of a 21-day cycle) for 6 cycles. This was followed by a post-completion phase in which no study treatment was administered.
Outcomes	**PRIMARY**: PFS by independent central review **SECONDARY**: OS, percentage change in tumour size, the proportion of patients with an objective response (RECIST v.1.1), cancer antigen 125 (CA-125) response (Gynecological Cancer InterGroup criteria), the proportion of patients with a RECIST or CA-125 response (ovarian cancer response)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patient randomisation was stratified (using an interactive voice response [IVR]system) based on:1) number of prior platinum-containing treatment lines received(1 or >1) and 2) time to disease progression following completion of the previous platinum-containing therapy(>6 to <=12 months or >12 months)."
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessors for central RECIST review were blinded to treatment groups
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patients accounted for from randomisation, although 6 patients in control group withdrew before starting treatment
Selective reporting (reporting bias)	Low risk	Outcomes pre-specified on clinical trial registry website
Other bias	Unclear risk	• Industry-sponsored trial with several authors disclosing a financial conflict of interest.

PAOLA-1

Study characteristics

Methods	**Study design**: a randomised, double-blind, phase 3 study **Accrual**: Jul 2015 to September 2017 **Location of recruitment sites**: multi-country (11 countries) **Funding**: Arcagy Research, AstraZeneca, Merck Sharp & Dohme (a subsidiary of Merck), and F. Hoffmann–La Roche.

PAOLA-1 *(Continued)*

	Median follow-up time (primary analysis): 22.7 months (range, 18.0 to 27.7) olaparib arm, and 24.0 months (range, 18.7 to 27.7) placebo arm. Combined groups: 22.9 months. The randomisation ratio was 2:1 stratified by the outcome of first-line treatment at screening and BRCA status.
Participants	806 pts meeting the following criteria underwent randomisation to trial arms: • 18 years or older; • newly-diagnosed advanced FIGO stage III or IV, high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer or other nonmucinous epithelial ovarian cancers provided they had a deleterious germline BRCA1 or BRCA2 mutation; • after first-line treatment with platinum taxane chemotherapy plus bevacizumab (no evidence of disease or a clinical complete or partial response); • ECOG 0-1. The median age of pts was 61.0 years (range 32.0–87.0) in olaparib arm (OLA) and 60 years (range 26.0 to 85.0) in placebo (PLB) only arm. Serous histological type: OLA 519 (97%), PLB 253 (94%) BRCA positive: OLA 161 (30%), PLB 80 (30%) BRCA1: OLA 111 (22%), PLB 49 (18%) BRCA2: OLA 45 (8%), PLB 31 (12%) HRD mutations: OLA 255 (47%), PLB 132 (49%) The proportion of pts with the partial clinical response after platinum-based chemotherapy was 141 (26%) in OLA arm, and 75 (28%) pts in PLB arm. The ECOG PS was known for 796 pts: 0: OLA 378 (70%), PLB 189 (70%) 1: OLA 153 (28%), PLB 76 (28%)
Interventions	The experimental arm (537 pts) included OLA orally (300 mg twice daily) at least 3 weeks and no more than 9 weeks after the last dose of chemotherapy. The comparator arm (269 pts) included a matching placebo. Intravenous bevacizumab and chemotherapy were administered in both arms with bevacizumab continued after the randomisation as maintenance therapy (dose: 15 mg per kilogram of body weight every 3 weeks for a total duration of up to 15 months).
Outcomes	**PRIMARY**: investigator-assessed disease progression or death. Subgroup analyses of PFS and a blinded independent central review of PFS. **SECONDARY**: the time from randomisation until second disease progression or death, OS, the time until the first subsequent therapy or death, the global health status (quality of life dimension of the EORTC Quality of Life Questionnaire), and safety (NCI CTCAE v 4.03).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally with the use of a block design with stratification.
Allocation concealment (selection bias)	Low risk	Pts were assigned to trial arms (olaparib or matching placebo) with the use of an interactive Web or voice response system.

PAOLA-1 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple (participant, care provider, investigator)(source: NCTN)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Triple (participant, care provider, investigator)(source: NCTN)
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Efficacy data**: ITT population **Safety data**: safety population (all patients who received at least one dose of OLA or PLB): OLA 535/537 and PLB 267/269; **Health-related quality of life data**: used an imputation-based approach for missing questionnaires. Withdrawal before receiving the trial intervention: OLA 2, PLB 2.
Selective reporting (reporting bias)	Low risk	OS immature (secondary outcome) No concern over selective reporting
Other bias	Unclear risk	Industry-sponsored trial After discontinuation of the intervention, patients could receive other treatments at the investigators' discretion. AstraZeneca, Merck Sharp & Dohme (a subsidiary of Merck), and F. Hoffmann–La Roche were given the opportunity to review drafts of the manuscripts but were not asked to approve the final content because this was an academic-sponsored trial.

PRIMA

Study characteristics	
Methods	**Study design**: a randomised, double-blind, phase 3 trial **Accrual**: Jul 2016 - Jun 2018 **Location of recruitment sites**: International (20 countries) **Funding**: GlaxoSmithKline **Median follow-up (at the data cutoff):** 13.8 months (range, <1.0 to 28.0) The randomisation ratio was 2:1 stratified by the clinical response after first-line platinum-based chemotherapy (complete or partial response), receipt of neoadjuvant chemotherapy (yes or no), and homologous recombination status (deficient versus proficient or not determined).
Participants	733 pts meeting the following criteria underwent randomisation to trial arms: • 18 years or older; • newly-diagnosed, histologically-confirmed advanced cancer of the ovary, peritoneum, or fallopian tube; • high-grade serous or endometrioid tumours FIGO stage III or IV (including stage III disease with visible residual tumour after primary debulking surgery, inoperable stage III disease, or any stage IV disease, as well as those who had received neoadjuvant chemotherapy); • prior enrolment, all the pts had received six to nine cycles of first-line platinum-based chemotherapy resulting in a complete or partial response.

PRIMA *(Continued)*

	The median age of pts was 62 years (range 3 to 85) in niraparib (NIR) arm and 62 years (range 33 to 88) in placebo (PLB) arm. The high-grade serous type was present in 465 (95.5%) in NIR arm, and in 230 (93.5%) in PLB arm. BRCA mutation: NIR 152 (31%), PLB 71 (29%) The proportion of pts with BRCA1 or BRCA2 was not reported. HRD mutation: NIR 247 (51%), PLB 126 (51%) The ECOG performance status was known for 733 pts: ECOG 0: NIR 337 (69.2%), PLB 174 (70.7%) ECOG 1: NIR 150 (30.8%), PLB 72 (29.3%) The proportion of pts with the partial clinical response after platinum-based chemotherapy was 150 (30.8%) in NIR arm, and 74 (30.0%) in PLB arm.
Interventions	The experimental arm (487 pts) included NIR (300mg*) once daily continuously during a 28-day cycle. The comparator arm (246 pts) included PLB (once daily continuously over a 28-day cycle). *The trial was amended on 27 November 2017, to incorporate an individualised starting dose of 200 mg once daily for patients with a baseline body weight of less than 77 kg, a platelet count of less than 150,000 per cubic millimetre, or both.
Outcomes	**PRIMARY**: PFS by blinded independent central radiology review (in patients who had tumours with homologous-recombination deficiency and in the general population). **SECONDARY**: OS, the time until the first subsequent therapy, PFS 2 (defined as time from randomisation to progression while the patient was receiving a subsequent anticancer therapy), pharmacokinetic analyses, and patient-reported outcomes/QoL (scores on the FOSI, EQ-5D-5L, and EORTC-QLQ-C30/OV28 instruments), and safety (NCI CTCAE v4.03).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was performed in a double-blind manner with the use of an interactive Webresponse system, with stratification according to clinical response after first-line platinum-based chemotherapy (complete or partial response), receipt of neoadjuvant chemotherapy (yes or no), and status regarding tumour homologous recombination (deficient vs. proficient or not determined).
Allocation concealment (selection bias)	Low risk	Randomisation was performed in a double-blind manner with the use of an interactive Webresponse system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quadruple (participant, care provider, investigator, outcomes assessor) according to Clinical Trials.gov record.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The objective assessment of progressive disease was determined by central radiological and clinical review in a blinded manner, according to RECIST version 1.1.14. The primary endpoint was evaluated in a time-to-event analysis and was assessed by blinded independent central review. An independent radiological review and central clinician review that were conducted in a blinded manner were used to define the date of disease pro-

PRIMA *(Continued)*

		gression, and an identical schedule of assessments was used for the two trial groups.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy and safety data: ITT population (all randomised participants). Discontinued treatment: 307/484 NIR and 175/244 PLB Reasons for discontinuation given.
Selective reporting (reporting bias)	Low risk	No concern over selective reporting, however, QoL reported only on Figure (secondary outcome)
Other bias	Unclear risk	• Industry-sponsored trial with several authors disclosing a financial conflict of interest • The sponsor (GSK) was responsible for overseeing the collection, analysis, and interpretation of the data

SOLO 1

Study characteristics	
Methods	**Study design**: a randomised, double-blind, placebo-controlled, phase 3 trial **Accrual**: 3 September 2013 to 6 March 2015 **Location of recruitment sites**: multi-country (15 countries) **Funding**: AstraZeneca and Merck **Median follow-up time**: 40.7 months (IQR, 34.9 to 42.9) in olaparib arm, 41.2 months (IQR, 32.2 to 41.6) in the placebo arm. The randomisation ratio was 2:1 stratified by the clinical response after platinum-based chemotherapy (complete or partial).
Participants	391 pts meeting the following criteria underwent randomisation to trial arms: • aged 18 years or older, • newly-diagnosed advanced (FIGO stage III or IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (or a combination thereof), • mutation in *BRCA1*, *BRCA2*, or both (*BRCA1/2*) with a complete or partial clinical response after platinum-based chemotherapy. The mean age of pts was 53.6 years (SD 9.4) in olaparib arm (OLA) and 53.4 years (9.8) in placebo (PLB) arm. The number of pts with the high-grade serous type of ovarian cancer was 246 (95%) in OLA arm, and 130 (99%) in PLB arm. *BRCA* mutation status was known for all pts with 3 pts in OLA arm having *BRCA1* and *BRCA2* mutation. 388 patients had a centrally confirmed germline *BRCA1/2* mutation, and 2 patients had a centrally-confirmed somatic *BRCA1/2* mutation. *BRCA1*: OLA 191 (73%), PLB 91 (69%) *BRCA2*: OLA 66 (25%), PLB 40 (31%) Partial clinical response after platinum-based chemotherapy recorded in 47 (18%) pts in OLA arm and in 24 (18%) pts in PLB arm. The ECOG PS was known for 390 pts: ECOG 0: OLA 200 (77%), PLB 105 (80%)

SOLO 1 *(Continued)*

	ECOG 1: OLA 60 (23%), PLB 25 (19%) The proportion of participants with HRD mutation was not given.
Interventions	The experimental arm (260 pts) included oral olaparib (300 mg twice daily). Dose reduction to 250 mg and subsequently 200 mg is permitted following confirmation of toxicity. The comparator arm (131 pts) included matching placebo tablets. All pts received platinum-based chemotherapy without bevacizumab and had a complete or partial clinical response.
Outcomes	**PRIMARY**: investigator-assessed PFS (sensitivity analysis: as assessed by blinded independent central review) **SECONDARY**: PFS2 (the time from randomisation to second disease progression or death), OS, the time from randomisation to the first subsequent therapy or death, the time from randomisation to the second subsequent therapy or death, and health-related quality of life (the TOI score on FACT-O questionnaire), and safety (NCI CTCAE v4.0). **NB**: the analysis of health-related quality of life evaluated the change from baseline in the Trial Outcome Index score for the first 2 years.
Notes	A cross-over between trial groups was not specified in the protocol. After discontinuation of the trial intervention, patients could receive treatments at the investigators' discretion.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed centrally with a block design, with stratification according to the clinical response after platinum-based chemotherapy.
Allocation concealment (selection bias)	Low risk	Patients were assigned to a trial group through an interactive Web-based or voice-response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quadruple (participant, care provider, investigator, outcomes assessor) (source: ClinicalTrial.Gov)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quadruple (participant, care provider, investigator, outcomes assessor)(source: Clinical Trial.Gov)
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Efficacy and health-related quality of life data**: ITT population (all randomised participants) **Safety data**: safety population (all patients who received ≥1 dose of the trial intervention). **Discontinued treatment**: OLA 124/260 (48%) PLB 94/131 (72%) Reasons for discontinuation were given.
Selective reporting (reporting bias)	Low risk	No concern over selective reporting.
Other bias	Unclear risk	• Industry-sponsored trial with several authors disclosing a financial conflict of interest. • A cross-over between trial groups was not specified in the protocol. • Change of primary outcome due to a low rate of the originally planned outcome. Quote: *"The protocol was amended such that the primary analysis of PFS was to be performed when approximately 196 events had occurred (data*

SOLO 1 *(Continued)*

	maturity, approximately 50%) or when the last patient to undergo randomization had done so at least 3 years earlier, whichever came first."

SOLO 2

Study characteristics	
Methods	**Study design**: a randomised, double-blind, placebo-controlled, phase 3 study **Accrual**: 3 September 2013to 21 November 2014 **Location of recruitment sites:** multi-country (16 countries) **Funding**: AstraZeneca **Median follow-up time**: not reported. The randomisation ratio was 2:1 stratified by response to previous platinum chemotherapy and length of the platinum-free interval.
Participants	295 pts meeting the following criteria underwent randomisation to trial arms: • aged 18 years or older; • histologically confirmed, relapsed, high-grade serous ovarian cancer or high-grade endometrioid cancer; • including primary peritoneal or fallopian tube cancer; • platinum-sensitive disease; • with a germline *BRCA*1/2 mutation; • received at least two lines of previous chemotherapy; • ECOG at baseline of 0–1. The median age of pts was 56 years (IQR 51 to 63) in olaparib arm (OLA) and 56 years (IQR 49 to 63) in the placebo (PLB) arm. High-grade serous type tumour: OLA 183 (93%), PLB 86 (87%) *BRCA* mutation: OLA 190 (97%), PLB 96 (97%) *BRCA*1: OLA 132(67%), PLB 61 (62%) *BRCA*2: OLA 58 (30%), PLB 35 (35%) The ECOG PS was known for 293 pts: ECOG 0: OLA 162 (83%), PLB 77 (78%) ECOG 1: OLA 32 (16%), PLB 22 (22%) The number of pts with the partial clinical response to previous platinum-based chemotherapy was 105 (54%) in OLA arm, and 52 (53%) in PLB arm. The proportion of participants with HRD mutation was not given.
Interventions	The experimental arm (196 pts) included oral OLA (300 mg twice daily). The comparator arm (99 pts) included a matching PLB. In both cases, the interventions were administered until objective radiological disease progression as per RECIST as assessed by the investigator.
Outcomes	**PRIMARY:** investigator-assessed PFS **SECONDARY:** time to first subsequent therapy or death; time to second subsequent therapy or death; time to study treatment discontinuation or death; time to second progression (determined by RECIST,

SOLO 2 *(Continued)*

	serum CA-125 levels, or symptomatic progression); time to earliest progression (by RECIST or CA-125 levels) or death; investigator assessment of OS, health-related quality of life (change from baseline in TOI score of FACT-O), safety and tolerability (NCI CTCAE v4.0). Quote: "The patient-centred outcomes of QAPFS and TWiST were included as secondary endpoints in a planned QOL statistical analysis."[Friedlander 2018]
Notes	OLA dose reduction to 250 mg and subsequently 200 mg is permitted following confirmation of toxicity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation scheme was produced by a computer software program that generates random numbers (Global Randomisation System) and was loaded into an interactive voice and web response system database. […] Randomisation was completed within 8 weeks of the patients' last dose of chemotherapy, and was stratified by response to previous chemotherapy (complete vs partial) and length of the platinum-free interval (>6–12 months vs >12 months)".
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation scheme... was loaded into an interactive voice and web response system database. [...] Investigators (or nominated assistants) contacted the interactive voice and web response system centralised randomisation centre for allocation of randomised therapy. Treatment masking was achieved using individual treatment codes assigned by the interactive voice and web response system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Treatment assignment was masked for patients, those giving the interventions, data collectors, and data analysers
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treatment assignment was masked for patients, those giving the interventions, data collectors, and data analysers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Efficacy and patient-reported data: ITT population (all randomised participants) Discontinued treatment: OLA 112 (57%), PLB 86 (87%) (reasons reported) Reasons for discontinuation were given.
Selective reporting (reporting bias)	Low risk	OS immature (secondary outcome) No concern over selective reporting
Other bias	Unclear risk	• Industry-sponsored trial with several authors disclosing a financial conflict of interest.

SOLO 3

Study characteristics

Methods	**Study design**: a randomised, controlled, open-label, phase 3 trial **Accrual**: 24 February 2015 to 15 May 2018 **Location of recruitment sites**: multi-country (13 countries)

SOLO 3 *(Continued)*

	Funding: AstraZeneca **Median follow-up time:** 13.8 months (IQR, 7.51 to 22.08) OLA, 3.9 months (IQR, 0.03 to 12.75) chemotherapy The randomisation ratio was 2:1 stratified by type of chemotherapy (PLD versus paclitaxel vs gemcitabine versus topotecan), the number of prior lines of chemotherapy (2-3 versus >= 4), and the time to disease progression after the end of the last platinum-based chemotherapy regimen (6-12 months versus 12 months).
Participants	266 participants meeting the following criteria underwent randomisation to trial arms: • 18 years or older, • relapsed high-grade serous or high-grade endometrioid ovarian cancer, primary peritoneal cancer, and/or fallopian tube cancer, with at least 1 lesion (measurable and/or non measurable) that could be accurately assessed at baseline, • patients had a deleterious or suspected deleterious germline *BRCA* mutation (g*BRCA*m), • received at least 2 prior lines of platinum-based chemotherapy for ovarian cancer, • partially platinum-sensitive (progression 6 to 12 months after the end of the last platinum-based regimen) or platinum-sensitive (progression >12 months after the end of the last platinum-based regimen), • ECOG 0-2. The median age of pts was 59 years (range not reported) in olaparib arm (OLA) and 60 years (range not reported) in chemotherapy arm. High-grade serous type tumour: OLA 157 (88.2%), chemotherapy 80 (90.9%) *BRCA* mutation: OLA 170 (96%), chemotherapy 84 (91%) *BRCA1*: OLA 120 (67.4%), chemotherapy 52 (59.1%) *BRCA2*: OLA 50 (28.1%), chemotherapy 32 (36.4%) All participants had measurable disease according to RECIST 1.1 criteria at baseline. The ECOG PS was known for all pts: 0: OLA 135 (75.8%), chemotherapy 52 63 (71.6%) 1: OLA 42 (23.6), chemotherapy 52 25 (28.4%) 2: OLA 1 (0.6%), chemotherapy 52 0 The proportion of participants with HRD mutation was not given.
Interventions	The experimental arm (178 pts) included OLA orally 300 mg twice daily (two 150mg tablets twice a day); a total daily dose of 600 mg. The comparator arm (88 pts) included a physician's choice single-agent chemotherapy: PLD 50 mg/m2 on day 1 every 4 weeks; paclitaxel 80 mg/m2 on days 1, 8, 15, and 22 every 4 weeks; gemcitabine 1,000 mg/m2 on days 1, 8, and 15 every 4 weeks; or topotecan 4 mg/m2 on days 1, 8, and 15 every 4 weeks. The investigator decided about the chemotherapy type before pts random assignment.
Outcomes	**PRIMARY**:ORR (RECIST v1.1) assessed by blinded independent central review (BICR) **SECONDARY**: PFS as assessed by BICR; investigator-assessed PFS; time from random assignment to second progression or death (PFS2); OS; time from random assignment to first subsequent therapy or death (TFST); time to earliest progression by RECIST or cancer antigen-125 (CA-125) or death, and time from random assignment to study treatment discontinuation or death (TDT), HRQoL (TOI score for 48 weeks), and safety (NCI CTCAE v4.0)
Notes	
Risk of bias	

SOLO 3 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Random assignment was performed using an interactive voice and Web response system, and it used a block design with stratification according to the selected chemotherapy."
Allocation concealment (selection bias)	Low risk	Quote: "Random assignment was performed using an interactive voice and Web response system, and it used a block design with stratification according to the selected chemotherapy."
Blinding of participants and personnel (performance bias) All outcomes	High risk	None. open-label study.
Blinding of outcome assessment (detection bias) All outcomes	High risk	None. open-label study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	266 randomised and 223 (84% of randomised no.OLA 151/178 chemo 72/88, 82%) analysed for the primary outcome. Discontinued treatment: OLA 135 (76%), chemotherapy 75 (85%) Reasons for discontinuation were given.
Selective reporting (reporting bias)	Low risk	OS immature (secondary outcome) No concern over selective reporting.
Other bias	Unclear risk	• Industry-sponsored trial with several authors disclosing a financial conflict of interest. • Secondary to challenges in patient recruitment resulting from the entry of PARP inhibitors to routine clinical practice, the target PFS changed to ORR

Study 19 (Ledermann 2012)

Study characteristics	
Methods	**Study design**: a randomised, double-blind, placebo-controlled, phase 2 trial **Accrual**: 28 August 2008 to 9 February, 2010 **Location of recruitment sites**: multi-country (16 countries) **Funding**: AstraZeneca **Median follow-up time**: not reported The randomisation ratio was 1:1 stratified by the interval between disease progression and completion of their penultimate platinum-based regimen (6 -12 months versus >12 months), objective response to their most recent regimen (complete response versus partial response), and ancestry (Jewish versus non-Jewish).
Participants	265 pts meeting the following criteria underwent randomisation to trial arms: • 18 years or older, • recurrent ovarian or fallopian tube cancer or primary peritoneal cancer (high-grade (grade 2 or 3) serous features or a serous component),

Study 19 (Ledermann 2012) *(Continued)*

- sensitivity to platinum-based therapy (objective response to previous therapy for more than 6 months)

Women had to complete 2 courses of platinum-based chemotherapy and their most recent regimen induced an objective response (defined by RECIST guidelines or a CA125 response) with a normal CA125 prior to commencement of the study.

The median age of pts was 58 years in olaparib (OLA) arm and 59 years in placebo (PLB) arm.

BRCA positive: OLA 31 (22.8%) and PLB 28 (21.7%)

BRCA1: OLA 25(18%) and PLB 20 (16%)

BRCA2: OLA 6 (4%) and PLB 7 (5%)

Patients did not have mandatory BRCA1/2 testing as part of eligibility and factors known to affect BRCA status, e.g. Jewish ancestry, were balanced between groups.

At study entry, 40% of the overall study population had measurable disease.

The proportion of pts with high-grade serous type and HRD mutation were not given.

ECOG 0: OLA 110 (80%), PLB 95 (73%)
ECOG 1: OLA 23 (17%), PLB 30 (23%)
ECOG 2: OLA 1 (1%), PLB 2 (2%)
Unknown: OLA 2 (2%), PLB 2 (2%)

Interventions	The experimental arm (136 pts) included olaparib (400 mg twice daily) as maintenance therapy. The comparator arm (129 pts) included placebo tablets (twice daily) as maintenance therapy. All pts were allocated to trial arms within 8 weeks after completion of the last dose of platinum-based chemotherapy.
Outcomes	**PRIMARY**: PFS assessed by the site investigator and PFS by a blinded independent central review. **SECONDARY**: time to progression (RECIST v 1.0) or CA-125 level; objective response rate (RECIST v 1.0) or a combination of RECIST and CA-125 level); disease-control rate (RECIST v1.0), percentage change from baseline in the size of the target tumour lesion at weeks 12 and 24, OS, disease-related symptoms and health-related quality of life as reported by the patients, and safety (NCI CTCAE v3.0).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated"
Allocation concealment (selection bias)	Low risk	Quote: "Randomised by interactive voice response system"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding. Unique identifiers generated during randomisation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Review of CT scans was blinded. Blinded independent review of data

Study 19 (Ledermann 2012) *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	326 patients screened; 61 did not meet inclusion criteria, 265 randomised, 1 withdrew consent, all patients accounted for at end of study and displayed on CONSORT flowchart
Selective reporting (reporting bias)	Low risk	Outcomes selected in Clinical Trials.gov reported
Other bias	Unclear risk	Industry-led study and some authors had documented conflict of interest, but blinding secure and low risk of selective reporting bias as pre-determined at trial registration. Data collection and analysis were performed by the sponsor (AstraZeneca), and all the authors had full access to the data. Principle Investigators were not employed by AstraZeneca.

VELIA

Study characteristics	
Methods	**Study design**: a randomised, placebo-controlled, double-blind, phase 3 study **Accrual**: July 015 to July 2017 **Location of recruitment sites**: multi-country (202 sites in 10 countries) **Funding**: AbbVie **Median follow-up time**: 28 months (at the time of the database lock) The randomisation ratio was 1:1:1 stratified by the timing of surgery and residual disease after primary surgery, the paclitaxel schedule, stage of the disease, geographic region, and germline BRCA status.
Participants	1140 pts meeting the following criteria underwent randomisation to trial arms: • 18 years or older, • received an initial histological diagnosis of high-grade serous (FIGO II & IV epithelial ovarian, fallopian tube, or primary peritoneal carcinoma), high-grade serous adenocarcinoma, • ECOG 0-2, • primary cytoreductive surgery had to be between 1 - 12 weeks after surgery, • measurable disease or non-measurable disease. The median age of pts was 62 years in VEL combo arm (range 22 to 88), 62 years (range 30 to 85) in VEL throughout arm, and 62 years (range 33 to 86) in PLB. BRCA positive: VEL combo 98 (29%), VEL throughout 108 (31%), PLB 92 (27%) The proportion of pts with BRCA1 or BRCA2 was not reported. HRD mutations: VEL combo 206 (63%), VEL throughout 214 (63%), PLB 207 (63%) The ECOG PS was known for 1124 pts: ECOG 0: VEL combo 210 (56%), VEL throughout 224 (59%), PLB 226 (61%) ECOG 1: VEL combo 157 (42%), VEL throughout 141 (37%), PLB 138 (37%) ECOG 2: VEL combo 9 (2%), VEL throughout 12 (3%), PLB 7 (2%) The proportion of pts with high-grade serous type and with RECIST measurable disease were not given.
Interventions	There were two experimental arms: veliparib combination arm (VEL combo, 383 pts) where pts received chemotherapy plus veliparib followed by placebo maintenance, and veliparib throughout arm

VELIA *(Continued)*

	(VEL throughout, 382 pts) where pts received chemotherapy plus veliparib followed by veliparib maintenance. Comparator arm (PLB, 375 pts) included chemotherapy plus placebo followed by placebo maintenance. Chemotherapy comprised of carboplatin (given at an AUC of 6 mg per mL per minute, every 3 weeks) and paclitaxel (175 mg per square metre of body-surface area, administered every 3 weeks, or 80 mg per square metre, weekly). Veliparib dose during chemotherapy was 150 mg orally twice daily. After successful completion of chemotherapy (without disease progression), pts received single-agent veliparib (300 mg twice daily for 2 weeks followed by 400 mg if there were no side effects during the initial phase).
Outcomes	**PRIMARY**: investigator-assessed PFS in the VELthroughout arm vs PLB arm. This was analysed sequentially in the BRCA-mutation cohort, the HRD cohort, and the ITT population. **SECONDARY**: OS in the VEl throughout arm vs PLB; PFS and OS in the VEL combo arm vs PLB arm; the Disease-Related Symptom score (a subset of NFOSI-18) in the BRCA-mutation cohort, the HRD cohort, and the intention to treat population; tumour assessment according to RECIST v1.1 and safety (NCI CTCAE v 4.03).
Notes	Cross-over to VEL was not allowed in the trial. The data cutoff date for the primary analysis was May 3, 2019.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A bottle number randomisation schedule and a subject randomisation schedule will be generated by the Clinical Statistics Department at AbbVie prior to the start of the study. A copy of all randomisation schedules will be kept by the Clinical Statistics Department at AbbVie and a copy will be forwarded to the IRT vendor.
Allocation concealment (selection bias)	Low risk	Interactive Response Technology (IRT) was utilised to screen and randomise pts. The site contacted the IRT to obtain a pts number once they signed the informed consent.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	AbbVie, the Investigator, the study site personnel and the pts were blinded to a type of the therapy (VEL or placebo) throughout the course of the study. All pts were treated with open-label carboplatin and paclitaxel.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	(...) all pts were followed as planned for survival and investigators, and pts were blinded to reduce bias. The subsequent OS analyses will occur when the required numbers of OS endpoints are accrued.
Incomplete outcome data (attrition bias) All outcomes	Low risk	**Efficacy data**: ITT population (all randomised) **Lost to follow-up**: VEL combo 2, VEL throughout 2, PLB 1 **Withdrawn by investigator**: VEL combo 19, VEL throughout 20, PLB 2 **Discontinued treatment**: VEL combo 363, VEL throughout 348, PLB 355 Reasons for discontinuation were given.
Selective reporting (reporting bias)	Low risk	OS immature (secondary outcome) No concern over selective reporting
Other bias	Unclear risk	• Industry-sponsored trial with several authors disclosing a financial conflict of interest. • HDR population post hoc analysis: Quote: *"On the basis of emerging efficacy data regarding patients with HRD tumours the protocol was amended to add testing variables for the primary and secondary outcomes within this cohort."*

***BRCA* :** breast cancer susceptibility gene; **CI:** confidence interval;**CT:** computerised tomography: **ECOG:** Eastern Cooperative Oncology Group; **g*BRCA*m:** germline BRAC mutation;**GCIG:** Gynaecologic Cancer Intergroup;**HGSOC:** high grade serous ovarian cancer; **HR:** hazard ratio; **HRD:** homologous recombination deficient; **IQR:** interquartile range;**ITT:** intention-to-treat; **IV: i**ntravenous;**NIR:** niraparib; **NR:** not reported;**OLA:** olaparib; **OR:** odds ratio;**ORR:** objective response rate;**OS:** overall survival;**PFS:** progression-free survival; **PLD:** pegylated liposomal; **VEL:** veliparib doxorubicin;**PS:** performance status; TWIST: Time Without Significant Symptoms of Toxity; **RECIST:** Response Evaluation Criteria in Solid Tumours.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al Hadidi 2018	SR/meta-analysis
Audeh 2009	Phase II, single-arm trial of the oral PARP inhibitor OLA (AZD2281) in BRCA-deficient advanced ovarian cancer (ASCO 2009 meeting abstract)
Audeh 2010	Non-randomised, phase II, single-arm study (update of Audeh 2009)
BAROCCO	Comparitor arm contains a VEGF inhibitor in combination with the PARPi, therefore off protocol.
CNO CN 01335640 2016	Irrelevant intervention
Coleman 2014	Non-randomised phase II trial; no control group
Del Campo 2017	irrelevant study design - analysis of rate of platinum resistance within control group of NOVA study
Dockery 2017a	SR/meta-analysis of toxicity of PARPi
Dockery 2017b	SR/meta-analysis
EUCTR2017-004058-40-BE 2018	Irrelevant comparator
EUCTR2017 004456 30 HU 2018	Irrelevant comparator
Fisher 2018	SR/meta-analysis
Fong 2006	Phase I pharmacokinetic (PK) and pharmacodynamic (PD) evaluation of a small molecule inhibitor of Poly(ADP-ribose) polymerase (PARP), KU-0059436 (Ku) in patients with advanced tumours (ASCO 2006 meeting abstract)
Fong 2008	Results from a phase I study of AZD2281 (KU-0059436), a PARP (poly(ADP-ribose) polymerase) inhibitor with single-agent anticancer activity in patients with BRCA-deficient ovarian cancer (ASCO 2008 meeting abstract)
Fong 2009	Non-randomised phase I clinical trial analysing the pharmacokinetic and pharmacodynamic characteristics of OLA (AZD2281). Selection was aimed at having a study population enriched in carriers of a BRCA1 or BRCA2 mutation
Gelmon 2011	Phase 2, multicentre, open-label, non-randomised study
Hettle 2020	Irrelevant comparator
Kristeleit 2016a	Meta-analysis of 2 studies
Kristeleit 2016b	SR/meta-analysis

Study	Reason for exclusion
Kristeleit 2019	SR/meta-analysis
Lee 2014	Biomarker study of RCT comparing olaparib plus/minus cediranib: wrong study design
Lee 2019	Wrong study design
Lheureux 2017	A comparative molecular analysis of Study 19 (NCT00753545), a randomized phase II trial assessing olaparib maintenance after response to platinum-based chemotherapy in HGSOC
Liu 2014b	As for Lui 2014a; wrong comparator
Liu 2017	Irrelevant study design
Lui 2014a	Comparison of Olaparib versus Olaparib and Cediranib - no randomisation of Olaparib; 2 references to this study.
Matulonis 2015	Irrelvant study design
Matulonis 2016	Irrelevant study design
McNeish 2014	Non-randomised study (ARIEL 2)
Min 2019	SR/meta-analysis
Mirza 2015	Irrelevant intervention
Mirza 2018	Irrelevant study design
Moore 2014	Wrong study design - part of ongoing study but this is a sub-study on effects of high fat food on pharmacokinetics
Moore 2019	Irrelevant study design
NCT02485990 2015	Irrelevant study design:An Open Label Dose Escalation/Expansion Study of Tremelimumab Alone or Combined With Olaparib for Recurrent or Persistent EOC (Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Carcinoma)
NCT02836028 2016	Irrelevant study design: A Phase 2, Multiple-Cohort, Open-Label, International Study of Talazoparib Monotherapy and Talazoparib Plus Temozolomide in Women With Relapsed Ovarian, Fallopian Tube, and Peritoneal Cancer
NCT03579316 2018	Irrelevant comparator (adavosertib (AZD11775 +/- olaparib) so no conventional chemotherapy arm
NCT03740165 2018	Irrelevant comparator - chemotherapy (platinum-based) plus: • Pembrolizumab + Olaparib, • Pembrolizumab + Placebo • Placebo
NCT03783949 2018	Irrelevant intervention: A multicentre, open-label, three-arm randomised Phase II trial assessing the safety and efficacy of the HSP90inhibitor ganetespib in combination with carboplatin followed by maintenance treatment withniraparib versus ganetespib plus carboplatin followed by ganetespib and niraparib versus carboplatin in combination with standard chemotherapy followed by niraparib Maintenance treatment in platinum-sensitive ovarian cancer
Nitecki 2020	SR/meta-analysis

Study	Reason for exclusion
Orbegoso Aguilar 2018	Irrelevant study design
Oza 2017	Irrelevant study design
Qian 2015	SR/meta-analysis
Rimel 2020	Irrelevant study design
Ruscito 2020	SR/meta-analysis
Swisher 2017	Irrelevant study design
Thein 2018	SR/meta-analysis
Yap 2007	Wrong study design - Phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of KU-0059436 (Ku), a small molecule inhibitor of poly(ADP-ribose) polymerase (PARP) in cancer patients, including BRCA1/2 mutation carriers (ASCO 2007 meeting abstract)

***BRCA* :** breast cancer susceptibility gene; **HGSOC:** high grade serous ovarian cancer; **OLA:** olaparib; RCT: randomised controlled trial; **SR:** systematic review; **VEGF:** vascular endothelial growth factor

Characteristics of ongoing studies *[ordered by study ID]*

ARIEL4

Study name	ARIEL4
Methods	Study design: a randomised, open-label, phase 3 study. Accrual: September, 2016 to June, 2024 (estimated completion) Location of recruitment sites: multi-country (> 100 sites) Funding: Clovis Oncology, inc.
Participants	Target pts: 345 • 18 years or older • Histologically-confirmed diagnosis of high-grade serous, grade 2 or grade 3 endometrioid epithelial ovarian, fallopian tube or primary peritoneal cancer • Received more than 2 prior chemotherapy regimens and relapsed or progressive disease as confirmed by radiological assessment • No prior PARP inhibitor treatment or single-agent paclitaxel • Deleterious BRCA1 or BRCA2 mutation The proportion of patients with BRCA1, BRCA2 and HDR mutations is not yet reported
Interventions	Intervention arm: Rucaparib 600 mg orally twice daily. Comparator arm: monotherapy platinum (cisplatin or carboplatin) or platinum-based doublet chemotherapy (carboplatin/paclitaxel, carboplatin/gemcitabine, or cisplatin/gemcitabine administered per local standard of care and regulations. Specific comparator will depend on platinum status and investigator decision.
Outcomes	PRIMARY: investigator assessed PFS [from date of randomisation until the date of first documented progression or date of death from any cause, whichever came first, RECIST v1.1]

ARIEL4 *(Continued)*

	SECONDARY: OS, safety and tolerability (a composite outcome)[from NCTN], investigator-assessed ORR (RECIST v 1.1), ORR/CA-125 response, duration of response
Starting date	September, 2016
Contact information	
Notes	

ATHENA (GOG-3020/ENGOT-OV45)

Study name	ATHENA (GOG-3020/ENGOT-OV45)
Methods	Study design: a randomised, double-blind, placebo-controlled phase III study. Accrual dates: M14 ay 2018 to 30 Dec, 2030 (estimated completion date). Location of recruitment sites: multi-country (>270 sites worldwide). Funding: Clovis Oncology, inc.
Participants	Target participants: 1000 • Newly-diagnosed advanced (FIGO stage III-IV) epithelial ovarian, fallopian tube, or primary peritoneal cancer. • Completed cytoreductive surgery, including at least a bilateral salpingo-oophorectomy and partial omentectomy, either prior to chemotherapy (primary surgery) or following neoadjuvant chemotherapy (interval debulking) • Completed first-line platinum-based chemotherapy and surgery with a response, in the opinion of the Investigator • Sufficient tumour tissue for planned analysis • ECOG 0-1 • >=20 years of age in Japan, Taiwan and South Korea; in all other participating countries >= 18 years of age to consent Exclusion: Any prior treatment for ovarian cancer, other than the first-line platinum regimen. The proportion of participants with BRCA1. BRCA2 and HDR mutations is not yet reported.
Interventions	Participants in the intervention group were allocated to one of three arms; intervention 1: oral rucaparib + intravenous nivolumab, intervention 2: oral rucaparib + IV placebo, intervention 3: oral rucaparib + IV placebo. The comparison group were given oral placebo + IV placebo. All participants will be followed up for approximately 10 years.
Outcomes	PRIMARY: Investigator assessed PFS. SECONDARY: Blinded independent central review (BICR) PFS; OS; ORR; Duration of response; Number of participants with treatment-emergent Adverse Events (AEs) as assessed by CTCAE v4 (or higher) as a measure of safety and tolerability; Number of participants with serious AEs as a measure of safety and tolerability; Number of participants with laboratory abnormalities as a measure of safety and tolerability.
Starting date	14 May 2018
Contact information	
Notes	

DUETTE

Study name	DUETTE
Methods	**Study design**: a phase 2 randomised, multi-centre study **Accrual**: August 2020 to 20 Feb 2023 (estimated completion date) **Location of recruitment sites**: multi-country (66 countries) **Funding**: AstraZeneca
Participants	Target participants: 192 (64 in each arm according to protocol) • Histologically-diagnosed high-grade epithelial ovarian cancer, • Platinum-sensitive relapse on, or after, completion of at least 6 months of any prior PARP inhibitor maintenance therapy (a minimum of 12 months is required if the patient received PARP inhibitor maintenance following first-line chemotherapy). Disease relapse in the second-line or third-line setting is allowed. • ECOG 0-1. Proportion of participants with BRCA1, BRCA2 and HDR mutations is not yet reported.
Interventions	Intervention arm: participants were allocated to either intervention 1 (ceralasertib+olaparib): Ceralasertib 160 mg once daily orally or orally on days 1 to 7 plus olaparib 300 mg twice daily orally continuous (28-day cycle) or Intervention 2 (olaparib monotherapy): Olaparib 300 mg twice daily orally, daily continuous. Comparator arm: placebo to match olaparib twice daily orally, daily continuous. Estimated follow-up duration of 2.5 years.
Outcomes	PRIMARY: PFS (determined by blinded independent central review according to RECIST 1.1) (SA: using investigator assessed PFS). SECONDARY: OS, time to second objective disease progression, objective response rate, duration of response, safety, and tolerability.
Starting date	7 August 7 2020
Contact information	
Notes	

DUO-O

Study name	DUO-O
Methods	**Study design**: a phase III randomised, double-blind, placebo-controlled, multicentre study. **Accrual**: January 2019 to November 2025 (estimated completion date). **Location of recruitment sites**: Multi-country (>214 countries) **Funding**: AstraZeneca
Participants	Target participants: 1254

DUO-O *(Continued)*

	• Newly-diagnosed, histologically-confirmed, advanced (Stage III-IV) high grade epithelial ovarian cancer including high grade serious, high-grade endometrioid, clear cell ovarian cancer or carcinosarcoma, primary peritoneal cancer and/or fallopian-tube cancer; • Age ≥18 years [in Japan < 20 years] • All patients should be candidates for cytoreductive surgery either: upfront primary surgery or plan to undergo chemotherapy with interval debulking surgery; • Evidence of presence or absence of BRCA1/2 mutation in tumour tissue • ECOG 0-1 Proportion of participants with BRCA1, BRCA2 and HDR mutations is not yet reported.
Interventions	Participants allocated to either one of two intervention arms. Intervention 1: platinum-based chemotherapy in combination with bevacizumab and durvalumab followed by maintenance bevacizumab, durvalumab and olaparib placebo. Intervention 2: platinum-based chemotherapy in combination with bevacizumab and durvalumab followed by maintenance bevacizumab, durvalumab and olaparib. Comparator arm: platinum-based chemotherapy in combination with bevacizumab and durvalumab placebo (saline IV infusion) followed by maintenance bevacizumab, durvalumab placebo (saline IV infusion) and olaparib placebo (tablets). Expected follow-up duration of up to 7 years.
Outcomes	PRIMARY: PFS (assessed by modified RECIST 1.1.). SECONDARY: OS, ORR, duration of response, Health-related quality of life, secondpProgression (PFS2), pathological complete response, duration of response (DoR), and more 20 secondary outcomes.
Starting date	January 2019
Contact information	
Notes	

ENGOT-OV43

Study name	ENGOT-OV43
Methods	**Study design**: a randomised, double-blind study. **Accrual**: 18 December 2018 to 8 August 2025 (estimated study completion date). **Location of recruitment sites**: multi-country (225 countries) **Funding**: Merck & Co, Int.
Participants	Target participants: 1086 • FIGO III or IV Epithelial Ovarian Cancer primary peritoneal cancer, or fallopian tube cancer • Completed primary debulking surgery or is eligible for primary debulking surgery or is a potential candidate for interval debulking surgery • Candidate for carboplatin and paclitaxel chemotherapy, to be administered in the adjuvant or neoadjuvant setting • ECOG 0-1 Exclusion:

ENGOT-OV43 *(Continued)*

	• Known or suspected deleterious mutation (germline or somatic) in either BRCA1 or BRCA 2
Interventions	Participants allocated to one of two intervention arms; Intervention 1: pembrolizumab + olaparib - carboplatin/paclitaxel via intravenous (IV) infusion for five 3-week cycles PLUS pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles plus olaparib 300 mg via oral tablet twice each day, starting with Cycle 7. Intervention 2: Pembrolizumab+Placebo for Olaparib - carboplatin/paclitaxel via IV infusion for five 3-week cycles starting in Cycle 1 PLUS pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles PLUS placebo for olaparib via oral tablet BID, starting with Cycle 7. Comparator arm: carboplatin/paclitaxel via IV infusion for five 3-week cycles plus placebo for pembrolizumab (normal saline or dextrose) via IV infusion on day 1 of each 3-week cycle for up to 35 cycles plus placebo for olaparib via oral tablet twice daily, starting with Cycle 7. Estimated follow-up duration: up to 6 years.
Outcomes	PRIMARY: PFS, OS. SECONDARY: PFS Per RECIST 1.1 as assessed by blinded independent central review, PFS after next-line treatment (PFS2), number of participants who experience an adverseeEvent,nNumber of participants who discontinue study treatment due to an AE, QoL, plus 5 more outcomes (NCTN).
Starting date	18 December 2018
Contact information	
Notes	

ENGOT-OV44/FIRST

Study name	ENGOT-OV44/FIRST
Methods	**Study design**: a randomised, double-blind, placebo-controlled, phase 3 study. **Accrual**: 11 October 2018 to J22 July, 2026 (estimated study completion date). **Location of recruitment sites**: multi-country (196 countries) **Funding**: Tesaro, Inc.
Participants	Target participants: 1228 • >= 18 years of age • Histologically-confirmed diagnosis of high-grade non-mucinous epithelial ovarian, fallopian tube, or primary peritoneal cancer: FIGO Stage III or IV or Tumor, Node and Metastasis (TNM) staging criteria • ECOG 0-1 Proportion of participants with BRCA1, BRCA2 or HDR mutations is not yet reported.
Interventions	Participants allocated to one of two intervention arms. Intervention 1: carboplatin+paclitaxel+bevacizumab (standard of care, SOC) + dostarlimab in cycle 1 followed by SOC with chemotherapy treatment dostarlimab, and maintenance treatment of bevacizumab with niraparib and dostarlimab. Intervention 2: SOC + niraparib in cycle 1 followed by SOC with chemotherapy treatment dostarlimab placebo from cycles 2 to 6 and maintenance treatment of bevacizumab with niraparib and dostarlimab placebo

ENGOT-OV44/FIRST *(Continued)*

	Comparator arm: SOC + placebo in cycle 1 followed by SOC with chemotherapy treatment with dostarlimab placebo from cycles 2 to 6 and maintenance treatment of bevacizumab along with niraparib placebo and dostarlimab placebo. Estimated follow-up duration: up to 5 years.
Outcomes	PRIMARY: PFS (for PD-L1 positive participants and all participants); SECONDARY: 48 secondary outcomes on NCTN including investigator-assessed PFS, OS, number of overall participants with SAEs.
Starting date	11 October 2018
Contact information	
Notes	

ICON 9

Study name	ICON 9
Methods	**Study design**: a randomised, phase 3 study. **Accrual**: 15 June 2018 to December 2023 (estimated study completion date). **Location of recruitment sites**: multi-country (41 countries). **Funding**: CRUK & AstraZeneca.
Participants	Target participants: 618 • >= 18 years of age; • CT or MRI proven relapsed disease (measurable or non-measurable abnormalities supported by GCIG CA125 criteria of progression), or have had debulking surgery for first relapse; • Evidence of response to chemotherapy mid-treatment (post 3 or 4 cycles), either by CA125, on a CT/MRI scan, or no evidence of progression having undergone surgical debulking; • Prior front-line maintenance therapy with bevacizumab is permitted; • ECOG 0-1; • Life expectancy ≥ 16 weeks; Proportion of participants with BRCA1, BRCA2 and HDR mutations is not yet reported.
Interventions	Intervention arm: olaparib 300 mg twice daily and cediranib 20 mg twice daily Comparator arm: olaparib 300 mg twice daily Estimated follow-up duration: up to 3 years.
Outcomes	PRIMARY: PFS (date of randomisation to the date of objective progression (investigator assessed using RECIST v1.1) or date of death from any cause (in the absence of progression), OS (date of randomisation to the date of death from any cause). SECONDARY: Ttxicity, alt. PFS and OS, adherence to maintenance therapy, TSST, QoL, cost-effectiveness, response rate.
Starting date	15 June 2018
Contact information	

ICON 9 *(Continued)*

Notes	Co-primary endpoints to be assessed using a fixed-sequence gatekeeping approach: (1) progression-free survival, all patients; (2) progression-free survival, BRCA wild type; (3) overall survival, all patients; (4) overall survival, BRCA wild type.

JAVELIN

Study name	JAVELIN
Methods	**Study design**: a randomised, open-label, multi-centre, phase III study. **Accrual**:19 July 2018 to 1 October 2020 (discontinued). **Location of recruitment sites**: multi-country (73 countries). **Funding**: Pfizer.
Participants	Participants: 79. • Previously untreated Stage III-IV epithelial ovarian, fallopian tube, or primary peritoneal cancer; are candidates for platinum-based CTX + bevacizumab; and have completed primary debulking surgery or are candidates for neoadjuvant CTX with planned interval debulking surgery. • ECOG 0-1. The proportion of participants with BRCA1, BRCA2 and HDR mutations is not reported.
Interventions	Intervention 1: platinum-based chemotherapy + avelumab followed by avelumab + talazoparib maintenance. Intervention 2: platinum-based chemotherapy followed by talazoparib maintenance. Comparator arm: platinum-based chemotherapy + bevacizumab followed by bevacizumab maintenance. Estimated follow-up duration: up to 3 years.
Outcomes	PRIMARY: PFS. SECONDARY: OS, Euro Quality of Life (EQ-5D-5L), NFOSI-18, PFS2, drug-kinetics specific.
Starting date	
Contact information	
Notes	Study discontinued 1 October 2020

NCT02392676 2015

Study name	NCT02392676 (2015)
Methods	**Study design:** not reported. **Accrual**: withdrawn 2 May 2016 **Location of recruitment sites**: not reported. **Funding**: AstraZeneca.

NCT02392676 2015 *(Continued)*

Participants	No enrolment.
Interventions	Intervention arm: olaparib 300 mg orally twice daily Comparator arm: placebo matching olaparib 300 mg orally twice daily
Outcomes	Not reported.
Starting date	Not reported.
Contact information	
Notes	

NCT02489006 2015

Study name	NCT02489006
Methods	A Phase II, openl-abel, randomised, multi-centre study
Participants	patients with platinum-sensitive recurrent high-grade serous ovarian/primary peritoneal or fallopian tube cancer
Interventions	Neoadjuvant olaparib prior to surgery, followed by platinum-based chemotherapy/olaparib post surgery versus neoadjuvant olaparib prior to surgery, followed by olaparib post surgery
Outcomes	Primary outcomes: biomarkers (1. Difference in levels of PAR or PARP-1 before and after study treatment [Time Frame: 4-8 weeks]; 2. Mutations in BRCA1/2, RAD51B, RAD51C, RAD51D, PPM1D, FANCM, BRIP1, PALB2 and BARD1 in germline tissue compared to tumour tissue [Time Frame: 2.5 years]. Secondary outcomes: adverse events; molecular response rates; PFS; circulating tumour DNA levels; gene expression changes; secondary mutation rate; blood biomarkers
Starting date	19 July 2016
Contact information	Amit Oza, M.D
Notes	

NCT02502266 2015

Study name	
Methods	A Randomised phase II/III study
Participants	Women with recurrent platinum-resistant or -refractory ovarian, fallopian tube, or primary peritoneal cancer
Interventions	Combination of cediranib and olaparib compared to cediranib or olaparib alone, or standard of care chemotherapy
Outcomes	PFS, OS, ORR; AEs, QoL

NCT02502266 2015 *(Continued)*

Starting date	5 Feb 2016
Contact information	Jung-min Lee, NRG Oncology
Notes	Not all study arms will meet inclusion criteria

NCT04239014 2020

Study name	NCT04239014 (2020)
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

NEO

Study name	NEO (2017)
Methods	**Study design**: a Phase II, open-label, randomised, multi-centre study. **Accrual**: 19 July 2016 to December 2021 (estimated study completion date). **Location of recruitment sites**: multi-country. **Funding**: University Health Network, Toronto.
Participants	Target participants: 71 • >= 18 years of age • Platinum-sensitive, histologically-proven recurrent high-grade serous ovarian/primary peritoneal or fallopian tube cancer • Suitable for surgical debulking • Progression-free interval of at least 6 months prior to registration • At least one prior line of platinum-based chemotherapy • ECOG 0-1 • Life expectancy of greater than 3 months Proportion of participants with BRCA1, BRCA2 and HDR mutations not reported.
Interventions	Intervention arm: olaparib, orally, at 300 mg twice per day, for 6 weeks (+/- 2 weeks) prior to surgery followed by clinicians choice platinum-based chemotherapy after surgery, followed by olaparib 300 mg twice daily continuously after chemotherapy

NEO *(Continued)*

	Comparator arm: olaparib, orally, at 300 mg twice per day, for 6 weeks (+/- 2 weeks) prior to surgery and after surgery. Estimated follow-up duration: up to 2.5 years.
Outcomes	PRIMARY: difference in levels of PAR or PARP-1 before and after study treatment, mutations in BRCA1/2, RAD51B, RAD51C, RAD51D, PPM1D, FANCM, BRIP1, PALB2 and BARD1 in germline tissue compared to tumour tissue. SECONDARY: frequency of adverse events, by description and grade, response rate to olaparib in the neoadjuvant period, PFS, Levels of ctDNA compared to levels of CA125, Gene expression changes in tumour tissue before and after treatment with olaparib, secondary mutation rate in surgical tumour specimens following PARP therapy and at progression, changes in blood based biomarkers using ctDNA before, during and after treatment with oOlaparib.
Starting date	19 July 2019 2016
Contact information	
Notes	

NOGGO OV42/MAMOC

Study name	NOGGO-OV42/MAMOC
Methods	**Study design**: a randomised, double-blind, placebo-controlled, multi-centre study. **Accrual**: 3 March 2020 **Location of recruitment sites**: multi-country (17 sites) **Funding**: Northern Eastern German Society of Gynaecological Oncology; Institut für Klinische Krebsforschung IKF GmbH at Krankenhaus Nordwest; Clovis Oncology, Inc.
Participants	Target participants: 190 • >= 18 years of age • Histologically-confirmed, advanced (FIGO stage IIIA, IIIB, IIIC, or IV of the 2014 FIGO classification) serous or high-grade endometrioid (based on local histopathological findings) ovarian cancer, fallopian tube cancer, primary peritoneal cancer and clear cell carcinoma of the ovary in first-line therapy • Treatment with Bevacizumab for 12 to 15 months, independent of dosage • ECOG 0-1 Proportion of participants with BRCA1, BRCA2 and HDR mutations is not yet reported.
Interventions	Intervention arm: rucaparib treatment (600 mg) after receiving bevacizumab for 12 to 15 months. Comparator arm: placebo treatment after receiving bevacizumab for 12 to 15 months. Cycles continue in both arms until disease progression and/or death, unacceptable adverse events, patient and/or investigator decision, other protocol stopping criteria. Estimated follow-up duration: up to 48 months.
Outcomes	PRIMARY: PFS SECONDARY: PFS2, QoL, OS, Determination of time to next medical intervention, time to next subsequent therapy, number of participants with treatment-related adverse events and/or SAEs as assessed by CTCAE v4.03

NOGGO OV42/MAMOC *(Continued)*

Starting date	3 March 2020
Contact information	
Notes	

NORA

Study name	NORA
Methods	**Study design**: a randomised, double-blind, placebo-controlled, multi-centre, phase 3 trial **Accrual**: 8 June 2017 to 15 April 15 2021 (estimated study completion date). **Location of recruitment sites**: China **Funding**: Zai Lab (Shanghai) Co., Ltd.
Participants	Target participants: 265 • >= 18 years of age • High-grade serous or dominantly high-grade serous ovarian cancer; • Two lines of platinum-containing chemotherapy, complete response (CR) or partial response (PR) after first-line platinum-containing chemotherapy, and after received at least 4 cycles of platinum-containing (must be carboplatin or cisplatin or nedaplatin) in second-line platinum-containing chemotherapy. • ECOG 0-1 Proportion of participants with BRCA1, BRCA2 and HDR mutations not reported.
Interventions	Intervention arm: ZL-2306(nirapairb) The starting dose is 300 mg or 200 mg based on patient's body weight. Comparator arm: the starting dose is the matched dose of placebo (3 capsules or 2 capsules). Estimated follow-up duration: 35 months.
Outcomes	PRIMARY: PFS SECONDARY: chemotherapy-free interval, time to first subsequent anti-cancer treatment, OS
Starting date	8 June 2015
Contact information	
Notes	Active, not recruiting.

OCTOVA

Study name	OCTOVA (2017)
Methods	**Study design**: a randomised, open-label, phase II trial. **Accrual**: 9 March 2017to 30 November 2021 (estimated study completion date). **Location of recruitment sites**: United-Kingdom.UK

OCTOVA *(Continued)*

	Funding: AstraZeneca, University of Oxford.
Participants	Target Participants: 139 • >=16 years of age; • Relapsed epithelial ovarian, primary peritoneal or fallopian tube cancer who have relapsed within 12 months of previous platinum-based therapy • Measurable disease by RECIST Version 1.1 performed in past 4 weeks • At least one lesion, not previously irradiated, that can be accurately measured at baseline as ≥ 10 mm in the longest diameter • ECOG PS 0-2 • Life expectancy > 12 weeks in terms of disease related mortality Proportion of participants with BRCA1, BRCA2 and HDR mutations not reported.
Interventions	Participants allocated to one of two intervention arms.Intervention 1: olaparib, oral, 300 mg twice daily; until progression. Intervention 2: olaparib, oral, 300 mg twice daily and cediranib, tablet, 20 mg once daily; until progression. Comparator arm: paclitaxel, IV weekly, 80 mg/m2; until progression. Estimated follow-up duration not reported.
Outcomes	PRIMARY: PFS SECONDARY: AE using CTCAE v4.03, OS, ORR (on RECIST v1.1; based GCIG CA125), QoL (EORTC-QLQ C30, EQ5D, OV28)
Starting date	9 March2017
Contact information	
Notes	

OREO

Study name	OReO (2017)
Methods	**Study design**: a randomised, double-blind, placebo-controlled, multi-centre, phase 3B trial. **Accrual**: 8 June 2017 to 7 May 2021 (estimated study completion date). **Location of recruitment sites**: multi-country (96 sites worldwide) **Funding**: AstraZeneca.
Participants	Target participants: 228 • >= 18 years of age; • Histologically-diagnosed relapsed non-mucinous epithelial ovarian cancer (EOC) (including primary peritoneal and/or fallopian tube cancer) • Documented BRCA1/2 status • One prior PARPi therapy PARPi therapy of any agent (including olaparib) used in a maintenance setting For the BRCA1/2 (+ve) cohort • Patients must not have received bevacizumab during course of treatment • ECOG 0-1 • A life expectancy ≥16 weeks

OREO *(Continued)*	
	Proportion of participants with documented BRCA1, BRCA2 and HDR mutations not reported.
Interventions	Intervention arm:olaparib 300 mg tablets administered orally twice daily continuously. Comparator arm: matching placebo 300 mg tablets administered orally twice daily continuously. Estimated follow-up duration: 3 years.
Outcomes	PRIMARY: PFS (until objective radiological disease progression as determined by the investigator or other discontinuation criteria are met.) SECONDARY: OS, time to progression by GCIG criteria, time to first subsequent treatment commencement, time to second subsequent treatment commencement, time to study treatment discontinuation, HRQoL, Number of patients with AEs, Number of patients with AESI.
Starting date	8 June 2017
Contact information	
Notes	

AE: adverse event; **CT:** computed tomography; **CTAE:** Common Terminology Criteria for Adverse Events; **HRD:** homologous recombination deficient; **IV:** intravenous; **MRI:** magnetic resonance imaging; **ORR:** objective response rare; **OS:** overall survival;**PARPi:** poly (ADP-ribose) polymerase) inhibitors; **PFS:** progression-free survival;**QoL:** quality of life;**RECIST:** Response Evaluation Criteria in Solid Tumours.

DATA AND ANALYSES

Comparison 1. Newly diagnosed EOC: PARPi with chemotherapy compared with chemotherapy alone

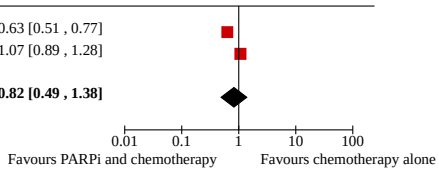
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Progression-free survival	2	1564	Hazard Ratio (IV, Random, 95% CI)	0.82 [0.49, 1.38]
1.2 Progression-free survival by BRCA status	2	1493	Hazard Ratio (IV, Random, 95% CI)	0.74 [0.47, 1.17]
1.2.1 Participants with *BRCA* mutation	2	427	Hazard Ratio (IV, Random, 95% CI)	0.62 [0.16, 2.36]
1.2.2 Participants without BRCA mutation	2	1066	Hazard Ratio (IV, Random, 95% CI)	0.86 [0.59, 1.25]
1.3 Progression-free survival by HRD status	2	1327	Hazard Ratio (IV, Random, 95% CI)	0.79 [0.45, 1.36]
1.3.1 Participants with HRD mutation	2	800	Hazard Ratio (IV, Random, 95% CI)	0.60 [0.19, 1.97]
1.3.2 Participants without HRD mutation	2	527	Hazard Ratio (IV, Random, 95% CI)	1.02 [0.83, 1.25]
1.4 Objective response rate (no response)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Quality of Life - European Organization for Research and Treatment of Cancer Questionnaire QLQ-C30	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.6 Any severe adverse event (grade 3 or higher)	2	1549	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.07, 1.20]

Analysis 1.1. Comparison 1: Newly diagnosed EOC: PARPi with chemotherapy compared with chemotherapy alone, Outcome 1: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	PARPi with chemotherapy Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
PAOLA-1 (1)	-0.462035	0.105099	537	269	49.5%	0.63 [0.51 , 0.77]
VELIA (2)	0.067659	0.091839	383	375	50.5%	1.07 [0.89 , 1.28]
Total (95% CI)			**920**	**644**	**100.0%**	**0.82 [0.49 , 1.38]**

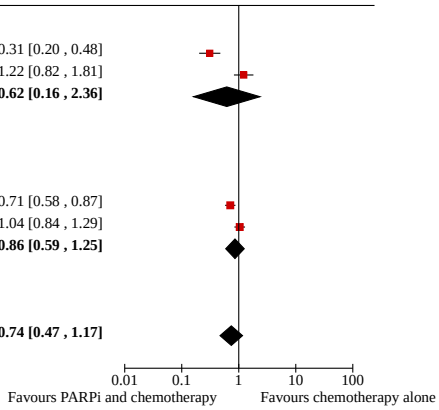
Heterogeneity: Tau² = 0.13; Chi² = 14.40, df = 1 (P = 0.0001); I² = 93%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



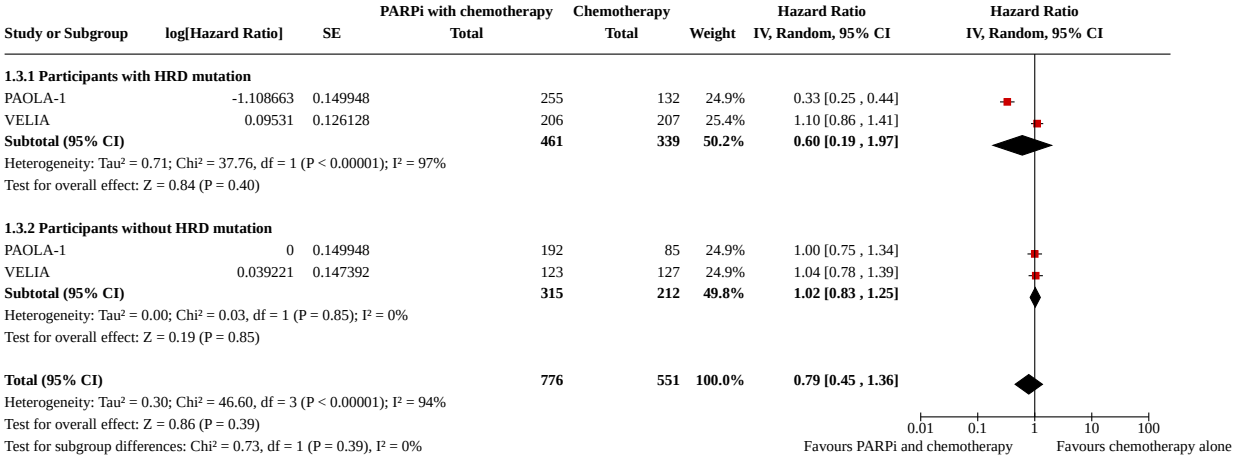
Footnotes
(1) assessed by blinded reviewer; PARP inhibitor: olaparib; chemotherapy with bevacizumab
(2) assessed by investigator; PARP inhibitor: velaparib

Analysis 1.2. Comparison 1: Newly diagnosed EOC: PARPi with chemotherapy compared with chemotherapy alone, Outcome 2: Progression-free survival by BRCA status

Study or Subgroup	log[Hazard Ratio]	SE	PARPi with chemotherapy Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
1.2.1 Participants with *BRCA* mutation						
PAOLA-1	-1.171183	0.217967	157	80	22.8%	0.31 [0.20 , 0.48]
VELIA	0.198851	0.200575	98	92	23.5%	1.22 [0.82 , 1.81]
Subtotal (95% CI)			**255**	**172**	**46.3%**	**0.62 [0.16 , 2.36]**
Heterogeneity: Tau² = 0.89; Chi² = 21.39, df = 1 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.2.2 Participants without BRCA mutation						
PAOLA-1	-0.34249	0.106352	380	189	26.9%	0.71 [0.58 , 0.87]
VELIA	0.039221	0.10944	243	254	26.8%	1.04 [0.84 , 1.29]
Subtotal (95% CI)			**623**	**443**	**53.7%**	**0.86 [0.59 , 1.25]**
Heterogeneity: Tau² = 0.06; Chi² = 6.26, df = 1 (P = 0.01); I² = 84%						
Test for overall effect: Z = 0.80 (P = 0.42)						
Total (95% CI)			**878**	**615**	**100.0%**	**0.74 [0.47 , 1.17]**
Heterogeneity: Tau² = 0.19; Chi² = 30.33, df = 3 (P < 0.00001); I² = 90%						
Test for overall effect: Z = 1.30 (P = 0.19)						
Test for subgroup differences: Chi² = 0.22, df = 1 (P = 0.64), I² = 0%						

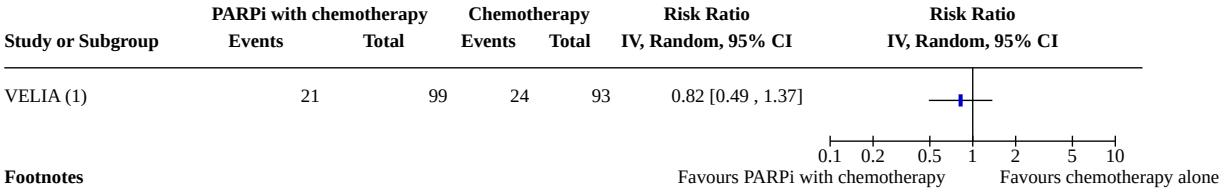


Analysis 1.3. Comparison 1: Newly diagnosed EOC: PARPi with chemotherapy compared with chemotherapy alone, Outcome 3: Progression-free survival by HRD status



Study or Subgroup	log[Hazard Ratio]	SE	PARPi with chemotherapy Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
1.3.1 Participants with HRD mutation						
PAOLA-1	-1.108663	0.149948	255	132	24.9%	0.33 [0.25 , 0.44]
VELIA	0.09531	0.126128	206	207	25.4%	1.10 [0.86 , 1.41]
Subtotal (95% CI)			**461**	**339**	**50.2%**	**0.60 [0.19 , 1.97]**
Heterogeneity: Tau² = 0.71; Chi² = 37.76, df = 1 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 0.84 (P = 0.40)						
1.3.2 Participants without HRD mutation						
PAOLA-1	0	0.149948	192	85	24.9%	1.00 [0.75 , 1.34]
VELIA	0.039221	0.147392	123	127	24.9%	1.04 [0.78 , 1.39]
Subtotal (95% CI)			**315**	**212**	**49.8%**	**1.02 [0.83 , 1.25]**
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Total (95% CI)			**776**	**551**	**100.0%**	**0.79 [0.45 , 1.36]**
Heterogeneity: Tau² = 0.30; Chi² = 46.60, df = 3 (P < 0.00001); I² = 94%						
Test for overall effect: Z = 0.86 (P = 0.39)						
Test for subgroup differences: Chi² = 0.73, df = 1 (P = 0.39), I² = 0%						

Analysis 1.4. Comparison 1: Newly diagnosed EOC: PARPi with chemotherapy compared with chemotherapy alone, Outcome 4: Objective response rate (no response)

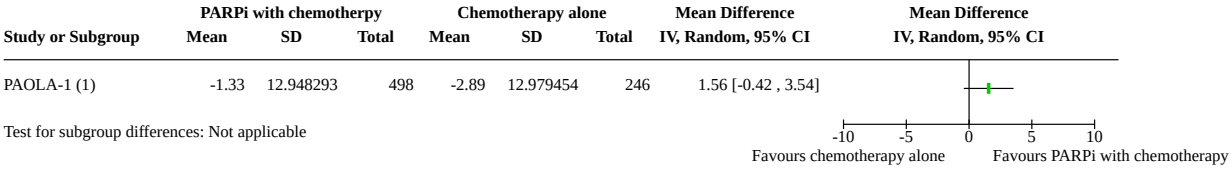


Study or Subgroup	PARPi with chemotherapy Events	Total	Chemotherapy Events	Total	Risk Ratio IV, Random, 95% CI
VELIA (1)	21	99	24	93	0.82 [0.49 , 1.37]

Footnotes

(1) PARP inhibitor: velaparib

Analysis 1.5. Comparison 1: Newly diagnosed EOC: PARPi with chemotherapy compared with chemotherapy alone, Outcome 5: Quality of Life - European Organization for Research and Treatment of Cancer Questionnaire QLQ-C30



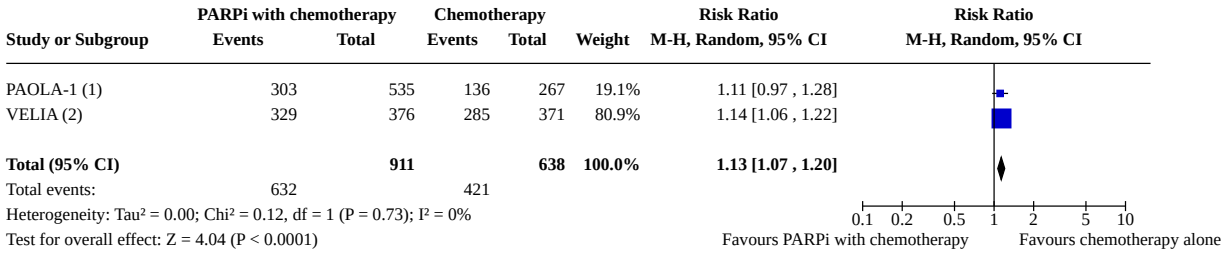
Study or Subgroup	PARPi with chemotherpy Mean	SD	Total	Chemotherapy alone Mean	SD	Total	Mean Difference IV, Random, 95% CI
PAOLA-1 (1)	-1.33	12.948293	498	-2.89	12.979454	246	1.56 [-0.42 , 3.54]

Test for subgroup differences: Not applicable

Footnotes

(1) adjusted mean change from baseline

Analysis 1.6. Comparison 1: Newly diagnosed EOC: PARPi with chemotherapy compared with chemotherapy alone, Outcome 6: Any severe adverse event (grade 3 or higher)



Footnotes

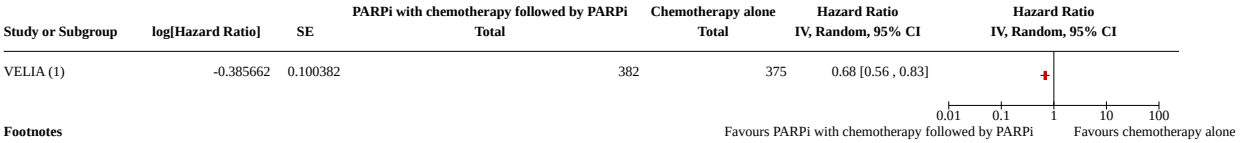
(1) PARP inhibitor: olaparib; chemotherapy with bevacizumab

(2) PARP inhibitor: velaparib

Comparison 2. Newly diagnosed EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone

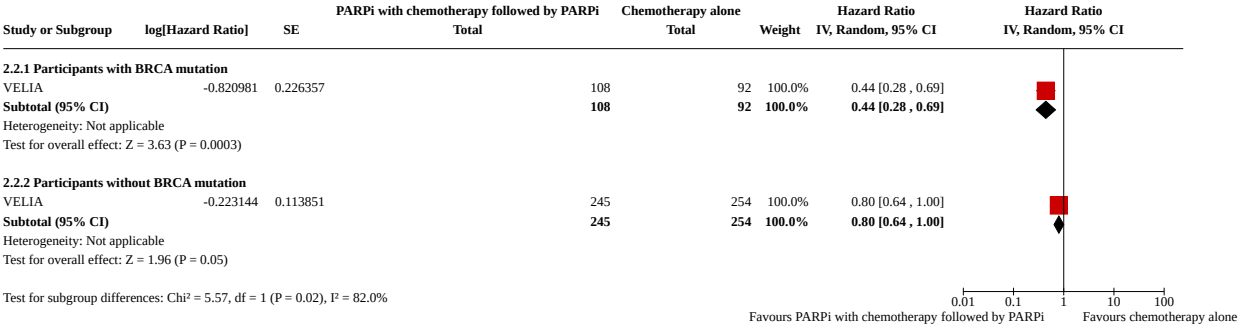
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
2.2 Progression-free survival by BRCA status	1		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
2.2.1 Participants with BRCA mutation	1	200	Hazard Ratio (IV, Random, 95% CI)	0.44 [0.28, 0.69]
2.2.2 Participants without BRCA mutation	1	499	Hazard Ratio (IV, Random, 95% CI)	0.80 [0.64, 1.00]
2.3 Progression-free survival by HRD status	1		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
2.3.1 Participants with HRD mutation	1	421	Hazard Ratio (IV, Random, 95% CI)	0.57 [0.43, 0.76]
2.3.2 Participants without HRD mutation	1	249	Hazard Ratio (IV, Random, 95% CI)	0.81 [0.60, 1.09]
2.4 Objective response rate (no response)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.5 Any severe adverse event (grade 3 or higher)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Newly diagnosed EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone, Outcome 1: Progression-free survival

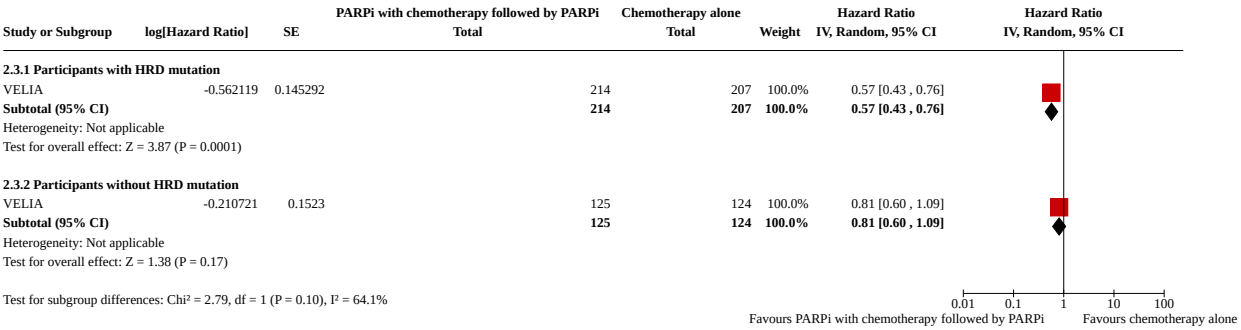


Footnotes
(1) assessed by investigator; PARP inhibitor: velaparib

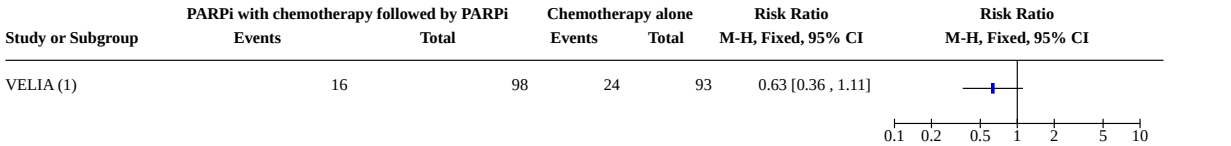
Analysis 2.2. Comparison 2: Newly diagnosed EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone, Outcome 2: Progression-free survival by BRCA status



Analysis 2.3. Comparison 2: Newly diagnosed EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone, Outcome 3: Progression-free survival by HRD status

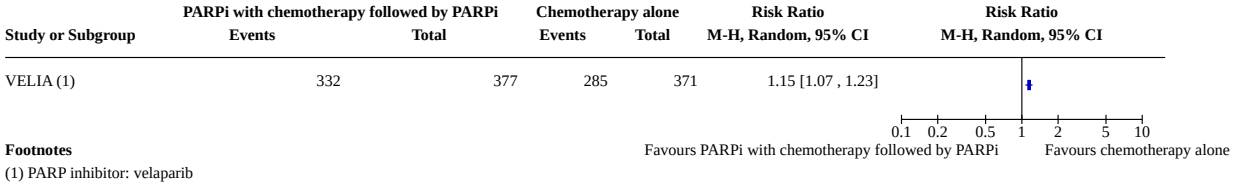


Analysis 2.4. Comparison 2: Newly diagnosed EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone, Outcome 4: Objective response rate (no response)



Footnotes
(1) PARPi: velaparib

Analysis 2.5. Comparison 2: Newly diagnosed EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone, Outcome 5: Any severe adverse event (grade 3 or higher)



Footnotes
(1) PARP inhibitor: velaparib

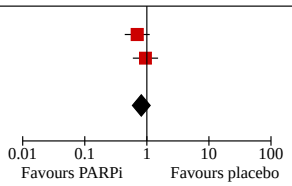
Comparison 3. Newly diagnosed EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Overall survival	2	1124	Hazard Ratio (IV, Random, 95% CI)	0.81 [0.59, 1.13]
3.2 Overall survival by HRD status	1		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
3.2.1 Participants with HRD mutation	1	373	Hazard Ratio (IV, Random, 95% CI)	0.61 [0.27, 1.38]
3.2.2 Participants without HRD mutation	1	249	Hazard Ratio (IV, Random, 95% CI)	0.51 [0.27, 0.97]
3.3 Progression-free survival	2	1124	Hazard Ratio (IV, Random, 95% CI)	0.42 [0.19, 0.92]
3.4 Progression-free survival by BRCA status	2		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
3.4.1 Participants with *BRCA* mutation	2	613	Hazard Ratio (IV, Random, 95% CI)	0.33 [0.23, 0.46]
3.4.2 Participants without BRCA mutation	1	150	Hazard Ratio (IV, Random, 95% CI)	0.50 [0.31, 0.82]
3.5 Progression-free survival by HRD status	1		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
3.5.1 Participants with HRD mutation	1	373	Hazard Ratio (IV, Random, 95% CI)	0.43 [0.31, 0.59]
3.5.2 Participants without HRD mutation	1	249	Hazard Ratio (IV, Random, 95% CI)	0.68 [0.49, 0.94]
3.6 Quality of Life - Trial Outcome Index score of Functional Assessmentof Cancer Therapy—Ovarian Cancer questionnaire	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.7 Any severe adverse event (grade 3 or higher)	2	1118	Risk Ratio (M-H, Random, 95% CI)	2.87 [1.65, 4.99]

Analysis 3.1. Comparison 3: Newly diagnosed EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	PARPi Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
PRIMA (1)	-0.356675	0.236061	487	246	50.6%	0.70 [0.44 , 1.11]
SOLO 1 (2)	-0.051293	0.238804	260	131	49.4%	0.95 [0.59 , 1.52]
Total (95% CI)			**747**	**377**	**100.0%**	**0.81 [0.59 , 1.13]**

Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable



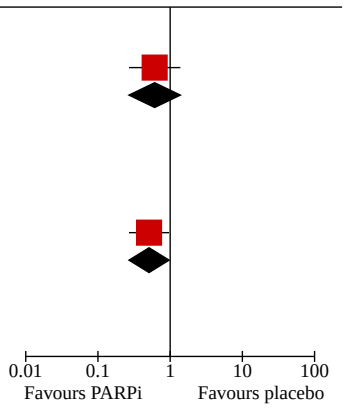
Footnotes
(1) Based on interim analysis (10.8% maturity); PARP inhibitor: niraparib
(2) Based on immature OS data (21% maturity); population: participants only with BRCA mutation; PARP inhibitor: olaparib

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 3.2. Comparison 3: Newly diagnosed EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 2: Overall survival by HRD status

Study or Subgroup	log[Hazard Ratio]	SE	PARPi Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
3.2.1 Participants with HRD mutation						
PRIMA	-0.494296	0.418027	247	126	100.0%	0.61 [0.27 , 1.38]
Subtotal (95% CI)			**247**	**126**	**100.0%**	**0.61 [0.27 , 1.38]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
3.2.2 Participants without HRD mutation						
PRIMA	-0.673345	0.326249	169	80	100.0%	0.51 [0.27 , 0.97]
Subtotal (95% CI)			**169**	**80**	**100.0%**	**0.51 [0.27 , 0.97]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.06 (P = 0.04)						

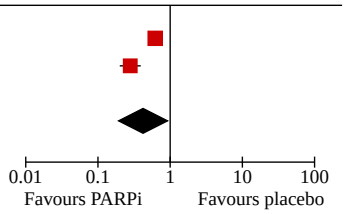
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%



Analysis 3.3. Comparison 3: Newly diagnosed EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 3: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	PARPi Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
PRIMA (1)	-0.478036	0.106816	487	246	51.4%	0.62 [0.50 , 0.76]
SOLO 1 (2)	-1.272966	0.170368	260	131	48.6%	0.28 [0.20 , 0.39]
Total (95% CI)			**747**	**377**	**100.0%**	**0.42 [0.19 , 0.92]**

Heterogeneity: Tau² = 0.30; Chi² = 15.63, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 2.18 (P = 0.03)
Test for subgroup differences: Not applicable

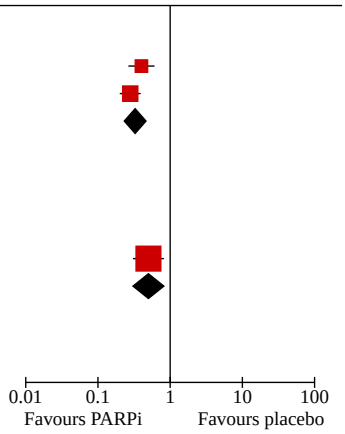


Footnotes
(1) assessed by blinded reviewer; PARP inhibitor: niraparib
(2) assessed by blinded reviewer; population: participants only with *BRCA* mutation; PARP inhibitor: olaparib

Analysis 3.4. Comparison 3: Newly diagnosed EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 4: Progression-free survival by BRCA status

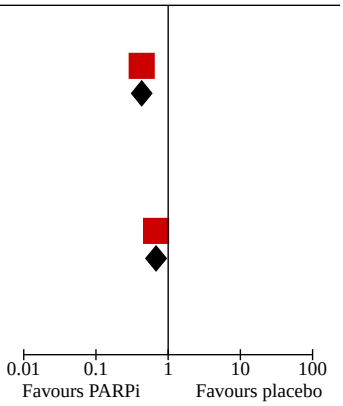
Study or Subgroup	log[Hazard Ratio]	SE	PARPi Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
3.4.1 Participants with *BRCA* mutation						
PRIMA	-0.916291	0.21207	152	70	43.7%	0.40 [0.26 , 0.61]
SOLO 1	-1.272966	0.170368	260	131	56.3%	0.28 [0.20 , 0.39]
Subtotal (95% CI)			**412**	**201**	**100.0%**	**0.33 [0.23 , 0.46]**
Heterogeneity: Tau² = 0.03; Chi² = 1.72, df = 1 (P = 0.19); I² = 42%						
Test for overall effect: Z = 6.31 (P < 0.00001)						
3.4.2 Participants without BRCA mutation						
PRIMA	-0.693147	0.251243	95	55	100.0%	0.50 [0.31 , 0.82]
Subtotal (95% CI)			**95**	**55**	**100.0%**	**0.50 [0.31 , 0.82]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.76 (P = 0.006)						

Test for subgroup differences: Chi² = 1.90, df = 1 (P = 0.17), I² = 47.4%



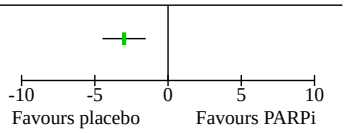
Analysis 3.5. Comparison 3: Newly diagnosed EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 5: Progression-free survival by HRD status

Study or Subgroup	log[Hazard Ratio]	SE	PARPi Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
3.5.1 Participants with HRD mutation						
PRIMA	-0.84397	0.164174	247	126	100.0%	0.43 [0.31 , 0.59]
Subtotal (95% CI)			**247**	**126**	**100.0%**	**0.43 [0.31 , 0.59]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.14 (P < 0.00001)						
3.5.2 Participants without HRD mutation						
PRIMA	-0.385662	0.166196	169	80	100.0%	0.68 [0.49 , 0.94]
Subtotal (95% CI)			**169**	**80**	**100.0%**	**0.68 [0.49 , 0.94]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.32 (P = 0.02)						
Test for subgroup differences: Chi² = 3.85, df = 1 (P = 0.05), I² = 74.0%						



Analysis 3.6. Comparison 3: Newly diagnosed EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 6: Quality of Life - Trial Outcome Index score of Functional Assessmentof Cancer Therapy—Ovarian Cancer questionnaire

Study or Subgroup	PARPi Mean	PARPi SD	PARPi Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
SOLO 1 (1)	0.3	2.344307	237	3.3	8.247087	125	-3.00 [-4.48 , -1.52]

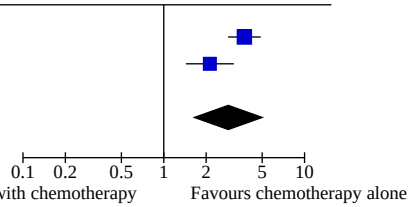


Footnotes

(1) adjusted mean change from baseline

Analysis 3.7. Comparison 3: Newly diagnosed EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 7: Any severe adverse event (grade 3 or higher)

Study or Subgroup	PARPi Events	PARPi Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
PRIMA (1)	341	484	46	244	53.3%	3.74 [2.86 , 4.88]
SOLO 1 (2)	102	260	24	130	46.7%	2.13 [1.44 , 3.14]
Total (95% CI)		**744**		**374**	**100.0%**	**2.87 [1.65 , 4.99]**
Total events:	443		70			
Heterogeneity: Tau² = 0.13; Chi² = 5.48, df = 1 (P = 0.02); I² = 82%						
Test for overall effect: Z = 3.74 (P = 0.0002)						
Test for subgroup differences: Not applicable						



Footnotes

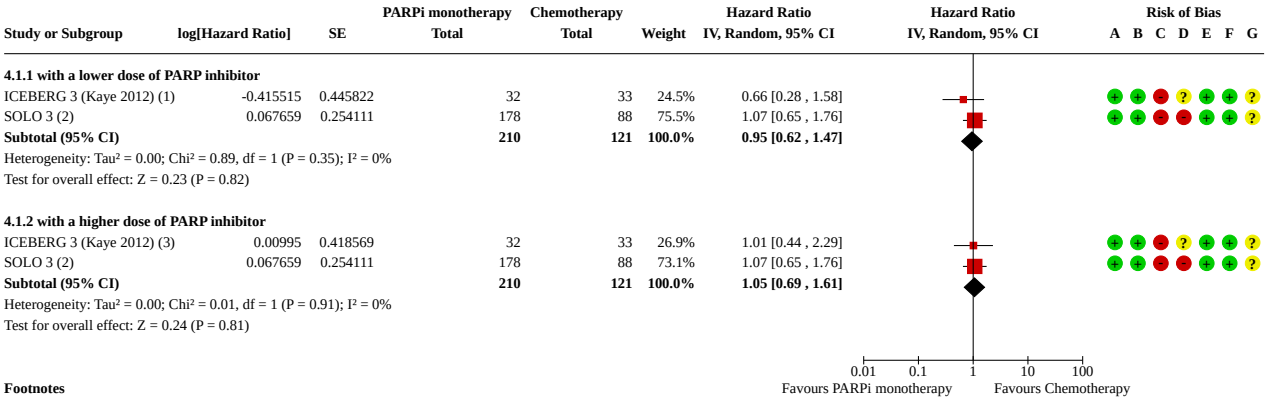
(1) PARP inhibitor: niraparib

(2) PARP inhibitor: olaparib

Comparison 4. Platinum-sensitive recurrent EOC: PARPi monotherapy compared with chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Overall survival	2		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
4.1.1 with a lower dose of PARP inhibitor	2	331	Hazard Ratio (IV, Random, 95% CI)	0.95 [0.62, 1.47]
4.1.2 with a higher dose of PARP inhibitor	2	331	Hazard Ratio (IV, Random, 95% CI)	1.05 [0.69, 1.61]
4.2 Progression-free survival	3	739	Hazard Ratio (IV, Random, 95% CI)	0.88 [0.56, 1.38]
4.3 Progression-free survival by BRCA status	3		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
4.3.1 Participants with *BRCA* mutation	3	363	Hazard Ratio (IV, Random, 95% CI)	0.97 [0.42, 2.25]
4.3.2 Participants without BRCA mutation	1	0	Hazard Ratio (IV, Random, 95% CI)	1.41 [1.07, 1.86]
4.4 Objective response rate (no response)	3	696	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.56, 1.67]
4.5 Quality of Life - Trial Outcome Index score of Functional Assessmentof Cancer Therapy—Ovarian Cancer questionnaire	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.6 Any severe adverse event (grade 3 or higher)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with chemotherapy, Outcome 1: Overall survival



Study or Subgroup	log[Hazard Ratio]	SE	PARPi monotherapy Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F G
4.1.1 with a lower dose of PARP inhibitor								
ICEBERG 3 (Kaye 2012) (1)	-0.415515	0.445822	32	33	24.5%	0.66 [0.28 , 1.58]		+ + - ? + + ?
SOLO 3 (2)	0.067659	0.254111	178	88	75.5%	1.07 [0.65 , 1.76]		+ + - - + + ?
Subtotal (95% CI)			**210**	**121**	**100.0%**	**0.95 [0.62 , 1.47]**		
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.35); I² = 0%								
Test for overall effect: Z = 0.23 (P = 0.82)								
4.1.2 with a higher dose of PARP inhibitor								
ICEBERG 3 (Kaye 2012) (3)	0.00995	0.418569	32	33	26.9%	1.01 [0.44 , 2.29]		+ + - ? + + ?
SOLO 3 (2)	0.067659	0.254111	178	88	73.1%	1.07 [0.65 , 1.76]		+ + - - + + ?
Subtotal (95% CI)			**210**	**121**	**100.0%**	**1.05 [0.69 , 1.61]**		
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%								
Test for overall effect: Z = 0.24 (P = 0.81)								

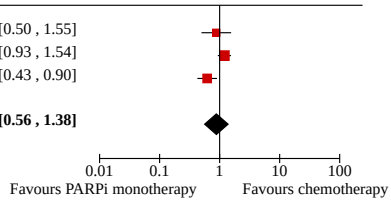
Footnotes

(1) olaparib dose 200 mg; population: only participants with *BRCA* mutation, 50% with platinum resistant disease
(2) immature OS data; population: only participants with *BRCA* mutation
(3) olaparib dose 400 mg; population: only participants with *BRCA* mutation, 50% with platinum resistant disease

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 4.2. Comparison 4: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with chemotherapy, Outcome 2: Progression-free survival



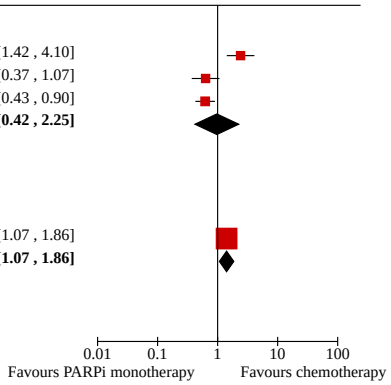
Study or Subgroup	log[Hazard Ratio]	SE	PARPi monotherapy Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
ICEBERG 3 (Kaye 2012) (1)	-0.127833	0.290269	64	33	26.2%	0.88 [0.50 , 1.55]	
NCT02446600 (2)	0.182322	0.128664	189	187	39.5%	1.20 [0.93 , 1.54]	
SOLO 3 (3)	-0.478036	0.191243	178	88	34.3%	0.62 [0.43 , 0.90]	
Total (95% CI)			**431**	**308**	**100.0%**	**0.88 [0.56 , 1.38]**	
Heterogeneity: Tau² = 0.12; Chi² = 8.32, df = 2 (P = 0.02); I² = 76%							
Test for overall effect: Z = 0.55 (P = 0.58)							
Test for subgroup differences: Not applicable							

Footnotes

(1) combined arms with 200 and 400 mg olaparib; population: only participants with *BRCA* mutation, 50% with platinum resistant disease
(2) comparison: olaparib vs chemotherapy
(3) assessed by blinded reviewer; population: only participants with *BRCA* mutation

Analysis 4.3. Comparison 4: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with chemotherapy, Outcome 3: Progression-free survival by BRCA status

Study or Subgroup	log[Hazard Ratio]	SE	PARPi monotherapy Total	Chemotherapy Total	Weight	Hazard Ratio IV, Random, 95% CI
4.3.1 Participants with *BRCA* mutation						
ICEBERG 3 (Kaye 2012) (1)	0.88	0.270413	64	33	32.6%	2.41 [1.42 , 4.10]
NCT02446600 (2)	-0.462035	0.270901	0	0	32.6%	0.63 [0.37 , 1.07]
SOLO 3 (3)	-0.478036	0.191243	178	88	34.8%	0.62 [0.43 , 0.90]
Subtotal (95% CI)			**242**	**121**	**100.0%**	**0.97 [0.42 , 2.25]**
Heterogeneity: Tau² = 0.49; Chi² = 18.76, df = 2 (P < 0.0001); I² = 89%						
Test for overall effect: Z = 0.07 (P = 0.94)						
4.3.2 Participants without BRCA mutation						
NCT02446600 (2)	0.34359	0.141053	0	0	100.0%	1.41 [1.07 , 1.86]
Subtotal (95% CI)			**0**	**0**	**100.0%**	**1.41 [1.07 , 1.86]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.44 (P = 0.01)						
Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.41), I² = 0%						

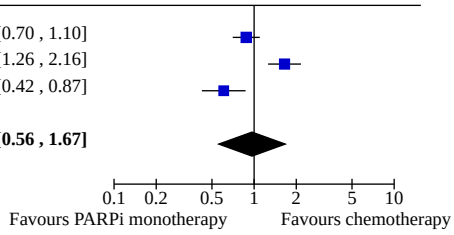


Footnotes

(1) olaparib (combined arms 200 and 400 mg) ; population: 50% with platinum resistant disease
(2) comparison: olaparib vs chemotherapy; the number of participants per treatment arm for this subgroup was not reported
(3) comparison: olaparib vs chemotherapy; assessed by blinded reviewer

Analysis 4.4. Comparison 4: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with chemotherapy, Outcome 4: Objective response rate (no response)

Study or Subgroup	PARPi monotherapy Events	Total	Chemotherapy Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ICEBERG 3 (Kaye 2012)	46	64	27	33	34.6%	0.88 [0.70 , 1.10]
NCT02446600 (1)	90	189	54	187	33.7%	1.65 [1.26 , 2.16]
SOLO 3	42	151	33	72	31.7%	0.61 [0.42 , 0.87]
Total (95% CI)		**404**		**292**	**100.0%**	**0.97 [0.56 , 1.67]**
Total events:	178		114			
Heterogeneity: Tau² = 0.21; Chi² = 23.07, df = 2 (P < 0.00001); I² = 91%						
Test for overall effect: Z = 0.12 (P = 0.90)						
Test for subgroup differences: Not applicable						

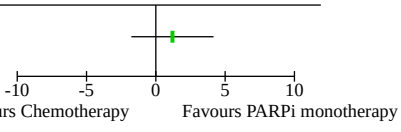


Footnotes

(1) data reported in the conference abstract as percentages; comparison: PARP inhibitor (olaparib) versus chemotherapy

Analysis 4.5. Comparison 4: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with chemotherapy, Outcome 5: Quality of Life - Trial Outcome Index score of Functional Assessmentof Cancer Therapy—Ovarian Cancer questionnaire

Study or Subgroup	PARPi monotherapy Mean	SD	Total	Chemotherapy Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
SOLO 3 (1)	-2.4	11.1	167	-3.6	9.8	62	1.20 [-1.76 , 4.16]

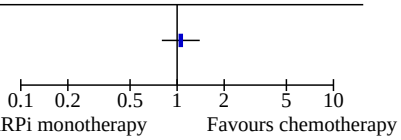


Footnotes

(1) adjusted mean change from baseline; data source: ClinicalTrials.gov

Analysis 4.6. Comparison 4: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with chemotherapy, Outcome 6: Any severe adverse event (grade 3 or higher)

Study or Subgroup	PARPi monotherapy Events	Total	Chemotherapy Events	Total	Risk Ratio M-H, Fixed, 95% CI
SOLO 3 (1)	89	178	36	76	1.06 [0.80 , 1.39]



Footnotes

(1) comparison: olaparib vs chemotherapy

Comparison 5. Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy)

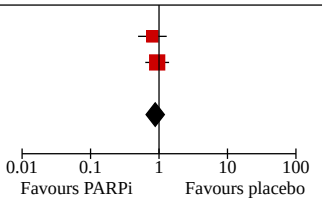
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Overall survival	2	560	Hazard Ratio (IV, Random, 95% CI)	0.88 [0.65, 1.20]
5.2 Progression-free survival	4	1677	Hazard Ratio (IV, Random, 95% CI)	0.34 [0.28, 0.42]
5.3 Progression-free survival by BRCA status	3		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
5.3.1 Participants with *BRCA* mutation	3	685	Hazard Ratio (IV, Random, 95% CI)	0.27 [0.20, 0.36]
5.3.2 Participants without BRCA mutation	2	511	Hazard Ratio (IV, Random, 95% CI)	0.50 [0.39, 0.63]
5.4 Progression-free survival by HRD status	2		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
5.4.1 Participants with HRD mutation	2	516	Hazard Ratio (IV, Random, 95% CI)	0.35 [0.27, 0.46]
5.4.2 Participants without HRD mutation	1	0	Hazard Ratio (IV, Random, 95% CI)	0.58 [0.36, 0.93]
5.5 Objective response rate (no response)	2	312	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.83, 0.97]
5.6 Quality of Life - European Quality of Life 5-dimensions questionnaire	1	339	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.01, 0.05]
5.6.1 Participants with *BRCA* mutation	1	106	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.05, 0.06]
5.6.2 Participants without *BRCA* mutation	1	233	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.01, 0.06]
5.7 Quality of Life - Trial Outcome Index score of Functional Assessmentof Can-	1	279	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-2.16, 2.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
cer Therapy—Ovarian Cancer questionnaire				
5.8 Quality of Life - Quality adjusted Progression-free survival (QA-PFS)	2	858	Mean Difference (IV, Fixed, 95% CI)	6.41 [5.37, 7.44]
5.9 Quality of Life - Quality adjusted Progression-free survival (QA-PFS) by BRCA status	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.9.1 Participants with BRCA mutation	2	490	Mean Difference (IV, Fixed, 95% CI)	7.66 [6.19, 9.13]
5.9.2 Participants without BRCA mutation	1	161	Mean Difference (IV, Fixed, 95% CI)	2.71 [0.78, 4.64]
5.10 Quality of Life - Time without symptoms of treatment toxicity (TWiST)	2	858	Mean Difference (IV, Fixed, 95% CI)	6.52 [5.69, 7.35]
5.11 Quality of Life - Time without symptoms of treatment toxicity (TWiST) by BRCA status	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.11.1 Participants with BRCA mutation	2	490	Mean Difference (IV, Fixed, 95% CI)	8.62 [7.37, 9.87]
5.11.2 Participants without BRCA mutation	1	161	Mean Difference (IV, Fixed, 95% CI)	3.10 [1.85, 4.35]
5.12 Any severe adverse event (grade 3 or higher)	4	1665	Risk Ratio (IV, Random, 95% CI)	2.62 [1.85, 3.72]

Analysis 5.1. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 1: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	PARPi Total	Placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
SOLO 2 (1)	-0.223144	0.245712	196	99	40.9%	0.80 [0.49 , 1.29]
Study 19 (Ledermann 2012) (2)	-0.0619	0.2042	136	129	59.1%	0.94 [0.63 , 1.40]
Total (95% CI)			**332**	**228**	**100.0%**	**0.88 [0.65 , 1.20]**

Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable

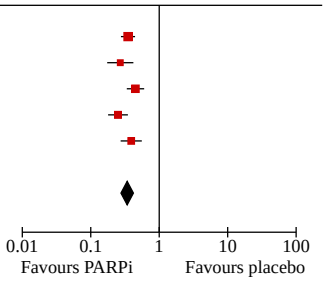


Footnotes
(1) Based on immature OS (24% data maturity); population: only participants with *BRCA* mutation
(2) Based on interim analysis, immature OS (38% data maturity)

Analysis 5.2. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 2: Progression-free survival

Study or Subgroup	log[Hazard Ratio]	SE	PARPi Total	placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
ARIEL3 (1)	-1.049822	0.121037	375	189	25.9%	0.35 [0.28 , 0.44]
NOVA (2)	-1.309333	0.224585	138	65	14.3%	0.27 [0.17 , 0.42]
NOVA (3)	-0.798508	0.149113	234	116	22.1%	0.45 [0.34 , 0.60]
SOLO 2 (4)	-1.386294	0.16964	196	99	19.6%	0.25 [0.18 , 0.35]
Study 19 (Ledermann 2012) (1)	-0.941609	0.181507	136	129	18.3%	0.39 [0.27 , 0.56]
Total (95% CI)			**1079**	**598**	**100.0%**	**0.34 [0.28 , 0.42]**

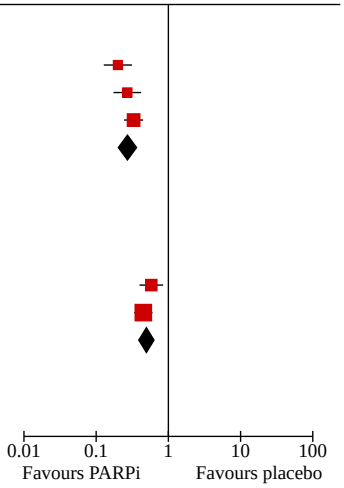
Heterogeneity: Tau² = 0.03; Chi² = 8.44, df = 4 (P = 0.08); I² = 53%
Test for overall effect: Z = 10.11 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) assessed by blinded reviewer
(2) assessed by blinded reviewer; population: participants with only *BRCA* mutation
(3) assessed by blinded reviewer; population: participants without *BRCA* mutation
(4) assessed by blinded reviewer; population: 97% of participants had *BRCA* mutation

Analysis 5.3. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 3: Progression-free survival by BRCA status

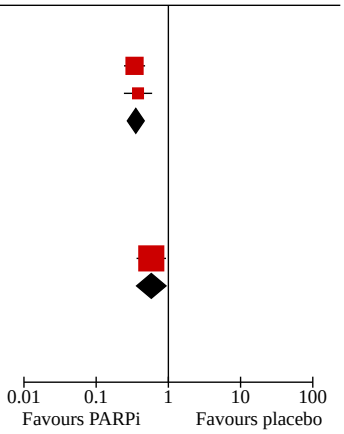
Study or Subgroup	log[Hazard Ratio]	SE	PARPi Total	placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
5.3.1 Participants with *BRCA* mutation						
ARIEL3 (1)	-1.609438	0.229797	130	66	27.7%	0.20 [0.13 , 0.31]
NOVA (2)	-1.309333	0.224585	138	65	28.6%	0.27 [0.17 , 0.42]
SOLO 2 (3)	-1.108663	0.154629	190	96	43.7%	0.33 [0.24 , 0.45]
Subtotal (95% CI)			**458**	**227**	**100.0%**	**0.27 [0.20 , 0.36]**
Heterogeneity: Tau² = 0.03; Chi² = 3.30, df = 2 (P = 0.19); I² = 39%						
Test for overall effect: Z = 8.82 (P < 0.00001)						
5.3.2 Participants without BRCA mutation						
ARIEL3	-0.544727	0.192292	107	54	38.6%	0.58 [0.40 , 0.85]
NOVA	-0.798508	0.149113	234	116	61.4%	0.45 [0.34 , 0.60]
Subtotal (95% CI)			**341**	**170**	**100.0%**	**0.50 [0.39 , 0.63]**
Heterogeneity: Tau² = 0.00; Chi² = 1.09, df = 1 (P = 0.30); I² = 8%						
Test for overall effect: Z = 5.67 (P < 0.00001)						
Test for subgroup differences: Chi² = 9.82, df = 1 (P = 0.002), I² = 89.8%						



Footnotes
(1) assessed by blinded reviewer
(2) assessed by blinded reviewer;
(3) assessed by investigator

Analysis 5.4. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 4: Progression-free survival by HRD status

Study or Subgroup	log[Hazard Ratio]	SE	PARPi Total	placebo Total	Weight	Hazard Ratio IV, Random, 95% CI
5.4.1 Participants with HRD mutation						
ARIEL3 (1)	-1.07881	0.171456	236	118	64.2%	0.34 [0.24 , 0.48]
NOVA (2)	-0.967584	0.229464	106	56	35.8%	0.38 [0.24 , 0.60]
Subtotal (95% CI)			**342**	**174**	**100.0%**	**0.35 [0.27 , 0.46]**
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 7.56 (P < 0.00001)						
5.4.2 Participants without HRD mutation						
NOVA (3)	-0.544727	0.239359	0	0	100.0%	0.58 [0.36 , 0.93]
Subtotal (95% CI)			**0**	**0**	**100.0%**	**0.58 [0.36 , 0.93]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.28 (P = 0.02)						
Test for subgroup differences: Chi² = 3.21, df = 1 (P = 0.07), I² = 68.8%						

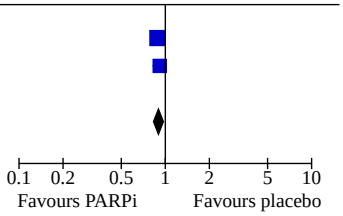


Footnotes

(1) assessed by blinded reviewer;
(2) assessed by blinded reviewer; population: only participants with *BRCA* mutation
(3) number of pts not given

Analysis 5.5. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 5: Objective response rate (no response)

Study or Subgroup	PARPi Events	PARPi Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
ARIEL3 (1)	115	141	61	66	54.2%	0.88 [0.79 , 0.98]
Study 19 (Ledermann 2012)	50	57	46	48	45.8%	0.92 [0.82 , 1.03]
Total (95% CI)		**198**		**114**	**100.0%**	**0.90 [0.83 , 0.97]**
Total events:	165		107			
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 2.76 (P = 0.006)						
Test for subgroup differences: Not applicable						

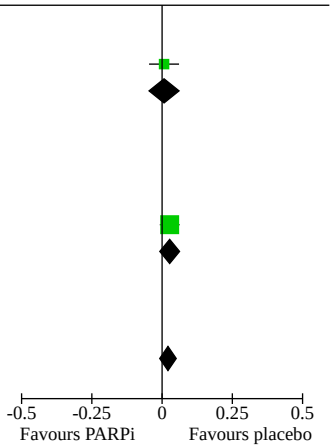


Footnotes

(1) PARP inhibitor: rucaparib

Analysis 5.6. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 6: Quality of Life - European Quality of Life 5-dimensions questionnaire

Study or Subgroup	PARPi Mean	PARPi SD	PARPi Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
5.6.1 Participants with *BRCA* mutation								
NOVA (1)	0.801	0.16	60	0.794	0.12	46	30.2%	0.01 [-0.05 , 0.06]
Subtotal (95% CI)			**60**			**46**	**30.2%**	**0.01 [-0.05 , 0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.80)								
5.6.2 Participants without *BRCA* mutation								
NOVA (1)	0.81	0.14	139	0.783	0.13	94	69.8%	0.03 [-0.01 , 0.06]
Subtotal (95% CI)			**139**			**94**	**69.8%**	**0.03 [-0.01 , 0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.51 (P = 0.13)								
Total (95% CI)			**199**			**140**	**100.0%**	**0.02 [-0.01 , 0.05]**
Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%								
Test for overall effect: Z = 1.40 (P = 0.16)								
Test for subgroup differences: Chi² = 0.38, df = 1 (P = 0.54), I² = 0%								

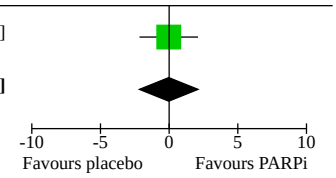


Footnotes

(1) First post-progression the European Quality of Life–5 Dimensions questionnaires Health Utility Index score among all patients with disease progression

Analysis 5.7. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 7: Quality of Life - Trial Outcome Index score of Functional Assessmentof Cancer Therapy—Ovarian Cancer questionnaire

Study or Subgroup	PARPi Mean	PARPi SD	PARPi Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
SOLO 2 (1)	-2.9	8.479631	185	-2.87	8.641742	94	100.0%	-0.03 [-2.16 , 2.10]
Total (95% CI)			**185**			**94**	**100.0%**	**-0.03 [-2.16 , 2.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.03 (P = 0.98)								
Test for subgroup differences: Not applicable								

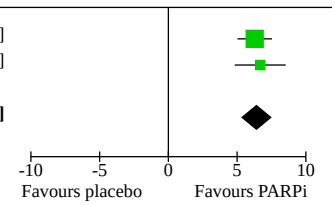


Footnotes

(1) adjusted mean change from baseline

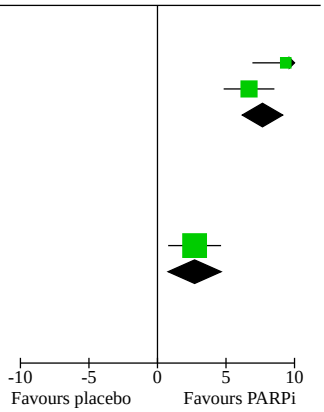
Analysis 5.8. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 8: Quality of Life - Quality adjusted Progression-free survival (QA-PFS)

Study or Subgroup	PARPi Mean	PARPi SD	PARPi Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
ARIEL3	12.02	10.192957	375	5.74	5.017768	189	68.5%	6.28 [5.02 , 7.54]
SOLO 2	13.96	10.96	195	7.28	5.22	99	31.5%	6.68 [4.83 , 8.53]
Total (95% CI)			**570**			**288**	**100.0%**	**6.41 [5.37 , 7.44]**
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%								
Test for overall effect: Z = 12.09 (P < 0.00001)								
Test for subgroup differences: Not applicable								



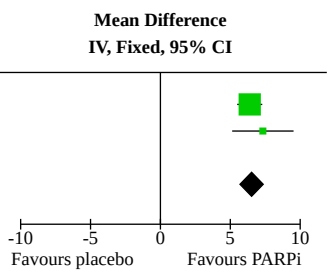
Analysis 5.9. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 9: Quality of Life - Quality adjusted Progression-free survival (QA-PFS) by BRCA status

Study or Subgroup	PARPi Mean	PARPi SD	PARPi Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
5.9.1 Participants with BRCA mutation								
ARIEL3	15.28	12.188229	130	5.92	5.125479	66	36.6%	9.36 [6.93 , 11.79]
SOLO 2	13.96	10.96	195	7.28	5.22	99	63.4%	6.68 [4.83 , 8.53]
Subtotal (95% CI)			**325**			**165**	**100.0%**	**7.66 [6.19 , 9.13]**
Heterogeneity: Chi² = 2.95, df = 1 (P = 0.09); I² = 66%								
Test for overall effect: Z = 10.20 (P < 0.00001)								
5.9.2 Participants without BRCA mutation								
ARIEL3	8.13	7.826159	107	5.42	4.634592	54	100.0%	2.71 [0.78 , 4.64]
Subtotal (95% CI)			**107**			**54**	**100.0%**	**2.71 [0.78 , 4.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.75 (P = 0.006)								
Test for subgroup differences: Chi² = 15.98, df = 1 (P < 0.0001), I² = 93.7%								



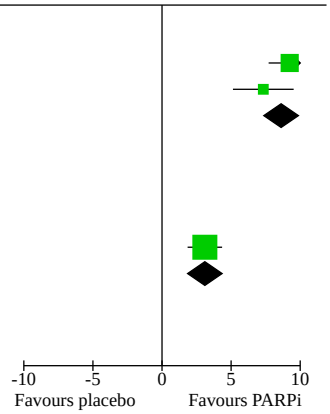
Analysis 5.10. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 10: Quality of Life - Time without symptoms of treatment toxicity (TWiST)

Study or Subgroup	PARPi Mean	PARPi SD	PARPi Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
ARIEL3	12.75	7.33696	375	6.36	3.519407	189	85.7%	6.39 [5.49 , 7.29]
SOLO 2	15.03	12.79	195	7.7	6.42	99	14.3%	7.33 [5.13 , 9.53]
Total (95% CI)			**570**			**288**	**100.0%**	**6.52 [5.69 , 7.35]**
Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² = 0%								
Test for overall effect: Z = 15.41 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Analysis 5.11. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 11: Quality of Life - Time without symptoms of treatment toxicity (TWiST) by BRCA status

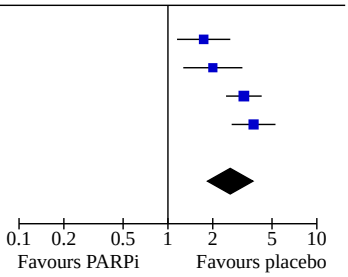
Study or Subgroup	PARPi Mean	PARPi SD	PARPi Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
5.11.1 Participants with BRCA mutation								
ARIEL3	15.85	7.145818	130	6.61	3.742413	66	67.5%	9.24 [7.72 , 10.76]
SOLO 2	15.03	12.79	195	7.7	6.42	99	32.5%	7.33 [5.13 , 9.53]
Subtotal (95% CI)			**325**			**165**	**100.0%**	**8.62 [7.37 , 9.87]**
Heterogeneity: Chi² = 1.96, df = 1 (P = 0.16); I² = 49%								
Test for overall effect: Z = 13.49 (P < 0.00001)								
5.11.2 Participants without BRCA mutation								
ARIEL3	9.03	5.687009	107	5.93	2.363092	54	100.0%	3.10 [1.85 , 4.35]
Subtotal (95% CI)			**107**			**54**	**100.0%**	**3.10 [1.85 , 4.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.87 (P < 0.00001)								
Test for subgroup differences: Chi² = 37.42, df = 1 (P < 0.00001), I² = 97.3%								



Analysis 5.12. Comparison 5: Platinum-sensitive recurrent EOC: PARPi monotherapy compared with placebo after chemotherapy (maintenance therapy), Outcome 12: Any severe adverse event (grade 3 or higher)

Study or Subgroup	PARPi Events	PARPi Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Study 19 (Ledermann 2012) (1)	48	136	26	128	23.4%	1.74 [1.15 , 2.62]
SOLO 2 (1)	71	195	18	99	21.8%	2.00 [1.27 , 3.16]
NOVA (2)	272	367	41	179	28.6%	3.24 [2.46 , 4.26]
ARIEL3 (3)	222	372	30	189	26.2%	3.76 [2.68 , 5.28]
Total (95% CI)		**1070**		**595**	**100.0%**	**2.62 [1.85 , 3.72]**
Total events:	613		115			

Heterogeneity: Tau² = 0.09; Chi² = 11.19, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 5.39 (P < 0.00001)
Test for subgroup differences: Not applicable



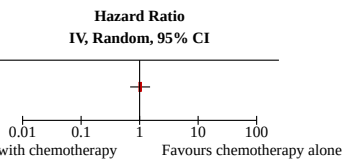
Footnotes
(1) PARP inhibitor: olaparib
(2) PARP inhibitor: niraparib; Treatment emergent AE
(3) PARP inhibitor: rucaparib; Treatment emergent AE

Comparison 6. Platinum-sensitive recurrent EOC: PARPi with chemotherapy compared with chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
6.2 Objective response rate (no response)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.3 Any severe adverse event (grade 3 or higher)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6: Platinum-sensitive recurrent EOC: PARPi with chemotherapy compared with chemotherapy alone, Outcome 1: Progression-free survival

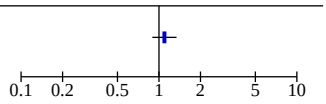
Study or Subgroup	log[Hazard Ratio]	SE	PARPi with chemotherapy Total	Chemotherapy alone Total	Hazard Ratio IV, Random, 95% CI
Kummar 2015 (1)	0.0198	0.2	37	38	1.02 [0.69 , 1.51]



Footnotes
(1) PARP inhibitor: veliparib; population: only participants with *BRCA* mutation

Analysis 6.2. Comparison 6: Platinum-sensitive recurrent EOC: PARPi with chemotherapy compared with chemotherapy alone, Outcome 2: Objective response rate (no response)

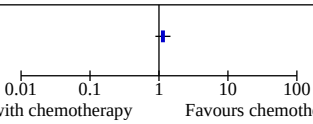
Study or Subgroup	PARPi with chemotherapy Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Kummar 2015 (1)	30	34	29	36	1.10 [0.89 , 1.34]	



Footnotes
(1) PARP inhibitor: veliparib

Analysis 6.3. Comparison 6: Platinum-sensitive recurrent EOC: PARPi with chemotherapy compared with chemotherapy alone, Outcome 3: Any severe adverse event (grade 3 or higher)

Study or Subgroup	PARPi with chemotherapy Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Oza 2015 (1)	53	81	43	75	1.14 [0.89 , 1.47]	



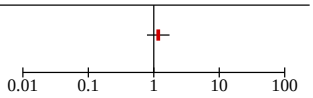
Footnotes
(1) safety data from the combination phase

Comparison 7. Platinum-sensitive recurrent EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Overall survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
7.2 Progression-free survival	1		Hazard Ratio (IV, Random, 95% CI)	Totals not selected
7.3 Progression-free survival by BRCA status	1		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
7.3.1 Participants with BRCA mutation	1	41	Hazard Ratio (IV, Random, 95% CI)	0.21 [0.08, 0.55]
7.3.2 Participants without BRCA mutation	1	66	Hazard Ratio (IV, Random, 95% CI)	0.77 [0.41, 1.44]
7.4 Objective response rate (no response)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.5 Any severe adverse event (grade 3 or higher)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7: Platinum-sensitive recurrent EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone, Outcome 1: Overall survival

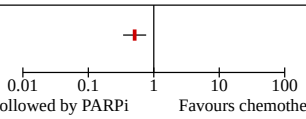
Study or Subgroup	log[Hazard Ratio]	SE	[Not identical] Total	[Not identical] Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Oza 2015 (1)	0.157	0.2024	81	81	1.17 [0.79 , 1.74]	



Footnotes
(1) Final analysis (62% mature data); PARP inhibitor: olaparib

Analysis 7.2. Comparison 7: Platinum-sensitive recurrent EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone, Outcome 2: Progression-free survival

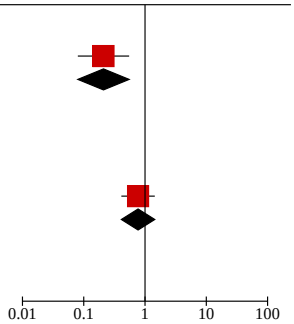
Study or Subgroup	log[Hazard Ratio]	SE	[Not identical] Total	[Not identical] Total	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Oza 2015 (1)	-0.6733	0.2069	81	81	0.51 [0.34 , 0.77]	



Footnotes
(1) PARP inhibitor: olaparib

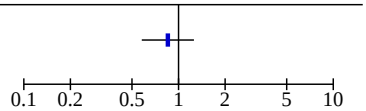
Analysis 7.3. Comparison 7: Platinum-sensitive recurrent EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone, Outcome 3: Progression-free survival by BRCA status

Study or Subgroup	log[Hazard Ratio]	SE	[Not identical] Total	[Not identical] Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
7.3.1 Participants with BRCA mutation							
Oza 2015	-1.560648	0.491818	20	21	100.0%	0.21 [0.08 , 0.55]	
Subtotal (95% CI)			**20**	**21**	**100.0%**	**0.21 [0.08 , 0.55]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 3.17 (P = 0.002)							
7.3.2 Participants without BRCA mutation							
Oza 2015	-0.261365	0.320476	34	32	100.0%	0.77 [0.41 , 1.44]	
Subtotal (95% CI)			**34**	**32**	**100.0%**	**0.77 [0.41 , 1.44]**	
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.82 (P = 0.41)							
Test for subgroup differences: Chi² = 4.90, df = 1 (P = 0.03), I² = 79.6%							



Analysis 7.4. Comparison 7: Platinum-sensitive recurrent EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone, Outcome 4: Objective response rate (no response)

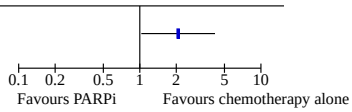
Study or Subgroup	[Not identical] Events	[Not identical] Total	[Not identical] Events	[Not identical] Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Oza 2015 (1)	29	81	34	81	0.85 [0.58 , 1.26]	



Footnotes
(1) PARP inhibitor: olaparib

Analysis 7.5. Comparison 7: Platinum-sensitive recurrent EOC: PARPi with chemotherapy and as maintenance therapy compared with chemotherapy alone, Outcome 5: Any severe adverse event (grade 3 or higher)

Study or Subgroup	PARPi with chemotherapy and as maintenance Events	Total	Chemotherapy alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
Oza 2015	19	56	9	55	2.07 [1.03 , 4.18]

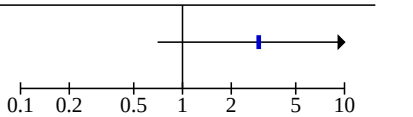


Comparison 8. Platinum-resistant recurrent EOC: PARPi monotherapy compared with chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Objective response rate (no response)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.2 Any severe adverse event (grade 3 or higher)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Platinum-resistant recurrent EOC: PARPi monotherapy compared with chemotherapy, Outcome 1: Objective response rate (no response)

Study or Subgroup	PARPi Events	Total	Chemotherapy Events	Total	Risk Ratio M-H, Fixed, 95% CI
CLIO (1)	12	67	2	33	2.96 [0.70 , 12.44]

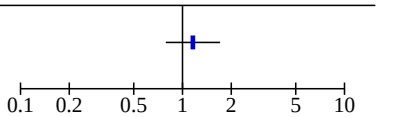


Footnotes

(1) unconfirmed ORR ; data from conference abstract (2019)

Analysis 8.2. Comparison 8: Platinum-resistant recurrent EOC: PARPi monotherapy compared with chemotherapy, Outcome 2: Any severe adverse event (grade 3 or higher)

Study or Subgroup	PARPi Events	Total	Chemotherapy Events	Total	Risk Ratio M-H, Fixed, 95% CI
CLIO (1)	40	67	17	33	1.16 [0.79 , 1.70]



Footnotes

(1) data from conference abstract (2019)

ADDITIONAL TABLES

Table 1. Overview of included studies

Study ID	Intervention/s (name and n)	Control (name and n)	Sample size	Randomisation ratio	First-line treatment or relapsed disease	*BRCA* status	Somatic *BRCA*	Germline *BRCA*	HRD Status	Participants with measurable disease (RECIST)	Prior treatment	Platinum-related status
Newly-diagnosed EOC												
PAOLA-1	Olaparib+Bevacizumab (537)	Placebo+Bevacizumab (269)	806	2:1	First-line	30% BRCA+	NR	NR	48%	27%	Platinum–taxane chemotherapy plus bevacizumab	PS / first-line treatment
PRIMA	Niraparib (487)	Placebo (246)	733	2:1	First-line	30% BRCA+	NR	NR	51%	NR	All the patients had received six to nine cycles of first-line platinum-based chemotherapy	PS / first-line treatment
SOLO 1	Olaparib (260)	Placebo (131)	391	2:1	First-line	All BRCA+ ~70% BRCA1+ ~30% BRCA2+	1%	99%	NR	NR	Platinum-based chemotherapy without bevacizumab	PS / first-line-treatment
VELIA	Veliparib+Chemotherapy followed by placebo (383) Veliparib+Chemotherapy followed by veliparib (382)	Placebo+Chemotherapy followed by placebo (375)	1140	1:1:1	First-line	30% BRCA+	29%	71%	NR	NR	Participants who undergo primary cytoreductive surgery	PS / first-line treatment
Relapsed EOC												

Table 1. Overview of included studies *(Continued)*

Kummar 2015	Veliparib+Chemotherapy (37)	Chemotherapy (38)	75	1:1	Relapsed	40% BRCA+	NR	NR	NR	All	All patients were required to have received at least one line of standard therapy	Not reported
Oza 2015	Olaparib+Chemotherapy followed by Olaparib (81)	Chemotherapy followed by no treatment (81)	162	1:1	Relapsed	Information available for 107 of 162 pts 38% BRCA+	0%	100%	NR	NR	Maximum of 3 platinum-based therapies	PS (52%) & PPS (48%)
AVANOVA2	Niraparib + Bevacizumab (48)	Niraparib (49)	97	1:1	Relapsed	34% BRCA+	29%	71%	NR	All	Previous platinum-containing therapy for primary disease but ≤1 prior non-platinum-containing regimen for recurrent disease	PS (66%) or PPS (34%)
NCT02446600	Cediranib+Olaparib (189) Olaparib (189)	Chemotherapy (187)	565	1:1:1	Relapsed	23.7% BRCA+	NR	NR	NR	NR	platinum and non-platinum based chemotherapy	PS (details unavailable)
SOLO 3	Olaparib (178)	Chemotherapy (88)	266	2:1	Relapsed	All BRCA+ ~65% BRCA1+ ~31% BRCA2+	0%	100%	NR	All	At least 2 prior lines of platinum-based chemotherapy	PS (37%) or PPS (62%)
ICEBERG 3 (Kaye 2012)	Olaparib 200 mg (32) Olaparib 400 mg (32)	Placebo (33)	97	1:1:1	Relapsed	All BRCA+ 80% BRCA1	0%	100%	NR	All	platinum-based chemotherapy regimen (another non-PLD chemotherapy after this was permitted)	PR (~50%) and PPS
ARIEL3	Rucaparib (375)	Placebo (189)	564	2:1	Relapsed	35% BRCA+	30%	70%	28%**	37%	At least 2 previous platinum-based	PS or PPS

Table 1. Overview of included studies *(Continued)*

											chemotherapy regimens; prior BEV treatment permitted except BEV maintenance	
NOVA	Niraparib (372)	Placebo (181)	553	2:1	Relapsed	38% BRCA+	0%	100%	40%**	49%*	At least two previous lines of platinum-based chemotherapy	PS (61%) & PPS (39%)**
Study 19 (Ledermann 2012)	Olaparib (136)	Placebo (129)	265	1:1	Relapsed	22% BRCA+	0%	100%	NR	40%	Two or more platinum-based regimens	PS (60%) & PPS (40%)*
SOLO 2	Olaparib (196)	Placebo (99)	295	2:1	Relapsed	97% BRCA+	0%	100%	NR	All?	At least two previous lines of platinum-based chemotherapy	PS
CLIO	Olaparib (67)	Chemotherapy (33)	100	2:1	Relapsed	NR	NR	NR	NR	NR	At least 1 previous line of chemotherapy	PR (100%)

PS: Platinum sensitive;**PPS:** partially-platinum sensitive; **PR:** platinum-resistant; **NR:** not reported.
** This was defined as in the manscript (or with high dgree loss of hetrogenicity) and is limited to *BRCA* wild type.

Table 2. Health related Quality of Life (HRQoL) measures in the included studies

Study ID	Primary HRQoL measures	Outcomes
Newly-diagnosed EOC		
PAOLA-1	EORTC QLQ-C30	Estimated between-group difference was 1.56 points (95% CI, −0.42 to 3.55)
PRIMA	FOSI, EQ-5D-5L, EORTC-QLQ-C30, and EORTC-QLQ- OV28.	"analysis of the EORTC-QLQ-C30 and EORTC-QLQ-OV28 did not indicate a difference in health-related quality of life scores of patients treated with niraparib vs. placebo"
SOLO 1	FACT-O TOI	At baseline, ~20% of patients in both groups reported being somewhat to very much bothered by post- chemotherapy side-effects. 5 weeks after end of chemotherapy, 30% of olaparib patients vs. 11% of placebo patients were still bothered by side- effects of maintenance treatment. "Approximately 10% more patients on olaparib than on placebo reported that they were somewhat or quite a bit bothered by side-effects, predominantly within the first 12 weeks of treatment."
VELIA	NFOSI-18	"Mean change from baseline in the NFOSI-18 Disease Related Symptom scores increased over time (indicating improvement), particularly after chemotherapy was completed (cycle 7 and beyond). The differences in the mean change from baseline in scores between treatment groups were small (range, 0.0 to 2.1) and were not considered to be clinically significant."
Relapsed/recurrent EOC		
ARIEL3	EQ-5D-5L; *QA-PFS; *Q-TWiST	QA-PFS months mean difference 6.28 (95% CI 4.85 to 7.47) in favour of PARPi and was 2.1-fold longer in the PARPi group than in the placebo group in the ITT population (mean months 12.02 vs. 5.74). Q-TWIST - months mean difference in >= G3+ SevAE 6.88 (95% CI 5.71 to 8.24) in favour of PARPi (mean months 13.32 vs. 6.44). Neither Q-TWiST nor QA-PFS were pre-specified outcomes in the ClinicalTrials.gov record.
NOVA	FOSI; EQ-5D-5L	baseline mean FOSI values: g*BRCA*mut cohort = 25 · 1 [SD 4 · 18] in PARPi group and 25 · 6 [3 · 84] in placebo group); non-g*BRCA*mut cohort = 25 · 4 [3 · 92] in PARPi group and 25 · 0 [4 · 07] in placebo group). Overall QOL scores remained stable during the treatment and pre-progression period; no significant differences were observed between the PARPi and placebo group. pre-progression EQ-5D-5L scores were similar between the two groups in both cohorts: g*BRCA*mut cohort = 0·838 [0·0097] in tPARPI group vs. 0·834 [0·0173] in placebo group; non-gBRCAmut cohort = 0·833 [0·0077] in PARPi group vs 0·815 [0·0122] in placebo group.

Table 2. Health related Quality of Life (HRQoL) measures in the included studies *(Continued)*

SOLO 2	TOI FACT-O (v2016); *Q-TWiST; *QA-PFS	No significant detrimental effect HRQOL analysed by change from baseline in TOI score (–3.1 vs –2.9, respectively, difference (PARPi minus placebo) –0.2; 95% CI –2.4 to 2.1; P=0.88). Adjusted average mean change from baseline over the first 12 months in TOI was -2·90 (95% CI -4·13 to -1·67) with PARPi and -2·87 (-4·64 to -1·10) with placebo (estimated difference -0·03; 95% CI -2·19 to 2·13; P = 0·98); Q-TWiST and QA-PFS improvement for patients on maintenance PARPi (due in part to prolonged PFS and delay in symptoms due to disease): Q-TWiST (13.5 vs. 7.2 months, difference 6.3; 95% CI 2.9 to 8.6; P<0.001): QA-PFS (mean 14.0 vs. 7.3 months for PARPi and placebo, respectively, difference 6.7 months; 95% CI 5.0 to 8.5; P<0.0001). Neither Q-TWiST nor QA-PFS were pre-specified outcomes in the ClinicalTrials.gov record.
SOLO 3	TOI FACT-O questionnaire Version 4; *Q-TWiST; *QA-PFS	Mean TOI scores at baseline were 73.2 in PARPi group and 71.8 in chemotherapy group. Overall least-squares mean change from baseline in TOI score was 22.3 with PARPi (n = 167) vs. 24.8 with chemotherapy (n = 62), with a between-group difference of 2.5 (95% CI, 20.5 to 5.5; P = 0.108). Neither Q-TWiST nor QA-PFS were pre-specified outcomes in the ClinicalTrials.gov record.

EQ-5D-5L: European QOL five-dimension five-level questionnaire; **FACT-O** Functional Assessment of Cancer Therapy-Ovarian Trial Outcome Index (TOI); **FOSI:** Functional Assessment of Cancer Therapy–Ovarian Symptoms Index;**g*BRCA*mut:** germline breast cancer susceptibility gene (*BRCA*) mutation; **NFOSI-18:** National Comprehensive Cancer Net- work Functional Assessment of Cancer Therapy Ovarian Symptom Index–18; **non–g*BRCA*mut:** no germline breast cancer susceptibility gene (*BRCA*) mutation; **PARPi:** poly ADP ribose polymerase inhibitor; **QA-PFS:** quality-adjusted progression-free survival; **Q-TWiST:** Quality-adjusted time without symptoms or toxicity; **TOI:** Trial outcome index.
*QA-PFS and Q-TWiST were post hoc analyses.

Table 3. Median Overall Survival time (months)

		PARP inhibitor		Control	
Study ID	**Comparison**	**Median (95%CI)**	**Total (N)**	**Median (95%CI)**	**Total (N)**
Newly-diagnosed EOC					
Medians not reported					
Recurrent, platinum-sensitive EOC					
Oza 2015	PARP inhibitor (OLA) with chemotherapy versus chemotherapy	33.8 (26.9, 38.5)	81	37.6 (27.8, 44.6)	81
Oza 2015 (1)	PARP inhibitor (OLA) with chemotherapy versus chemotherapy	not reached (26.9, not reached)	20	39.2 (31.5, not reached)	21
SOLO 3	PARP inhibitor (OLA) versus chemotherapy	37.8 (29.9, not reached)	178	39.4 (24.2, not reached)	88
Study 19 (Ledermann 2012)	PARP inhibitor (OLA) versus placebo after chemotherapy (maintenance therapy)	29.7 (NR)	136	29.9 (NR)	128

Table 3. Median Overall Survival time (months) *(Continued)*

Recurrent, platinum-resistant EOC
Medians not reported

EOC: epithelial ovarian cancer; **OLA:** olaparib; **NR:** not reported
(1) a subgroup with BRCA mutation;

Table 4. Median Progression-Free Survival time (months)

		PARP inhibitor		**Control**	
Study ID	**Comparison**	**Median (95%CI)**	**Total (N)**	**Median (95%CI)**	**Total (N)**
Newly-diagnosed EOC					
All participants					
PRIMA	PARP inhibitor (NIR) versus placebo (maintenance)	13.8 (NR)	487	8.2 (NR)	246
PAOLA-1	PARP inhibitor (OLA) with BEV versus BEV alone	22.1 (NR)	537	16.6 (NR)	269
VELIA	PARP inhibitor (VEL) with chemotherapy and as maintenance versus chemotherapy alone	23.5 (19.3 to 26.3)	382	17.3 (15.1 to 19.1)	375
VELIA	PARP inhibitor (VEL) with chemotherapy only (placebo in maintenance) versus chemotherapy alone	15.2 (14.1 to 17.3)	383	17.3 (15.1 to 19.1)	375
Participants with *BRCA* mutation					
PRIMA	PARP inhibitor (NIR) versus placebo	22.1 (NR)	152	10.9 (NR)	71
SOLO 1*	PARP inhibitor (OLA) versus placebo	not reached	260	13.8 (11.1, 18.2)	131
PAOLA-1	PARP inhibitor (OLA) with BEV versus BEV alone	37.2 (NR)	157	21.7 (NR)	80
VELIA	PARP inhibitor (VEL) with chemotherapy and as maintenance versus chemotherapy alone	34.7 (31.8, not reached)	108	22.0 (17.8, 29.1)	92
VELIA	PARP inhibitor (VEL) with chemotherapy (placebo in maintenance) versus chemotherapy alone	21.1 (17.0, 25.5)	98	22.0 (17.8, 29.1)	92
Subgroup: participants with HRD mutation					

Table 4. Median Progression-Free Survival time (months) *(Continued)*

PRIMA	PARP inhibitor (NIR) versus placebo	21.9 (NR)	247	10.4 (NR)	126
PAOLA-1	PARP inhibitor (OLA) with BEV versus BEV alone	37.2 (NR)	255	17.7 (NR)	132
VELIA	PARP inhibitor (VEL) with chemotherapy and as maintenance versus chemotherapy alone	31.9 (NR)	214	20.5 (NR)	207
VELIA	PARP inhibitor (VEL) with chemotherapy (placebo in maintenance) versus chemotherapy alone	18.1 (NR)	206	20.5 (NR)	207
(2) PARP inhibitor monotherapy compared with chemotherapy in recurrent EOC					
All participants					
SOLO 3*	PARP inhibitor (OLA) versus chemotherapy	13.4 (10.9, 14.1)	178	9.2 (7.6, 11.2)	88
NCT02446600*	PARP inhibitor (OLA) with CED versus chemotherapy	10.4 (NR)	189	10.3 (NR)	187
NCT02446600*	PARP inhibitor (OLA) versus chemotherapy	8.2 (NR)	189	10.3 (NR)	187
ICEBERG 3 (Kaye 2012)	PARP inhibitor (OLA 200 mg) versus chemotherapy	6.5 (5.5, 10.1)	32	7.1 (3.7, 10.7)	33
ICEBERG 3 (Kaye 2012)	PARP inhibitor (OLA 400 mg) versus chemotherapy	8.8 (5.4, 9.2)	32		
(3) PARP inhibitor compared with placebo after chemotherapy in recurrent EOC(maintenance therapy)					
All participants					
ARIEL3	PARP inhibitor (RUC) versus placebo	13.7 (11.0, 19.1)	375	5.4 (5.1, 5.5)	189
NOVA*	PARP inhibitor (NIR) versus placebo	21 (NR)	138	5.5 (NR)	65
Study 19 (Ledermann 2012)	PARP inhibitor (OLA) versus placebo	8.4 (NR)	136	4.8 (NR)	129
SOLO 2^	PARP inhibitor (OLA) versus placebo	19.1 (16.3, 25.7)	196	5.5 (5.2, 5.8)	99
Oza 2015	PARP inhibitor (OLA) with chemotherapy followed by PARP inhibitor as maintenance versus chemotherapy alone	12.2 (9.7, 15.0)	81	9.6 (9.1, 9.7)	81
Subgroup: participants with BRCA mutation					

Table 4. Median Progression-Free Survival time (months) *(Continued)*

SOLO 3*	PARP inhibitor (OLA) versus chemotherapy	13.4 (10.9, 14.1)	178	9.2 (7.6, 11.2)	88
NCT02446600*	PARP inhibitor (OLA) with CED versus chemotherapy	10.4 (NR)	189	10.3 (NR)	187
ARIEL3	PARP inhibitor (RUC) versus placebo	26.8 (19.2, not reached)	130	5.4 (4.9, 8.1)	66
NOVA*	PARP inhibitor (NIR) versus placebo	21 (NR)	138	5.5 (NR)	65
SOLO 2	PARP inhibitor (OLA) versus placebo	19.3 (16.5, 27.3)	190	5.5 (5.0, 5.8)	96
Kummar 2015*	PARP inhibitor (VEL) with chemotherapy versus chemotherapy alone	2.1 (NR)	37	2.3 (NR)	38
Oza 2015	PARP inhibitor (OLA) with chemotherapy versus chemotherapy alone	not reached (9.6, not reached)	20	9.7 (7.3, 10.0)	21
Subgroup: participants with HRD mutation					
ARIEL3	PARP inhibitor (RUC) versus placebo	22.9 (16.2, not reached)	236	5.5 (5.1, 7.4)	118
NOVA*	PARP inhibitor (NIR) versus placebo	12.9 (NR)	106	3.8 (NR)	56
(4) PARP inhibitor in recurrent ovarian cancer (various comparisons)					
All participants					
Kummar 2015*	PARP inhibitor (VEL) with chemotherapy versus chemotherapy alone	2.1 (NR)	37	2.3 (NR)	38
Oza 2015	PARP inhibitor (OLA) with chemotherapy followed by PARP inhibitor as maintenance versus chemotherapy alone	12.2 (9.7, 15.0)	81	9.6 (9.1, 9.7)	81
AVANOVA2	PARP inhibitor (NIR) with BEV versus PARP inhibitor (NIR) alone	11.9 (8.5, 16.7)	48	5.5 (3.8, 6.3)	49
Subgroup: participants with BRCA mutation					
Kummar 2015	PARP inhibitor (VEL) with chemotherapy versus chemotherapy alone	2.1 (NR)	37	2.3 (NR)	38
Oza 2015	PARP inhibitor (OLA) with chemotherapy versus chemotherapy alone	not reached (9.6, not reached)	20	9.7 (7.3, 10.0)	21

Table 4. Median Progression-Free Survival time (months) *(Continued)*

AVANOVA2	PARP inhibitor (NIR) with BEV versus PARP inhibitor (NIR) alone	14.4 (6.2, 22.7)	15	9.0 (3.9, 13.0)	18
Subgroup: participants with HRD mutation					
AVANOVA2	PARP inhibitor (NIR) with BEV versus PARP inhibitor (NIR) alone	11.9 (8.5, 22.9)	28	6.1 (3.9, 9.0)	30
(5) PARP inhibitor compared with chemotherapy in recurrent platinum-resistant ovarian cancer					
All participants					
CLIO	PARP inhibitor (OLA) versus chemotherapy	2.9 (NR)	67	3.4 (NR)	33

BEV: bevacizumab; **CED:** cediranib; **NIR:,** niraparib; **NR:** not reported; **OLA:** olaparib; **PARP:** poly adenosine diphosphate-ribose polymerase; **PLB:** placebo;**RUC:** rucaparib;**VEL:** veliparib.
*studies that recruited only participants with BRCA mutation;
^97% of participants in the SOLO2 study had a BRCA mutation.

APPENDICES

Appendix 1. CENTRAL search strategy

#1 ovar* and (cancer* or carcinom* or neoplasm* or tumor* or tumour* or malignan*)
#2 MeSH descriptor Ovarian Neoplasms explode all trees
#3 (#1 OR #2)
#4 MeSH descriptor DNA Repair Enzymes explode all trees
#5 MeSH descriptor DNA Repair explode all trees
#6 DNA repair
#7 MeSH descriptor Poly(ADP-ribose) Polymerases explode all trees
#8 PARP near/5 inhibit*
#9 poly ADP ribose polymerase near/5 inhibit*
#10 olaparib or AZD2281 or KU59436
#11 AG014699
#12 ABT-888
#13 BSI-201
#14 INO-1001
#15 MK4827
#16 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 (#3 AND #16)

Appendix 2. MEDLINE search strategy

1 randomized controlled trial.pt.
2 controlled clinical trial.pt.
3 randomized.ab.
4 placebo.ab.
5 drug therapy.fs.
6 randomly.ab.
7 trial.ab.
8 groups.ab.
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10 (animals not (humans and animals)).sh.
11 9 not 10
12 ovar*.mp.
13 (cancer* or carcinoma*or neoplasm* or tumor*or tumour*or malignan*).mp.

14 12 and 13
15 exp Ovarian Neoplasms/
16 14 or 15
17 exp DNA Repair Enzymes/
18 exp DNA Repair/
19 DNA repair.mp.
20 exp "Poly(ADP-ribose) Polymerases"/
21 (PARP adj5 inhibit*).mp.
22 (poly ADP ribose polymerase adj5 inhibit*).mp.
23 (olaparib or AZD2281 or KU59436).mp.
24 AG014699.mp.
25 ABT-888.mp.
26 BSI-201.mp.
27 INO-1001.mp.
28 MK4827.mp.
29 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 11 and 16 and 29

key:
pt=publication type
ab=abstract
fs=floating subheading
mp=title, original title, abstract, name of substance word, subject heading word
sh=subject heading

Appendix 3. Embase search strategy

1 exp Controlled Clinical Trial/
2 randomized.ab.
3 placebo.ab.
4 dt.fs.
5 randomly.ab.
6 trial.ab.
7 groups.ab.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 (animal not (human and animal)).sh.
10 8 not 9
11 (ovar* and (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan*)).mp.
12 exp Ovary Tumor/
13 11 or 12
14 exp Polydeoxyribonucleotide Synthase/
15 exp DNA Repair/
16 DNA repair.mp.
17 exp Nicotinamide Adenine Dinucleotide Adenosine Diphosphate Ribosyltransferase/
18 (PARP adj5 inhibit*).mp.
19 (poly ADP ribose polymerase adj5 inhibit*).mp.
20 (olaparib or AZD2281 or KU59436).mp.
21 AG014699.mp.
22 ABT-888.mp.
23 BSI-201.mp.
24 INO-1001.mp.
25 MK4827.mp.
26 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 10 and 13 and 26

key:
ab=abstract
fs=floating subheading
sh=subject heading
mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name

WHAT'S NEW

Date	Event	Description
31 July 2021	New citation required and conclusions have changed	12 new studies added and 15 ongoing studies identified
20 October 2020	New search has been performed	Search updated

HISTORY

Protocol first published: Issue 3, 2009
Review first published: Issue 6, 2010

Date	Event	Description
21 September 2016	Amended	Contact details updated.
3 August 2015	Amended	Typographical error amended.
30 April 2015	Amended	Literature search text amended
21 April 2015	New citation required and conclusions have changed	Updated review with four RCTs added.
21 April 2015	New search has been performed	Searches updated 21 April 2015
5 October 2013	New search has been performed	Search updated 5 October 2013.

CONTRIBUTIONS OF AUTHORS

AT and NR contributed equally to the review and are joint first authors.

For this latest update AW, JM, AT and NR sifted the results of the searches. AT, NR, JM and AW performed full text screening. Disagreements were resolved by discussion with JM. AT, AW, NR, JM, and ER contributed to data extraction, EW performed the data analysis, with the GRADE assessment performed by ER and JM. NR, AT, and JM contacted authors and pharmaceutical companies for additional information. NR, ER, and JM wrote the final review and all current authors approved the final version of the review.

DECLARATIONS OF INTEREST

AT - no conflict of interest declared.
NR - no conflict of interest declared.
AW - no conflict of interest declared.
ER - no conflict of interest declared.
JM - no conflict of interest declared.

SOURCES OF SUPPORT

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- Taunton and Somerset NHS Trust NHS Supporting Programmed Activity, UK

  JM (1 hr per/week)

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Changes between original protocol/review and first update

The title was changed to limit to PARPi for clarity.

Another comparison group of PARPi versus conventional chemotherapy was added following the publication of the original version of the review due to ongoing studies identified in the initial search. We analysed data from studies with women who had EOC sensitivity and were resistant to platinum treatment separately since these are heterogeneous populations. Subgroup analyses were not required since women in each study were limited to either platinum-resistant or platinum-sensitive disease. Future updates of the review will contain subgroup analyses based on platinum sensitivity, if appropriate. We will also perform subgroup analysis based on *BRC*A-mutation status. In addition, from ongoing studies identified in the original review, we knew that studies likely to be included were not powered for overall survival (OS). Objective Response Rate (ORR) was therefore added as a secondary outcome measure at the data extraction stage in this update since it was identified as a planned outcome measure from published protocols of ongoing studies online in the original review. The outcome 'toxicity' was renamed as 'adverse events' in the update of the review. Future versions of this review should include *BRC*A mutation status as a subgroup analysis.

Subsequent to the publication of the original protocol, Cochrane methods have changed, and it is recommended that the certainty of evidence should be assessed according to the GRADE system. GRADEpro software (GRADEpro 2014) was used to import data from Review Manager 5.3 (RevMan 2020) in order to create summary of findings tables (Summary of findings 6) according to guidance in the Cochrane Handbook Chapter 11. This allowed us to summarise the overall quality of evidence from studies included in each comparison. The following outcomes were included in the summary of findings tables by treatment comparisons:

- Overall survival
- Progression-free survival
- Severe adverse effects

Changes between the previous version of the review and the current version

As planned, a priori for subsequent updates at the time of the previous version of the review, we analysed the effects of interventions in a number of comparisons, since there are a number of clinical scenarios where it may be appropriate to use PARPi, each of which is a separate clinical question. These comparisons, based on different situations encountered clinically, are all clinically relevant questions. We, therefore, planned subgroup analyses by the line of treatment and by platinum sensitivity of disease at relapse. Furthermore, increased knowledge about the biology of ovarian cancer, since the original protocol, concerning BRCA somatic and germline mutations and HRD status of the tumour were found to be biological markers of response to PARPi and may enable these drugs to be used more selectively, avoiding treatment of women less likely to respond to treatment. Analysis of results by BRCA and HRD status was therefore planned from the outset for this update.

This review, therefore, represents an umbrella review of different theoretical clinical scenarios. These would include:

1. PARPi in treatment of newly-diagnosed EOC (first-line treatment);
   a. PARPi with chemotherapy versus chemotherapy alone;
   b. PARPi (or placebo) following chemotherapy (maintenance treatment);
2. PARPi in treatment of platinum-sensitive recurrent EOC;
   a. PARPi with chemotherapy versus chemotherapy alone;
   b. PARPi monotherapy versus chemotherapy;
   c. PARPi (or placebo) following chemotherapy (maintenance treatment);
3. PARPi in treatment of platinum-resistant recurrent EOC;
   a. PARPi with chemotherapy versus chemotherapy alone;
   b. PARPi monotherapy versus chemotherapy;
   c. PARPi (or placebo) following chemotherapy (maintenance treatment).

The summary of findings tables are presented for the most important comparisons.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*therapeutic use]; Benzimidazoles [adverse effects] [therapeutic use]; Disease-Free Survival; DNA Repair [*drug effects]; Neoplasm Recurrence, Local [*drug therapy]; Ovarian Neoplasms [*drug therapy] [genetics]; Phthalazines [adverse effects] [*therapeutic use]; Piperazines [adverse effects] [*therapeutic use]; *Poly(ADP-ribose) Polymerase Inhibitors; Randomized Controlled Trials as Topic

MeSH check words

Adult; Female; Humans